Investigating the Neurobiological and Cognitive Features of Anorexia Nervosa

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Abstract

**Objective:** Anorexia nervosa (AN) is a serious psychiatric condition characterised by significantly low body weight, a fear of weight gain and a disturbance in the experience of one’s own body weight or shape. The 12-month prevalence of AN is approximately 0.4% among females, and approximately one-tenth of that among males. AN is associated with exceptionally high morbidity rates, and a mortality rate among the highest of any psychiatric illness. AN is also associated with exceptionally high relapse rates. A major contributing factor for the high rates of morbidity and mortality experienced by these individuals is that the factors involved in the genesis and maintenance of the illness remain unclear, resulting in a hindrance in the improvement of current treatments or the development of new and more effective treatments. Though a number of treatment modalities have emerging evidence for efficacy, many patients remain under- or unresponsive. Thus, gaining a better understanding of the factors involved in the illness has the potential to lead to the development of more effective treatments in the future. Therefore, the aim of this thesis was to investigate the neurobiological and cognitive features of AN through a range of cognitive assessments, eyetracking tasks and functional neuroimaging measures. **Method:** Twenty-six right-handed female participants with AN and 27 healthy controls, matched for age, gender and premorbid intelligence participated in the study. Participants were required to attend three test sessions within a one week period that involved the completion of a variety of tasks. Included among these tasks were a cognitive battery, basic saccade tasks (prosaccade/antisaccade/no-go, memory-guided and self-paced saccade tasks), an emotional face processing task, a body size estimation task, a resting state functional magnetic resonance imaging (fMRI) scan, and a fixation task. **Results:** Participants with AN were found to demonstrate differences in performance on a variety of measures, relative to controls. AN participants showed a trend for poorer performance on a working memory task component of the cognitive battery which required the manipulation of visuospatial information. AN participants also displayed shorter prosaccade latencies and an increased rate of inhibitory errors on the memory-guided saccade task, but no significant difference in antisaccade, no-go or self-paced saccade performance. AN participants also demonstrated intact emotion identification of others, and relatedly, no significant difference in blood oxygen level dependent (BOLD) activity to face
stimuli depicting different emotions. BOLD activity was however found to significantly differ to participants’ own faces, with AN participants displaying increased activity in the right inferior and middle temporal gyri, and right lingual gyrus. AN participants also avoided fixating on salient features of their own face and showed hyperscanning behaviours to images of their own face, emotional face stimuli and biological motion stimuli. The estimation of body size of biological motion stimuli was, however, not found to differ between groups. Findings of the resting state analysis indicated reduced functional connectivity within the sensorimotor and visual network in AN, but no significant group difference in default mode network connectivity. Finally, AN participants were found to make saccadic intrusions, specifically square wave jerks (SWJs), at a greater rate than healthy controls during fixation. The rate of SWJs also negatively correlated with state anxiety in AN, but not in controls. Discussion: The findings of the study indicate distinctive eye movement differences and visuospatial processing deficits in individuals with AN. The findings are discussed in terms of their overlap with reported findings in anxiety disorders, and the potential brain areas contributing to these results. Specifically, the potential role of the superior colliculus and gamma-aminobutyric acid (GABA) in AN are implicated through a number of findings. Furthermore, the negative correlation between SWJ rate and state anxiety classified groups with very high accuracy and was identified as a distinctive biomarker for AN. The clinical implications of these findings are discussed, as are the potential directions for treatment focus.
Declaration

This is to certify that:

i. The thesis comprises only my original work towards the PhD except where indicated in the Preface.

ii. Due acknowledgement has been made in the text to all other material used.

iii. The thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Andrea Phillipou

February 2015
Preface

Two multi-author peer-reviewed publications were included in this thesis. Author contributions to each manuscript are indicated below.


Phillipou wrote the first draft of the manuscript. Rossell and Castle provided scientific input and editorial assistance. All authors contributed to and approved the final publication.


Phillipou was responsible for data collection and analysis, and writing the first draft of the manuscript. Rossell, Castle, Gurvich and Abel provided scientific input and editorial assistance. All authors contributed to and approved the final publication.

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Dedicated in loving memory of

Joanne Metaxas

4th February 1973 – 5th October 2008
<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>i</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>DECLARATION</td>
<td>v</td>
</tr>
<tr>
<td>PREFACE</td>
<td>vi</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xxvii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xxxi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xxxiii</td>
</tr>
<tr>
<td>CHAPTER 1: ANOREXIA NERVOSA</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Clinical description</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Associated features</td>
<td>2</td>
</tr>
<tr>
<td>1.3 Comorbid psychiatric conditions</td>
<td>3</td>
</tr>
<tr>
<td>1.4 Epidemiology</td>
<td>4</td>
</tr>
<tr>
<td>1.5 Course of the illness</td>
<td>6</td>
</tr>
<tr>
<td>1.6 Treatment approaches</td>
<td>6</td>
</tr>
<tr>
<td>1.6.1 Cognitive behaviour therapy (CBT)</td>
<td>7</td>
</tr>
<tr>
<td>1.6.2 Family therapy</td>
<td>8</td>
</tr>
</tbody>
</table>
CHAPTER 2: METHOD

2.1 Ethics approval

2.2 Participant recruitment

2.2.1 Recruitment procedure

2.2.2 Eligibility criteria

2.2.3 Sample size

2.3 Materials

2.3.1 Neuropsychological assessments

2.3.1.1 Clinical demographic record

2.3.1.2 Edinburgh Handedness Inventory (EHI)

2.3.1.3 Wechsler Test of Adult Reading (WTAR)

2.3.1.4 Mini International Neuropsychiatric Interview (MINI)

2.3.1.5 Eating Disorder Examination Questionnaire (EDE-Q)

2.3.1.6 Figure Rating Scale (FRS)

2.3.1.7 Montgomery-Asberg Depression Rating Scale (MADRS)

2.3.1.8 Depression Anxiety Stress Scale (DASS)

2.3.1.9 Personality Diagnostic Questionnaire (PDQ-4)

2.3.1.10 Toronto Alexithymia Scale (TAS-20)
4.1 Cognition in anorexia nervosa

4.1.1 Cognitive shifting and flexibility

4.1.2 Speed of processing, psychomotor speed and reaction time

4.1.3 Problem solving and decision making

4.1.4 Memory

4.1.5 Inhibition and impulsivity

4.1.6 Visuospatial processing and visual learning

4.1.7 Attention/vigilance and attentional bias

4.1.8 Social cognition

4.2 Cognition in anorexia nervosa: conclusions

4.3 Current study aims and hypotheses

4.4 Method

4.4.1 Participants

4.4.2 Materials

4.4.2.1 Cognitive battery

4.4.2.1.1 Speed of processing

4.4.2.1.2 Attention/vigilance

4.4.2.1.3 Working memory
4.4.2.1.4 Verbal learning 80
4.4.2.1.5 Visual learning 81
4.4.2.1.6 Reasoning and problem solving 81
4.4.2.1.7 Social cognition 81
4.4.2.1.8 Additional tasks 82
4.4.2.2 MATRICS Consensus Cognitive Battery (MCCB) scoring 83
4.4.2.3 Statistical analysis 83
4.4.3 Procedure 83
4.5 Results 84
4.5.1 Speed of processing 84
4.5.2 Attention/vigilance 86
4.5.3 Working memory 89
4.5.4 Verbal learning 90
4.5.5 Visual learning 91
4.5.6 Reasoning and problem solving 92
4.5.7 Social cognition 93
4.5.8 Overall cognition 94
4.6 Discussion 94
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6.1</td>
<td>Speed of processing</td>
<td>94</td>
</tr>
<tr>
<td>4.6.2</td>
<td>Attention/vigilance</td>
<td>95</td>
</tr>
<tr>
<td>4.6.3</td>
<td>Working memory</td>
<td>96</td>
</tr>
<tr>
<td>4.6.4</td>
<td>Verbal learning</td>
<td>97</td>
</tr>
<tr>
<td>4.6.5</td>
<td>Visual learning</td>
<td>97</td>
</tr>
<tr>
<td>4.6.6</td>
<td>Reasoning and problem solving</td>
<td>98</td>
</tr>
<tr>
<td>4.6.7</td>
<td>Social cognition</td>
<td>98</td>
</tr>
<tr>
<td>4.6.8</td>
<td>Summary and conclusions</td>
<td>98</td>
</tr>
</tbody>
</table>

CHAPTER 5: EYE MOVEMENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Saccade characteristics</td>
<td>103</td>
</tr>
<tr>
<td>5.2</td>
<td>Saccade tasks</td>
<td>104</td>
</tr>
<tr>
<td>5.3</td>
<td>Physiology of saccadic eye movements</td>
<td>105</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Subcortical areas</td>
<td>105</td>
</tr>
<tr>
<td>5.3.2</td>
<td>Cortical areas</td>
<td>107</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Physiology conclusions</td>
<td>110</td>
</tr>
<tr>
<td>5.4</td>
<td>Saccade research in humans</td>
<td>110</td>
</tr>
<tr>
<td>5.4.1</td>
<td>Reflexive saccade tasks</td>
<td>110</td>
</tr>
<tr>
<td>5.4.2</td>
<td>Volitionally controlled saccade tasks</td>
<td>111</td>
</tr>
</tbody>
</table>
5.4.3 Neuroimaging

5.4.3.1 Positron emission tomography (PET)

5.4.3.2 Functional magnetic resonance imaging (fMRI)

5.4.4 Saccade research: conclusions

5.5 Saccades and cognition

5.5.1 Prosaccades

5.5.2 Antisaccades

5.5.3 Go/no-go saccades

5.5.4 Memory-guided saccades

5.5.5 Self-paced saccades

5.6 Clinical populations

5.6.1 Schizophrenia

5.6.2 Personality characteristics and disorders

5.6.3 Mood disorders

5.6.4 Anxiety disorders

5.6.5 Childhood-onset disorders

5.6.6 Eating disorders

5.6.7 Saccade research in clinical populations: conclusions
5.7 Current study aims and hypotheses 137

5.8 Method 138

5.8.1 Participants 138

5.8.2 Tasks 138

5.8.2.1 Self-paced saccade task 138

5.8.2.2 Memory-guided saccade task 139

5.8.2.3 Prosaccade/antisaccade/no-go (PAN) saccade task 140

5.8.2.3.1 Magnetoencephalography (MEG) 141

5.8.2.3.2 Magnetic resonance imaging (MRI) 141

5.8.2.4 Analysis 142

5.8.2.4.1 Eye movements 142

5.8.2.4.2 Functional magnetic resonance imaging (fMRI) 142

5.8.2.4.3 Statistical analysis 143

5.8.2.4.3.1 Eye movements 143

5.8.2.4.3.2 Functional magnetic resonance imaging (fMRI) 143

5.8.3 Procedure 144

5.9 Results 144

5.9.1 Self-paced saccade task 144
5.9.2 Memory-guided saccade task 145

5.9.3 Prosaccade/antisaccade/no-go saccade (PAN) task 148

5.9.3.1 Eyetracking 148

5.9.3.2 Functional magnetic resonance imaging (fMRI) 152

5.9.3.2.1 Within groups analyses 152

5.9.3.2.2 Mixed-design analysis 157

5.10 Discussion 158

5.10.1 Self-paced saccade task 158

5.10.2 Memory-guided saccade task 159

5.10.3 Prosaccade/antisaccade/no-go saccade (PAN) task 161

5.10.3.1 Eyetracking 161

5.10.3.2 Functional magnetic resonance (fMRI) 163

5.10.4 Summary and conclusions 164

CHAPTER 6: EMOTION AND FACE PROCESSING 167

6.1 Emotion processing in anorexia nervosa 167

6.2 Emotion processing in the brain 171

6.2.1 Face processing and perception 172

6.2.1.1 Emotional face processing and perception 173
6.2.2 Visual scanpaths

6.2.2.1 Visual scanpaths to human faces

6.2.3 Emotional face processing in clinical populations

6.2.3.1 Schizophrenia

6.2.3.2 Childhood-onset disorders

6.2.3.3 Mood disorders

6.2.3.4 Anxiety disorders

6.2.3.5 Emotional face processing in clinical populations: conclusions

6.3 Own face processing in clinical populations

6.4 Current study aims and hypotheses

6.5 Method

6.5.1 Participants

6.5.2 Emotional faces task

6.5.2.1 Functional magnetic resonance imaging (fMRI) task

6.5.2.2 Behavioural task

6.5.2.3 Analysis

6.5.2.3.1 Behavioural data and eye movements

6.5.2.3.2 Functional magnetic resonance imaging (fMRI)
6.5.2.4 Statistical analysis

6.5.2.4.1 Behavioural data and eye movements

6.5.2.4.2 Functional magnetic resonance imaging (fMRI)

6.5.3 Procedure

6.6 Results

6.6.1 Behavioural

6.6.2 Eyetracking

6.6.2.1.1 Scanpath characteristics

6.6.2.1.2 Areas of interest (AOIs)

6.6.3 Functional magnetic resonance imaging (fMRI)

6.6.3.1 Within-groups analyses

6.6.3.2 Mixed-design analysis

6.7 Discussion

6.7.1 Behavioural

6.7.2 Eyetracking

6.7.3 Functional magnetic resonance imaging (fMRI)

6.8 Summary and conclusions

CHAPTER 7: RESTING STATE
7.1 Resting state functional connectivity in eating disorders  225

7.2 Clinical populations  228

7.2.1 Schizophrenia  228

7.2.2 Mood disorders  230

7.2.3 Anxiety disorders  232

7.2.4 Resting state functional connectivity in clinical populations: conclusions  234

7.3 Current study aims and hypotheses  235

7.4 Method  236

7.4.1 Participants  236

7.4.2 Task  236

7.4.3 Analysis  237

7.4.3.1 Statistical analysis  237

7.4.4 Procedure  238

7.5 Results  238

7.6 Discussion  241

7.6.1 Default mode network  241

7.6.2 Sensorimotor and visual network  242

7.6.3 Summary and conclusions  244
CHAPTER 8: BODY IMAGE

8.1 Body image in anorexia nervosa

8.2 Biological motion

8.3 Clinical populations

8.3.1 Autism spectrum disorder (ASD)

8.3.2 Schizophrenia

8.3.3 Obsessive compulsive disorder (OCD)

8.3.4 Eating disorders

8.4 Current study aims and hypotheses

8.5 Method

8.5.1 Participants

8.5.2 Biological motion task

8.5.2.1 Implicit biological motion task

8.5.2.2 Explicit biological motion task

8.5.2.3 Analysis

8.5.2.3.1 Behavioural data and eye movements

8.5.3 Statistical analysis

8.5.4 Procedure
8.6 Results

8.6.1 Behavioural

8.6.2 Eyetracking

8.6.2.1 Scanpath characteristics

8.6.2.2 Areas of interest (AOIs)

8.7 Discussion

8.7.1 Behavioural

8.7.2 Eyetracking

8.7.3 Summary and conclusions

CHAPTER 9: SQUARE WAVE JERKS AND ANXIETY AS DISTINCTIVE BIOMARKERS FOR ANOREXIA NERVOSA

CHAPTER 10: GENERAL DISCUSSION

10.1 Summary

10.2 Methodological considerations

10.3 Future research

10.4 Clinical implications

10.5 Conclusions

REFERENCES

APPENDIX A
APPENDIX B 421
APPENDIX C 433
APPENDIX D 535
APPENDIX E 595
APPENDIX F 599
List of Tables

Table 3.1  Number of anorexia nervosa participants taking different medications 55

Table 3.2  Number of participants expressing areas of body concern 56

Table 3.3  Number of anorexia nervosa participants meeting criteria for Axis I diagnoses as scored by the Mini International Neuropsychiatric Interview (MINI) 58

Table 3.4  Personality Diagnostic Questionnaire (PDQ-4) scores 60

Table 3.5  Number of individuals scoring positive for clinically significant personality disorders as assessed with the Personality Diagnostic Questionnaire (PDQ-4) 61

Table 3.6  Eating Disorder Examination Questionnaire (EDE-Q) scores 62

Table 3.7  Figure Rating Scale (FRS) scores 63

Table 3.8  Depression Anxiety Stress Scale (DASS) scores 65

Table 3.9  Barratt Impulsiveness Scale (BIS-11) scores 66

Table 3.10  Toronto Alexithymia Scale (TAS-20) scores 67

Table 3.11  Number of participants with high, low and intermediate Toronto Alexithymia Scale (TAS-20) scores 67

Table 4.1  Speed of processing domain scores 85
Table 4.2  Attention/vigilance domain scores  87
Table 4.3  Working memory domain scores  89
Table 4.4  Verbal learning domain scores  90
Table 4.5  Visual learning domain scores  91
Table 4.6  Reasoning and problem solving domain scores  92
Table 4.7  Social cognition domain scores  93
Table 4.8  Overall composite domain scores  94
Table 5.1  Self-paced saccade task performance  145
Table 5.2  Memory-guided saccade task performance  146
Table 5.3  Prosaccade/antisaccade/no-go saccade task response rates  149
Table 5.4  Saccade characteristics of correct prosaccade and antisaccade responses  151
Table 5.5  Saccade characteristics of corrected antisaccade errors and no-go saccade error responses  152
Table 5.6  Significant within groups contrasts for the prosaccade/antisaccade/no-go saccade task for anorexia nervosa participants  154
Table 5.7  Significant within groups contrasts for the prosaccade/antisaccade/no-go saccade task for control participants

Table 6.1  Rate of emotion identification errors, behavioural task

Table 6.2  Own face emotion responses, behavioural task

Table 6.3  Scanpath characteristics to own faces and faces of different emotion during the fMRI and behavioural tasks

Table 6.4  Feature fixation index (FFI) and feature duration index (FDI) scores for own faces and faces of different emotion during the fMRI and behavioural tasks

Table 6.5  Significant within groups contrasts for the emotional faces task for anorexia nervosa participants, own > neutral

Table 6.6  Significant within groups contrasts for the emotional faces task for control participants, own > neutral

Table 6.7  Significant activations for participants’ own faces compared to neutral faces between anorexia nervosa and control participants (own > neutral, anorexia nervosa > healthy controls)

Table 7.1  Significant nodes of connectivity, sensorimotor and visual network, anorexia nervosa > healthy controls

Table 8.1  Body size discrimination scores, explicit biological motion task
Table 8.2  Scanpath data (means and standard deviations) to stimuli of different body sizes and gender during implicit and explicit biological motion tasks

Table 8.3  Fixation count (means and standard deviations) to areas of interest (AOIs) of stimuli of different body sizes and gender during implicit and explicit biological motion tasks

Table 8.4  Dwell times (means and standard deviations) to areas of interest (AOIs) of stimuli of different body sizes and gender during implicit and explicit biological motion tasks

Table 8.5  Feature fixation and duration indices (FFI; FDI) (means and standard deviations) to stimuli of different body sizes and gender during implicit and explicit biological motion tasks

Table 10.1  Summary of findings in anorexia nervosa participants compared with healthy control participants

Table E1  Clinical and demographic information for anorexia nervosa participants who did not complete the entire study

Table E2  Clinical and demographic information for healthy control participants who did not complete the entire study
List of Figures

| Figure 3.1 | Highest level of education reported by participants | 52 |
| Figure 3.2 | Employment status reported by participants | 53 |
| Figure 3.3 | Treatment for anorexia nervosa at the time of testing | 54 |
| Figure 3.4 | Eating Disorder Examination Questionnaire (EDE-Q) median scores | 62 |
| Figure 3.5 | Figure Rating Scale (FRS) median scores | 64 |
| Figure 3.6 | Depression Anxiety Stress (DASS) scale severity ratings | 65 |
| Figure 5.1 | Frequency of individual 5° memory-guided saccade inhibitory error latencies, within 200 millisecond bins, for anorexia nervosa (A) and control (B) participants | 147 |
| Figure 5.2 | Frequency of individual 10° memory-guided saccade inhibitory error latencies, within 200 millisecond bins, for anorexia nervosa (A) and control (B) participants | 147 |
| Figure 5.3 | Frequency of individual prosaccade latencies, within 20 millisecond bins, for anorexia nervosa (A) and control (B) participants | 151 |
| Figure 6.1 | Areas of interest (AOIs) for a male stimulus displaying each emotion (from left to right: anger, disgust, fear, happy, sad, surprise and neutral) in the emotional faces task | 200 |

xxxii
Figure 6.2  Increased activity in anorexia nervosa participants (A) and healthy control participants (B) to own face stimuli compared to neutral face stimuli

Figure 6.3  Increased activity in the anorexia nervosa group compared to the control group in the right inferior and middle temporal gyri (A), and the right lingual gyrus (B) for participants’ own faces compared to neutral faces

Figure 7.1  Reduced functional connectivity in anorexia nervosa compared to healthy controls within the sensorimotor and visual network for seeds at the left secondary visual cortex (BA 18) (A), right secondary visual cortex (BA 18) (B), left associative visual cortex (BA 19) (C) and right associative visual cortex (BA 19) (D)

Figure 8.1  Biological motion stimuli of the thinnest (A) and heaviest (B) female body sizes, and thinnest (C) and heaviest (D) male body sizes

Figure 8.2  Areas of interest (AOIs) for a mid-weight female biological motion stimulus

Figure 8.3  Fixation count for anorexia nervosa (AN) and control groups for each gender and body size category of biological motion stimuli over the implicit and explicit biological motion tasks

Figure 8.4  Saccadic amplitude for anorexia nervosa (AN) and control groups for the implicit and explicit biological motion tasks
List of Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid

5-HT: serotonin

5-HTR1D: serotonin 1d receptor gene

ACC: anterior cingulate cortex

ADHD: attention deficit hyperactivity disorder

AN: anorexia nervosa

AN-BP: anorexia nervosa binge-eating purging subtype

AN-R: anorexia nervosa restricting subtype

ANOVA: analysis of variance

AOI: area of interest

Area LIP: lateral intraparietal lobule

ASD: autism spectrum disorder

BA: Brodmann area

BACS SC: Brief Assessment of Cognition in Schizophrenia: Symbol Coding

BD: bipolar disorder

BDD: body dysmorphic disorder

BDNF: brain derived neurotrophic factor

BETRS: Body Image and Eating Disorders Treatment and Recovery Service

BG: basal ganglia

BIS-11: Barratt Impulsiveness Scale
BMI: body mass index

BN: bulimia nervosa

BOLD: blood oxygen level dependent

BVMT-R™: Brief Visuospatial Memory Test – Revised

CAGEMIS: Cognitive and Genetic Explanations of Mental Illness Bio-Databank

CBT: cognitive behaviour therapy

COMT: catechol-O-methyltransferase

CPT-IP: Continuous Performance Test – Identical Pairs

CSF: cerebral spinal fluid

DA: dopamine

DASS: Depression Anxiety Stress Scale

DLPFC: dorsolateral prefrontal cortex

DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders 4 Text Revision

DWI: diffusion weighted imaging

EDE-Q: Eating Disorder Examination Questionnaire

EDNOS: eating disorder not otherwise specified

EEG: electroencephalography

EHI: Edinburgh Handedness Inventory

ERP: event-related potential

ESR1: oestrogen receptor 1
ESR2: oestrogen receptor 2

FDI: feature duration index

FEF: frontal eye fields

FFA: fusiform face area

FFI: feature fixation index

fMRI: functional magnetic resonance imaging

FRS: Figure Rating Scale

FWE: family-wise error corrected

GABA: gamma-aminobutyric acid

HESC: The University of Melbourne Health Sciences Human Sub-Committee

HPA: hypothalamic-pituitary-adrenal axis

HREC-A: St Vincent’s Human Research Ethics Committee A

HRF: hemodynamic response function

HVA: homovanillic acid

HVLT-R™: Hopkins Verbal Learning Test – Revised

ICA: independent components analysis

ICD-10: international classification of disease

IQ: intelligence quotient

LEAS: Level of Emotional Awareness Scale

LNS: Letter-Number Span

MADRS: Montgomery-Asberg Depression Rating Scale
MATRICS: Management and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery

MCCB: MATRICS Consensus Cognitive Battery

MDD: major depressive disorder

MEG: magnetoencephalography

MINI: Mini International Neuropsychiatric Interview

MNI: Montreal Neuroimaging Institute

MRI: magnetic resonance imaging

MSCEIT™: Mayer-Salovey-Caruso Emotional Intelligence Test

MT: middle temporal

NAB®: Neuropsychological Assessment Battery

NDSAC: Austin Health Non Drug Study Advisory Committee

OCD: obsessive compulsive disorder

OFA: occipital face area

OPRD1: opioid delta receptor gene

PAN: prosaccade/antisaccade/no-go

PDQ-4: Personality Diagnostic Questionnaire

PET: positron emission tomography

p-FDR: false discovery rate corrected p value

PICF: participant information sheet and consent form

pSTS: posterior superior temporal sulcus
rCBF: regional cerebral blood flow

ROI: region of interest

RME: reading the mind in the eyes

RMF: reading the mind in films

RMS: root-mean-squared

RMV: reading the mind in the voice

SAD: social anxiety disorder

SC: superior colliculus

SEF: supplementary eye fields

SMA: supplementary motor area

SPECT: single-photon emission computed tomography

SSRI: selective serotonin reuptake inhibitor

SPM: statistical parametric mapping

SUHREC: Swinburne’s Human Research Ethics Committee

SWJ: square wave jerk

TAS-20: Toronto Alexithymia Scale

TBI: traumatic brain injury

TE: echo time

TMC REC: The Melbourne Clinic Research Ethics Committee

TMS: transcranial magnetic stimulation

TMT-A: Trail Making Test: Part A
TMT-B: Trail Making Test: Part B

TR: repetition time

TS: Tourette’s syndrome

V1: primary visual cortex

V2: secondary visual cortex

V3, V4, V5: associative visual cortex

VTA: ventral tegmental area

WAIS: Wechsler Adult Intelligence Scale

WCST: Wisconsin Card Sort Test

WMS®-III: Wechsler Memory Scale

WTAR: Wechsler Rest of Adult Reading
Recent times have seen a shift to a ‘thin ideal’ as the cultural norm of Western societies. Although eating disorders and body image concerns are often regarded a recent phenomenon, their existence has been documented throughout history (Brumberg, 2000). Some of the earliest accounts of deliberate disordered eating come from the religious literature of medieval Europe, describing young Catholic women who would starve themselves in the name of God (Bynum, 1985), a condition termed anorexia mirabilis. Perhaps the most notable of these women was Saint Catherine of Siena. She was pronounced a female miracle as she was able to prolong fasting and refused all food except for a handful of herbs each day, and was also noted to occasionally place twigs in her throat to bring up any food she was force-fed (Brumberg, 2000); behaviours commonly seen in the more modern disordered eating conditions. The condition later termed anorexia nervosa by Sir William Gull (1874) was first described by Gull in 1868 at the annual meeting of the British Medical Association in Oxford.

1.1 Clinical description

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), anorexia nervosa (AN) is characterised by three main criteria: a restriction of energy intake relative to requirements which leads to significantly low body weight; the experience of intense fear of weight gain or persistent behaviour which interferes with weight gain; and a disturbance in the experience of one’s body weight or shape, or a persistent lack of recognition of the seriousness of the current low weight (American Psychiatric Association, 2013). The current diagnostic criteria differ from the earlier Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) which also included a criterion of amenorrhea in postmenarcheal females (American Psychiatric Association, 2000). AN can be categorised into two subtypes, the restricting type (AN-R) and binge-eating purging (AN-BP) type, which are used to specify the absence or regular engagement of bingeing-purging behaviour during the current episode of AN (American Psychiatric Association, 2013). AN-R is distinguished by weight loss accomplished through dieting, fasting, or excessive exercise, and not through regular engagement of binge eating or purging (American
Psychiatric Association, 2013), whereas AN-BP is characterised by regular engagement in binging and/or purging during the current episode of AN. The method of purging can take the form of self-induced vomiting, or the misuse of laxatives, diuretics, or enemas (American Psychiatric Association, 2013). Though AN can be categorised into these two subtypes, the distinction is not always clear and individuals with AN often alternate between the two over the course of their illness (Eddy et al., 2008). Individuals with AN are also likely to transition to or from bulimia nervosa (BN), usually within the first five years of the illness (Tozzi et al., 2005). AN differs from the related but distinct disorder BN in that individuals with BN experience recurrent episodes of binge-eating, recurrent inappropriate compensatory behaviour to prevent weight gain, self-evaluation influenced unduly by body shape and weight, and the disturbance does not occur during an episode of AN (American Psychiatric Association, 2013). Unlike AN, a diagnosis of BN does not require the presence of significantly low body weight.

1.2 Associated features

Individuals with AN often exhibit a number of physical signs and symptoms that can be attributed to starvation. In addition to amenorrhea in postmenarcheal females, physical examinations often reveal emaciation (Crisp, 1995), malnutrition or a nutritional imbalance (Melchior, 1998; G. F. M. Russell, 1967), electrolyte disturbances (Palla & Litt, 1988), abnormal hormone levels (Argente et al., 1997; Boyar et al., 1974; Gwirtsman et al., 1989; Sharp & Freeman, 1993), disturbances in cardiovascular function including bradycardia (Casiero & Frishman, 2006; Mont et al., 2003; Winston & Stafford, 2000), renal dysfunction (Pomeroy & Mitchell, 2002), and structural changes of the brain (R. J. Dolan, Mitchell, & Wakeling, 1988; Kerem & Katzman, 2003; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996). Semi-starvation in combination with purging behaviours can also cause dental (Hellstrom, 1977; Hurst, Lacey, & Crisp, 1977) and digestive problems (Mccallum et al., 1985). Other physical symptoms also include dryness and yellowing of the skin (Gupta, Gupta, & Haberman, 1987; Strumia, Varotti, Manzato, & Gualandi, 2001), the development of a fine hair over the body called lanugo (Gupta et al., 1987) and cold intolerance (Wakeling & Russell, 1970). Many psychological and personality features are also present in individuals with AN. Such features often prominent in the
condition include depressive symptoms (Pollice, Kaye, Greeno, & Weltzin, 1997; Wade, Bulik, Neale, & Kendler, 2000), high levels of anxiety (W. H. Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Pollice et al., 1997), perfectionism (Bastiani, Rao, Weltzin, & Kaye, 1995; Fairburn, Cooper, Doll, & Welch, 1999; Halmi et al., 2000; Srinivasagam, Kaye, Plotnicov, & Greeno, 1995; Wade et al., 2008), obsessive compulsive behaviours and thoughts (W. H. Kaye et al., 1992), and the need for control over the environment (Fairburn, Shafran, & Cooper, 1999). Individuals with AN-BP are also more likely than restricting type AN to exhibit impulse-control problems (Garner, Garfinkel, & O'Shaughnessy, 1985b; Vandereycken & Pierloot, 1983), abuse drugs or alcohol (Garfinkel, Moldofsky, & Garner, 1980; Garner et al., 1985b; Vandereycken & Pierloot, 1983) and have a personality disturbance which meets the criteria for borderline personality disorder (Sansone, Levitt, & Sansone, 2004).

1.3 Comorbid psychiatric conditions

AN is associated with a number of psychiatric comorbidities, one of the most prevalent being mood disorders. Various studies have indicated that individuals with AN have high levels of depressive symptoms and lifetime major depressive disorder (MDD) (D. L. Braun, Sunday, & Halmi, 1994; Eckert, Goldberg, Halmi, Casper, & Davis, 1982; Fornari et al., 1992; Halmi et al., 1991; Herzog, 1984; Kennedy et al., 1994; Laessle, Kittl, Fichter, Wittchen, & Pirke, 1987; Piran, Kennedy, Garfinkel, & Owens, 1985; Pollice et al., 1997). Additionally, longitudinal studies in individuals with AN have reported an elevated rate of continuing depressive symptoms and MDD in recovered sufferers (Cantwell, Sturzenberger, Burroughs, Salkin, & Green, 1977; Herpertz-Dahlmann et al., 2001; Holtkamp, Müller, Heussen, Remschmidt, & Herpertz-Dahlmann, 2005; Pollice et al., 1997). Similar findings have been reported for anxiety disorders, with high levels of anxiety symptoms and generalised anxiety disorder reported during the course of the illness (Bulik, Sullivan, Fear, & Joyce, 1997; Godart, Flament, Lecrubier, & Jeammet, 2000; Pollice et al., 1997), which often continue into recovery (Herpertz-Dahlmann et al., 2001; Pollice et al., 1997). Individuals with AN have also been reported to experience higher levels of social phobia than the general public (Godart et al., 2000; Holtkamp, Müller, et al., 2005; W. H. Kaye et al., 2004). The condition is also frequently associated with obsessive
compulsive traits and obsessive compulsive disorder (OCD) (Bastiani et al., 1996; Blinder, Cumella, & Sanathara, 2006; Godart et al., 2000; Halmi et al., 2000; W. H. Kaye et al., 2004; Pollice et al., 1997; Thornton & Russell, 1997), which have been found to persist into remission (Holtkamp, Müller, et al., 2005; Pollice et al., 1997; Srinivasagam et al., 1995).

Additionally, the rates of psychiatric comorbidity of some conditions, such as personality disorders and substance abuse, have been reported to significantly vary between the two AN subtypes. AN has been associated with high levels of comorbid personality disorders most commonly obsessive compulsive personality disorder, avoidant personality disorder and borderline personality disorder (Cassin & von Ranson, 2005; Gillberg, Råstam, & Gillberg, 1995; Sansone et al., 2004). Research has suggested that individuals with AN-R are more likely than individuals with AN-BP to experience avoidant personality disorder and obsessive compulsive personality disorder, and individuals with AN-BP have a higher probability of experiencing borderline personality disorder than individuals with AN-R (O'Brien & Vincent, 2003; Sansone et al., 2004). Furthermore, different rates of substance abuse have been reported for the two AN subtypes. Research has indicated that individuals with AN-BP are more likely to exhibit substance abuse than individuals suffering from AN-R (Garfinkel et al., 1980; Garner, Garfinkel, & O'Shaughnessy, 1985a; Herzog et al., 2006; Toner, Garfinkel, & Garner, 1986). In addition to abusing substances such as laxatives and diuretics to aid weight loss (Bulik et al., 1992), increased alcohol and licit and illicit drug use have been reported in this population (Herzog et al., 2006; Toner et al., 1986), with appetite suppressing drugs such as cocaine and amphetamines among the most abused drugs by eating disorder sufferers (Herzog et al., 2006).

1.4 Epidemiology

In 2014 an annual survey carried out by Mission Australia (Mission Australia, 2014), the National Survey of Young Australians, collected information from over 13,000 young people aged 15-19 years. The results from the survey indicated that body image concerns were one of the top three issues of personal concern for young people, a trend that has been increasing over the last few years. Though body image
concerns appear to be on the increase, the incidence of AN does not appear to be necessarily following this trend (Fombonne, 1995; Pawluck & Gorey, 1998). Various studies have reported an increase in the incidence of AN in recent times (Eagles, Johnston, Hunter, & Lobban, 1995; Hoek, 2006; Hoek & Van Hoeken, 2003; Lucas, Beard, O'Fallon, & Kurland, 1991), particularly for those aged in their twenties and thirties (Pawluck & Gorey, 1998), though the authors do not discount other plausible explanations such as increasing awareness of the condition and improved case detection. A comprehensive review of the literature conducted by Hoek & Van Hoeken (2003) reported an increase in the incidence of AN over the past century until the 1970’s, whose incidence since remained relatively stable. Rates of incidence and prevalence can also be difficult to estimate due to the nature of the condition as AN is often associated with a high level of denial about the illness and individuals with the condition rarely seek medical attention independently (Strober, 2004; Vandereycken, 2006). As incidence rates generally reflect admissions into mental health care, the rates may not truly reflect the incidence of AN in the community (Hoek & Van Hoeken, 2003).

According to the DSM-5, the 12-month prevalence of AN is 0.4% among females and approximately one-tenth of that among males (American Psychiatric Association, 2013). The crude mortality rate of individuals admitted into university hospitals with AN is over approximately 5% per decade (American Psychiatric Association, 2013), among the highest mortality rate of any psychiatric disorder (E. C. Harris & Barraclough, 1998; Sullivan, 1995). The prevalence of AN appears to be much greater in individuals with an upper or upper-middle class social status (Crisp, Palmer, & Kalucy, 1976; McClelland & Crisp, 2001), and in industrialised societies where there is an abundance of food, and where a slim physique is promoted as an attractive physical trait (Keel & Klump, 2003; M. N. Miller & Pumariega, 2001). Although AN may be more prevalent in Western cultures, the condition is not only seen in societies promoting a thin ideal, but is also reported in countries such as Kenya and Iran where a slim physique is not promoted as an attractive trait (Njenga & Kangethe, 2004; Nobakht & Dezhkam, 2000).
1.5 Course of the illness

Though the onset of AN can occur at any age, the typical age of onset is in mid to late adolescence, and rarely occurs in individuals over 40 years (American Psychiatric Association, 2013; Lucas et al., 1991). Within the first few years of onset, many individuals alternate between the AN-R and AN-BP subtypes, with many shifting to a diagnosis of BN (Eddy et al., 2008; Eddy et al., 2002; Tozzi et al., 2005). There is great variability in the course and outcome of AN with some individuals making a full recovery after a single episode, others fluctuating between weight gain and relapse, those who experience the illness chronically over many years, and those who die from the physical consequences of the condition (Norring & Sohlberg, 1993; Steinhausen, 2002; Strober, Freeman, & Morrell, 1997). Though recovery rates vary highly between studies depending on the definition used (i.e. weight restoration, psychological symptoms, or a combination of the two) (Couturier & Lock, 2006), the long-term recovery rate of AN is estimated to be approximately 50% of cases (Couturier & Lock, 2006; Steinhausen, 2002). Additionally, AN is associated with exceptionally high relapse rates, among the highest of any psychiatric condition (Eckert, Halmi, Marchi, Grove, & Crosby, 1995; Löwe et al., 2001; Norring & Sohlberg, 1993; Strober, Freeman, & Morrell, 1997; Zipfel, Löwe, Reas, Deter, & Herzog, 2000). A major contributing factor for the high rates of morbidity and mortality experienced by individuals with this condition is that the factors involved in the cause and maintenance of the condition are not clear, and although treatment modalities have emerging evidence for efficacy, many patients remain under- or unresponsive.

1.6 Treatment approaches

AN is an exceptionally difficult condition to treat. A high level of denial is associated with AN sufferers, and treatment is typically resisted (Strober, 2004). Though the illness is fundamentally a psychological disorder, it also results in serious physical consequences due to malnutrition which also need to be addressed. Initial refeeding is necessary for undernourished patients (Kohn, Madden, & Clarke, 2011), and prompt weight restoration has been suggested as the initial treatment focus (Yager & Andersen, 2005). Clinical practice guidelines for the treatment of AN suggests a
number of treatments, though the efficacy of these therapies are limited by the lack of high quality controlled trials (Hay et al., 2014; The Royal Australian and New Zealand College of Psychiatrists, 2005; Wilson & Shafran, 2005). However, a multidimensional approach is recommended and the predominant therapies to consider include cognitive behaviour therapy (CBT) and family therapy.

1.6.1 Cognitive behaviour therapy (CBT)

CBT is a treatment approach that addresses abnormal cognitions and behaviours that are thought to promote and maintain the condition. Individuals are taught to recognise cognitive distortions and to not act on them or to replace them with more positive and realistic ways of thinking and behaving (Costin, 2006). Although CBT has been recommended as a possible treatment for AN, particularly for adult patients (Wilson & Shafran, 2005), the empirical evidence of its effectiveness is rather poor. In one study, Pike, Walsh, Vitousek, Wilson, and Bauer (2003) investigated outcome and relapse rates of AN patients following hospitalisation. The patients were randomly assigned to one year of outpatient therapy, either CBT or nutritional counselling. The investigators reported that the group receiving nutritional counselling relapsed significantly earlier and at a higher rate than the group receiving CBT. However, other research has suggested that the therapy may be ineffective. An early study investigated the effectiveness of CBT compared to behavioural therapy and a control condition which consisted of nonspecific support, and found that none of the treatment types were significantly superior (Channon, De Silva, Hemsley, & Perkins, 1989). A more recent study of underweight AN outpatients compared CBT with interpersonal psychotherapy and nonspecific support (McIntosh et al., 2005). The investigators reported that contrary to their hypotheses, CBT was inferior to interpersonal therapy, and nonspecific support was superior to both specialised treatments. Additionally, Ball and Mitchell (2004) found no significant difference in recovery between CBT and behavioural family therapy in a group of outpatients with AN.
1.6.2 Family therapy

Family therapy is widely recommended as the standard treatment for children and adolescents with AN (Wilson & Shafran, 2005), though, it is also being used with adult patients (Bulik, Berkman, Brownley, Sedway, & Lohr, 2007). This type of therapy has been demonstrated to be more effective in younger sufferers with earlier onset than older patients presenting with a more chronic course of the illness (Eisler et al., 1997; G. F. M. Russell, Szmukler, Dare, & Eisler, 1987). However, the efficacy of this type of intervention also has limited research evidence. In a series of studies in adolescents, Robin and colleagues (Robin, Siegel, Koepke, & Moye, 1994; Robin, Siegel, & Moye, 1995; Robin et al., 1999) found that behavioural family therapy was more effective than individual therapy in improving weight gain, but not in improving eating attitudes and body shape dissatisfaction. In a study assessing the effectiveness of family therapy in comparison to family psychoeducation in adolescents with AN, the authors reported increased weight restoration following a four month period of treatment, but no difference between the two interventions (Geist, Heinmaa, Stephens, Davis, & Katzman, 2000). Furthermore, family therapy in adolescents appears to be as effective whether delivered short-term over six months, or long-term over one year (Lock, Agras, Bryson, & Kraemer, 2005), though this study did not assess the effectiveness of the treatment in comparison to other treatment approaches. In terms of family therapy for adults, Dare, Eisler, Russell, Treasure, and Dodge (2001) investigated four treatment types: family therapy, psychoanalytic psychotherapy and low contact routine treatment. All treatments resulted in modest improvement, and although family therapy was found to be superior to routine treatment it did not differ in effectiveness from the other treatments. Additionally, outpatient individual and family therapy has been reported as superior to no treatment at follow-up at one and two years (Crisp et al., 1991; Gowers, Norton, Halek, & Crisp, 1994).

1.6.3 Pharmacological treatments

Although pharmacological treatments are not currently considered a standard method of treatment for AN, some medications have been reported to potentially address certain aspects of the condition. Antidepressant medications are often suggested as potential treatments for AN as they are first-line agents in the treatment
of depression (Geddes et al., 2003), OCD (Dougherty, Rauch, & Jenike, 2004) and
BN (Whittal, Agras, & Gould, 2000), all of which are highly comorbid disorders
(Blinder et al., 2006), and are thought to share similar underlying neurobiological
abnormalities to AN, particularly serotonergic dysfunction (Jimerson, Lesem, Kaye,
Hegg, & Brewerton, 1990; W. H. Kaye, Gendall, & Strober, 1998; W. H. Kaye,
Gwirtsman, George, & Ebert, 1991). Two classes of antidepressant medication,
tricyclic antidepressants and selective serotonin re-uptake inhibitors (SSRIs), have
been of greatest research focus in the pharmacological treatment of AN.

SSRIs act to increase the extracellular level of serotonin by inhibiting its
reuptake into the presynaptic cell. Although various types of SSRIs exist, fluoxetine,
also known by its trade name Prozac, has been of particular research interest in the
treatment of AN. A number of open trials have reported improved outcomes,
including a reduction in depression and obsessive thoughts, and improvements in
eating behaviour, for individuals with AN taking fluoxetine (Gwirtsman, Guze,
Yager, & Gainsley, 1990; W. H. Kaye, Weltzin, Hsu, & Bulik, 1991) and other SSRIs
such as citalopram (Fassino, Leombruni, et al., 2002) and sertraline (Santonastaso,
Friederici, & Favaro, 2001). However, other studies have failed to find any significant
effects of SSRIs on the outcome of AN in open trials (Holtkamp, Konrad, et al., 2005;
Strober, Freeman, DeAntonio, Lampert, & Diamond, 1997). Randomised double-
blind placebo-controlled studies assessing the efficacy of fluoxetine in improving the
outcome of AN have failed to demonstrate any benefit of the treatment (Attia,
Haiman, Walsh, & Flater, 1998; Walsh et al., 2006). However, one randomised
controlled trial has reported significant findings with an increase in body weight and
reduction in eating disorder symptomatology, obsessive thoughts, and depressive and
anxious symptoms (W. H. Kaye et al., 2001).

Though not considered a treatment for AN, the use of atypical antipsychotics
is gaining increasing interest. Low doses of atypical antipsychotics are sometimes
prescribed for psychotic-like thinking, distressing anxiety and obsessionality in AN
(Bosanac, Norman, Burrows, & Beumont, 2005). The reasoning behind the potential
use of these types of drugs in the treatment of AN is that they address a number of
issues experienced by these individuals such as reducing anxiety, and they increase
appetite and enhance weight gain (McKnight & Park, 2010). In addition, individuals
with AN often exhibit behaviours observed in psychosis such as delusions (Bruch, 1962), which these medications also address. An antipsychotic of particular interest is olanzapine, a serotonin-dopamine antagonist generally used in the treatment of schizophrenia (Tollefson, Beasley Jr, Tran, & Street, 1997). An open trial assessing the effectiveness of olanzapine in the treatment of AN has reported a significant reduction in anxiety and eating disorder symptoms (Malina et al., 2003). Additionally, an open trial study using a typical antipsychotic, haloperidol, reported significantly lower eating disorder symptomatology and increased body mass index (BMI) (Cassano et al., 2003). However, no control groups were used in these open trial studies, limiting their significance. Randomised controlled trials have also been undertaken with olanzapine in the treatment of AN. In a study by Bissada, Tasca, Barber, and Bradwejn (2008), the researchers reported greater increase in weight, earlier achievement of target BMI and greater decrease of obsessive symptoms in the group of AN patients receiving olanzapine plus day hospital treatment in comparison to the control AN group receiving the placebo and day hospital treatment. A study by Brambilla et al. (2007) reported similar findings in that eating disorder symptomatology and BMI improved following treatment with olanzapine and CBT compared to the control group receiving CBT and a placebo. Furthermore, a randomised controlled trial of olanzapine in the treatment of the delusional aspects of cognitions in AN, specifically intrusive ruminations, has produced significant results (Mondraty et al., 2005). In comparison to AN patients receiving a typical antipsychotic, chlorpromazine, AN patients receiving olanzapine had a significant reduction in the degree of rumination.

1.6.4 Treatment conclusions

The research assessing effective treatments for AN is fairly limited, with the number of randomised controlled trials being relatively sparse (Bulik et al., 2007). Controlled trials are particularly difficult in this patient group as having a control group that does not receive a treatment would be unethical. Another important contributing factor to this lack of research into valuable treatments is that it is still very unclear what psychological, biological or neurological factors may play a role in the course of the illness (Polivy & Herman, 2002).
1.7 Aetiological theories

AN is a disorder of rather complex aetiology in which psychological, sociocultural, genetic and biological factors may significantly contribute to susceptibility. Although various theories have been postulated and a variety of potential risk factors identified, the aetiology of AN remains very unclear. Difficulties in investigating the aetiology of AN is attributed to many factors, some of which are true for other psychiatric illnesses, such as the inability to distinguish whether certain traits and characteristics are due to the illness or are innate in the individuals, whether there is a predisposition to the disease before any disturbances become evident, or whether there are specific triggers that set off the illness. Investigating the aetiology of AN though is particularly difficult as the condition is essentially a mental illness, but also results in serious physical consequences. Therefore, distinguishing between the effects of starvation and AN proves to be very problematic.

1.7.1 Sociocultural theories

The past century has seen the trend for a full and voluptuous ideal body shift to a slim and less curvaceous physique in Western societies (Garner & Garfinkel, 1980). Over this time the incidence of eating disorders has also increased (Hoek & Van Hoeken, 2003), suggesting a possible relationship between the two. However, a direct relationship has not been demonstrated. Studies assessing eating attitudes, body dissatisfaction and other eating disorder-related variables in nonclinical samples of the general public have suggested increased concerns in Western cultures about these issues. A study by Akan and Grilo (1995) found that Caucasian American women scored significantly higher on measures related to eating disorder phenomenology than Asian American and African American women. Similar findings have been demonstrated by Furnham and Alibhai (1983) who compared female residents of Kenya, Kenyan women who had immigrated to Britain and white British women. It was found that the Kenyan residents rated larger figures more favourably and smaller figures less favourably than the British group. They also found that the immigrated group reported similar results to the British group suggesting a dominant role that social and cultural factors play in the perception of body weight. Although AN is largely regarded as an illness predominantly affecting people from Western societies
(B. Dolan, 1991), a review by Keel and Klump (2003) reported that AN has been observed in every non-Western region of the world. Additionally, it has also been suggested that eating disorders are more prevalent in non-Western societies than might have been previously recognised, though this effect may be attributed to the adoption of Western values (M. N. Miller & Pumariega, 2001; Nasser, 1988). However, Caldwell, Brownell, and Wilfley (1997) found that after controlling for BMI, income and marital status, African American and white women were equally dissatisfied with their bodies. It is suggested that attitudes about body shape and weight are influenced by socioeconomic status rather than ethnicity. The investigators suggest that other studies may confound race and socioeconomic status. Similarly, AN has been observed to be substantially overrepresented in higher socioeconomic status groups (Crisp et al., 1976; Lindberg & Hjern, 2003; McClelland & Crisp, 2001). Though, it has been suggested that this relationship may lack empirical support, as the findings may be as a result of referral bias (Gard & Freeman, 1996). In other words, those who can financially afford therapeutic intervention are more likely to seek treatment.

The media are quite often blamed for the increasing pressure placed on women to be thin. They are often accused of distorting reality by portraying unnaturally slim models or celebrities in a positive light and condemning those who gain weight. Young influential women exposed to these images inevitably desire the socially endorsed slender body. An effect of media exposure on eating disorder symptomatology has been reported in a nonclinical sample of undergraduate students (Stice, Schupak-Neuberg, Shaw, & Stein, 1994), though it is less clear in relation to clinically diagnosed eating disorders. Levine and Murnen (2009) reviewed the literature pertaining to mass media as a causal risk factor for negative body image and disordered eating. The authors reported that though the media may promote an unrealistic body image, the engagement with mass media would be considered a variable risk factor rather than a causal risk factor. Sociocultural factors may play a role in promoting negative body image and disordered eating, but cannot be regarded as a causative factor for developing an eating disorder, as only a minority of individuals exposed to these factors ultimately develop an eating disorder.
1.7.2 Psychological theories

A great range of psychological theories and risk factors relating to AN have emerged since the condition was first identified. The influence of family dynamics, and parental pressure and attitudes to weight control and dieting, have been postulated with some research suggesting the possibility of a contribution of these factors (Pike et al., 2008), and other research revealing contradictory results (Garfinkel et al., 1983). Other studies have suggested that peer pressure may play a role, which may explain why specific groups such as dancers, models and elite athletes in sports emphasising slimness are more prone to developing eating disorder symptomatology (Garner & Garfinkel, 1980; Sundgot-Borgen, 1994; Zucker, Womble, Mliamson, & Perrin, 1999). Stice and Shaw (2002) report that perceived pressures to be thin increases the risk for body dissatisfaction which can result in elevated dieting, which subsequently increases the risk of developing AN. Furthermore, eating and dieting behaviours and attitudes, and body dissatisfaction have been associated with low self-esteem (Akan & Grilo, 1995; Berry & Howe, 2000), whereas high self-esteem has been indicated as a protective factor against the development of AN (Nicholls & Viner, 2009).

High levels of perfectionism and obsessionality are present in the illness, are found to persist after long-term recovery and have been suggested to play a role in the development and maintenance of the condition (Bastiani et al., 1996; Bastiani et al., 1995; Fairburn, Cooper, et al., 1999; Halmi et al., 2000; Holtkamp, Müller, et al., 2005; Pollice et al., 1997; Srinivasagam et al., 1995; Wade et al., 2008). Closely related to the high levels of perfectionism observed in individuals with AN is an increasingly popular theory of control first described by Bruch (Bruch, 1979). The theory describes that individuals with AN seek to control their surrounding environment as much as possible, including but not limited to their body shape and weight. However, individuals with AN often report feeling like they are out of control, a phenomenon coined the ‘control paradox’ (M. Lawrence, 1979). In a study by Fairburn and colleagues (1999), the authors explain that the need for self-control becomes primarily focused on eating in individuals with AN because dietary restriction provides direct and immediate evidence of self-control, which also acts as a maintenance mechanism for the condition.
1.7.3 Biological theories

Due to the presentation of AN, including onset typically shortly after puberty, emaciation and an apparent lack of appetite, it is not surprising that early theories regarding the aetiology of AN had largely focused on possible biological causes of the illness. Later in the twentieth century, aetiological theories had shifted to psychological and sociocultural causes. With increasing advances in technology, biological theories have begun to re-emerge.

1.7.3.1 Pregnancy and obstetric complications

Research has suggested that certain factors during pregnancy and childbirth may be associated with increased risk for the child developing AN. Higher maternal BMI has been found to be a protective factor for the development of AN in the child (Nicholls & Viner, 2009). A study investigating obstetric complications and its possible association with the development of AN utilised the Swedish Inpatient Register to identify individuals with a diagnosis of AN from 1987-1994 and matched five controls for each case. Information surrounding participants’ births was collected from the national birth register, rather than relying on parental recall, a major advantage of this study. It was found that cephalohaematoma and very preterm birth were associated with an increased risk of AN. In very preterm births, those who were small for their gestational age were at higher risk than those of higher birth weight for their gestational age (Cnattingius, Hultman, Dahl, & Sparen, 1999). An investigation by Favaro, Tenconi, and Santonastaso (2006) found that pregnancy complications including maternal anaemia, diabetes mellitus and preeclampsia significantly increased the risk of the child developing AN. It was also found that individuals with AN were more likely than controls to have had complications at delivery such as placental infarctions and having the umbilical cord wrapped around the neck. The authors suggest that these complications might increase the risk of an impairment of central nervous system development, or can result in a more acute form of hypoxia-ischemia that can result in brain damage particularly in the hippocampus and the cerebral cortex.
1.7.3.2 Family studies

Family studies have suggested a possible biological component to the illness. Family members of individuals diagnosed with AN have been found to be at much higher risk of AN than relatives of healthy control participants, 11.4 times as high in a study by Strober and colleagues (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). Family studies have also revealed that first-degree relatives of individuals with AN are significantly more likely to experience other psychiatric conditions including MDD, eating disorder not otherwise specified (EDNOS), generalised anxiety disorder, social phobia, OCD and obsessive compulsive personality disorder (Lilenfeld et al., 1998). Twin studies have revealed a substantially greater concordance for AN for monozygotic twins than dizygotic twins (Bulik, Sullivan, Wade, & Kendler, 2000; Holland, Hall, Murray, Russell, & Crisp, 1984; Holland, Sicotte, & Treasure, 1988). Similar results have also been found for concordance of monozygotic twins and not dizygotic twins for broadly defined AN, where individuals do not meet the strict criteria for AN (Klump, Miller, Keel, McGue, & Iacono, 2001).

1.7.3.3 Molecular genetics

A growing area of interest regarding the aetiology of AN is that of molecular genetics research. Two approaches are used in the molecular genetics analysis of a phenotype, association studies and family-based linkage studies. A linkage analysis undertaken by Grice et al. (2002) revealed modest, but non-significant, evidence linkage at markers on chromosomes 4, 11, 13 and 15. When restricting the sample to a subset of families in which at least two relatives had a diagnosis of AN-R, high significant linkage scores were reported for a marker on chromosome 4, and particularly chromosome 1. Devlin et al. (2002) found regions of suggestive linkage close to genome-wide significance on chromosome 1, 2 and 13. Linkage studies have also revealed that the serotonin 1d receptor gene (5-HTR1D) and the opioid delta receptor gene (OPRD1) may be involved in the susceptibility to AN (Bergen et al., 2003; K. M. O. Brown et al., 2007).

The OPRD1 gene has also been linked with risk for developing AN in a recent association study (Wang et al., 2010). The same study reported an association
between HTR1D and risk for AN-R. Association studies investigating a variety of genes thought to be involved in the condition have often produced contradictory results. In a large-scale study by Pinheiro et al. (2010), the investigators found that after adjusting for multiple comparisons, there were no statistically significant associations with any definition of AN, whether a general group or split into subtypes (Pinheiro et al., 2010). However, other studies have reported significant findings. The catechol-O-methyltransferase (COMT) gene which is involved in the inactivation of catecholamine neurotransmitters such as dopamine, epinephrine and norepinephrine, has been implicated in a variety of mental illness including schizophrenia (Egan et al., 2001), autism (James et al., 2006), anxiety (Enoch, Xu, Ferro, Harris, & Goldman, 2003) and OCD (Karayiorgou et al., 1997). The COMT gene has been associated with susceptibility to AN in a number of recent studies (Frieling et al., 2006; Frisch et al., 2001; Michaelovsky et al., 2005; Mikołajczyk, Śmiarowska, Grzywacz, & Samochowiec, 2006), though others have not found this association (Brandys et al., 2012; Dmitrzak-Węglarz et al., 2005; Gabrovsek et al., 2004). The brain derived neurotrophic factor (BDNF) gene has also been investigated in relation to AN. BDNF is involved in neuronal survival and differentiation during the development of the nervous system, synaptic efficiency and neuronal plasticity (Ribasés et al., 2004), and has also been found to play a role in inducing appetite suppression and reducing body weight (Pelleymounter, Cullen, & Wellman, 1995). Findings are again inconsistent regarding this gene’s association with AN with some researchers suggesting a possible association (Ribasés et al., 2003; Ribasés et al., 2005; Ribasés et al., 2004), and others who have reported no significant association (Ando et al., 2011; Brandys et al., 2011; Dardennes et al., 2007; Friedel et al., 2005).

Individuals with AN have often been found to display abnormal hypothalamic-pituitary-adrenal axis (HPA) function, demonstrated by increased cortisol levels in the ill state which reduce with weight gain (for a review see Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008). Hormonal changes related to HPA function have also been suggested as a possible cause of AN. Therefore, the investigation of genes related to hormones have been of interest to researchers investigating the aetiology of AN. The role of oestrogen has been implicated in the cause of AN for some time for a number of reasons. Higher levels of oestrogen are found in females than males and the same is true for the prevalence of AN (Rossouw, 2002). Also, the onset of AN is typically
around the age of puberty where there is an increase in oestrogen production in females (Sizonenko, 1978). Lower oestrogen levels have also been found in currently ill and recovered patients in comparison to groups of healthy controls (Brambilla et al., 2003; Ohwada, Hotta, Sato, Shibasaki, & Takano, 2007). It has been proposed that the disruption reported in the HPA in AN groups may be due to an alteration of the oestrogenic pathway in these individuals (Versini et al., 2010). In addition, it has been well documented that oestrogen is involved in the regulation of food intake and eating behaviour (Bonavera, Dube, Kalra, & Kalra, 1994). Oestrogen receptor 1 (ESR1) and oestrogen receptor 2 (ESR2) genes have therefore been of interest to researchers. A study by Rosenkranz and colleagues (1998) investigating the ESR2 gene in probands of weight extremes, including AN, suggested an association with susceptibility to AN. Additionally, an investigation undertaken by Eastwood, Brown, Markovic, and Pieri (2002) suggested that ESR2, but not ESR1, may be associated with susceptibility for AN. ESR1 was not found as a significant predictor of susceptibility to AN in this study, though a more recent study found a strong association between ESR1 polymorphisms and AN-R (Versini et al., 2010). Oestrogen also plays a role in modulating the serotonergic system (Östlund, Keller, & Hurd, 2003), a system largely implicated in the aetiology of AN.

Serotonin (5-HT) is a popular candidate in the aetiology of AN as it plays a role in a number of behaviours which are disturbed in the condition. 5-HT is involved in regulating feeding behaviour such as playing an inhibitory role in feeding, regulating meal size and controlling eating rate (Blundell, 1984; Leibowitz & Alexander, 1998; Simansky, 1995). It is also involved in obsessional behaviours, anxiety, impulse control, inhibition, attention and mood (Buhot, 1997; Higley & Linnoila, 1997; Lucki, 1998; Soubrie, 1986). Molecular genetic association studies in AN have revealed that 5-HT genes may be involved in the susceptibility for AN including the serotonin transporter gene (Fumeron et al., 2001; Y. Lee & Lin, 2010; Matsushita et al., 2004) and the serotonin receptor gene 5-HT2A (Collier et al., 1997; Enoch et al., 1998; Nacmias et al., 1999; Ricca et al., 2002; Rybakowski et al., 2006; Sorbi et al., 1998). Though, other studies have failed to identify associations between AN and the serotonergic genes (Ando et al., 2011; Campbell, Sundaramurthy, Markham, & Pieri, 1998; Di Bella, Catalano, Cavallini, Riboldi, & Bellodi, 2000;
A neurotransmitter system largely related to the serotonergic system (Daw, Kakade, & Dayan, 2002), which has also been implicated in the aetiology and course of AN, is the dopaminergic system. Dopamine (DA) plays an important role in eating behaviours, motivation, reinforcing behaviour and reward (Bassareo & Di Chiara, 1999; Holroyd & Coles, 2002; A. G. Phillips, Vacca, & Ahn, 2008; Roitman, Stuber, Phillips, Wightman, & Carelli, 2004; Schultz, Dayan, & Montague, 1997; Volkow et al., 2003; Wise, 2004); behaviours which are also found to be disturbed in AN (Fladung et al., 2010; Scheurink, Boersma, Nergårdh, & Södersten, 2010; Wagner, Aizenstein, Venkatraman, et al., 2007; Watson, Werling, Zucker, & Platt, 2010). DA gene polymorphisms have been reported in AN individuals in the DA D2 receptor gene (Bergen et al., 2005), and the DA D4 receptor gene (Bachner-Melman et al., 2007). However, a lack of association between the DA D3 receptor gene and the DA D4 gene have also been reported in other studies (Bruins-Slot et al., 1998; Hinney et al., 1999).

Other genes, including the norepinephrine transporter gene (Urwin et al., 2002) and the agouti-related protein gene (Vink et al., 2001), have been implicated in the aetiology of AN, though extensive studies are yet to be carried out. Though a variety of genes have been investigated, the genes related to dopaminergic and serotonergic function have been of greatest interest in the investigation of AN susceptibility as these systems play very important roles in behaviour disturbed in individuals with AN.

1.7.3.4 Neurobiology

Sections 1.7.3.4.1 – 1.7.3.4.2.4 of this thesis have been published in the Australian and New Zealand Journal of Psychiatry (Phillipou, Rossell, & Castle, 2014). The full text of this paper can be found in Appendix A.
1.7.3.4.1 Structural brain differences

Structural changes are frequently observed in the brains of individuals with AN, and are generally thought to reflect the effects of malnutrition and starvation. The illness is associated with enlargement of the cortical sulci and ventricles (Artmann, Grau, Adelmann, & Schleiffer, 1985; R. J. Dolan et al., 1988; Kingston et al., 1996; Swayze et al., 1996), and enlargement of the interhemispheric fissure (Artmann et al., 1985). Cerebral dystrophic changes have been found to correlate with weight loss, and the reversal of these changes has also been found to correlate with the normalisation of body weight (Artmann et al., 1985; Golden et al., 1996; Kingston et al., 1996; Swayze et al., 1996). However, one study found no significant change in ventricular size, but a significant degree of sulcal widening after patients had attained normal body weight (R. J. Dolan et al., 1988). A more recent study found no differences in ventricular size of AN patients, but enlarged external cerebral spinal fluid (CSF) spaces when compared to controls (Palazidou, Robinson, & Lishman, 1990). Individuals with AN have been reported to have larger total CSF volumes in the ventricles and sulci, and significantly reduced grey and white matter volumes (Boghi et al., 2011; Castro-Fornieles et al., 2009; Gaudio et al., 2011; Katzman et al., 1996; Katzman, Zipursky, Lambe, & Mikulis, 1997; Lambe, Katzman, Mikulis, Kennedy, & Zipursky, 1997; Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Mühlau et al., 2007; Roberto et al., 2011). Differences in white matter volume have, however, not been consistently found (Castro-Fornieles et al., 2009; Mainz et al., 2012; Mühlau et al., 2007). Follow-up studies in weight-recovered patients have reported elevated CSF volumes and persistent grey but not white matter deficits (Katzman et al., 1997; Lambe et al., 1997; Roberto et al., 2011). However, two studies have reported normalisation of grey matter and CSF volume in weight-recovered AN patients (Castro-Fornieles et al., 2009; Cowdrey, Filippini, Park, Smith, & McCabe, 2012; Mainz et al., 2012). Furthermore, a recent study by Lázaro et al. (2013) found no difference in grey or white matter volume between weight-recovered AN patients who were at 85% of their expected BMI for at least one month, and a group of healthy controls.

Specific brain structures have also been found to differ between AN patients and controls, including reduced size of the pituitary gland (Doraiswamy et al., 1991),
and a reduction of total hippocampus-amygdala formation volume (Giordano et al., 2001). Individuals with AN have also been found to have decreased grey matter in the anterior cingulate cortex (ACC) (Mühlau et al., 2007), and significantly reduced ACC volume whose degree of normalisation during treatment is related to outcome (McCormick et al., 2008). A more recent study has also reported a reduction of grey matter volume in both individuals currently ill with AN and weight-recovered patients (Friederich et al., 2012). This study also reported reduced grey matter volumes of the amygdala and putamen in ill individuals, and the supplementary motor area (SMA) in both weight-recovered patients and patients with a current diagnosis. Furthermore, in comparison to weight-recovered individuals, individuals ill with AN were found to have reduced grey matter volumes of the left amygdala and putamen, and the bilateral inferior temporal cortex. G. K. Frank, Shott, Hagman, and Mittal (2013) reported increased grey matter volume of the gyrus rectus and decreased insula volume compared to healthy controls. This study also reported reduced grey matter volume of the caudate and putamen and reduced inferior parietal white matter volume in weight-recovered AN, as well as reduced temporal white matter volume in both weight-recovered and ill AN. Other recent studies have also found decreased grey matter volumes in ill AN patients of the extrastriate body area (Suchan et al., 2010), and the middle cingulate cortex, precuneus, and inferior and superior parietal cortex (Gaudio et al., 2011). A recent study by Amianto et al. (2013) reported decreased grey matter in the lateral cerebellum, precuneus, and frontal orbital and cingulate cortices. Furthermore, a study by Boghi et al. (2011) found reduced grey matter of the frontal and parietal cortices, caudate nucleus, hypothalamus and cerebellum. Additionally, in this study the AN group was divided into two subgroups based on illness duration: those who had a diagnosis of more than nine years, and those who were being treated at first presentation of the illness. The group with shorter disease duration were found to have more evident hypothalamic atrophy, whereas the cerebellum was more affected in the group with longer disease duration, in comparison to healthy controls. Additionally, individuals with AN have been found to have reduced hippocampal volumes in comparison to healthy controls (Connan et al., 2006), and the size of the mesencephalon has also been found to be markedly reduced in ill AN patients which remains reduced in weight-restored individuals (Neumärker, Bzufka, Dudeck, Hein, & Neumärker, 2000).
Several recent studies have also utilised diffusion weighted imaging (DWI) to assess white matter pathways in AN. Kazlouski et al. (2011) reported poorer white matter integrity in the bilateral fimbria-fornix, fronto-occipital fasciculus and posterior cingulum in AN, irrespective of AN subgroup. The AN group also showed higher mean diffusivity in these areas, in addition to frontal, parietal, temporal and occipital areas. However, in a more recent study by Yau et al. (2013), the authors reported lower mean diffusivity in frontal, parietal and cingulum white matter tracts in weight-recovered AN, unlike the study by Kazlouski et al. (2011) who found higher mean diffusivity in these areas. Yau et al. (2013) reported poorer white matter integrity in weight-recovered AN who had a history of more severe illness. Frieling et al. (2012) investigated white matter integrity in a group of individuals with a current diagnosis of AN combined with individuals weight-recovered from the illness, and a sample of healthy participants. This study reported regional decreases in white matter of the posterior thalamic radiation bilaterally and the mediodorsal thalamus in the combined AN group. Decreases were also reported in the left superior longitudinal fasciculus, bilateral posterior coronal radiate and left middle cerebellar peduncle. Additionally, no differences were found between the two subgroups of AN, currently ill or weight-recovered.

1.7.3.4.2 Functional brain differences

1.7.3.4.2.1 Neuronal systems

A neuronal system of particular interest in relation to the neurobiology of AN is the 5-HT system. Research in AN has mainly focused on the main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and the 5-HT receptors 5-HT\textsubscript{1A} and 5-HT\textsubscript{2A}. Individuals with AN in the ill state have significantly lower CSF basal concentrations of the 5-HT metabolite 5-HIAA (W. H. Kaye, Ebert, Raleigh, & Lake, 1984; W. H. Kaye, Gwirtsman, George, & Jimerson, 1988). However, those recovered from AN have significantly increased 5-HIAA levels in comparison to healthy controls (W. H. Kaye, Gwirtsman, et al., 1991), particularly those recovered from the binge-eating purging subtype of AN (W. H. Kaye, Ebert, Gwirtsman, & Weiss, 1984).
Recent neuroimaging studies have investigated 5-HT binding differences in the brain. In a study undertaken by Bailer and colleagues (2007), the investigators reported that ill AN individuals had increased 5-HT\textsubscript{1A} binding in the subgenual, mesial temporal, orbital frontal, and raphae brain regions, and the prefrontal, lateral temporal, ACC, and parietal regions. Similar findings have been reported for 5-HT\textsubscript{1A} binding in ill participants (Bailer, Frank, Henry, Price, Meltzer, Mathis, et al., 2007; Galusca et al., 2008), whereas recovered AN sufferers have been reported to have diminished binding potential for 5-HT\textsubscript{2A} and increased binding potential of 5-HT\textsubscript{1A}. Audenaert et al. (2003) reported significantly reduced 5-HT\textsubscript{2A} binding in the left frontal cortex as well as the left and right parietal and occipital cortices of individuals with AN in comparison to control participants. Bailer et al. (2005) reported increased 5-HT\textsubscript{1A} binding potential of the dorsal raphe, and the cingulate, lateral and medial temporal, lateral and medial orbitofrontal, parietal and prefrontal cortices in weight-recovered AN. Studies investigating the specific subtypes of AN found that weight-restored AN-R participants had reduced 5-HT\textsubscript{2A} receptor activity in the subgenual and pregenual cingulate cortex, and mesial temporal and parietal cortical areas (G. K. Frank et al., 2002), whereas reduced 5-HT\textsubscript{2A} receptor activity in the subgenual cingulate, and the mesial temporal, lateral temporal, parietal and occipital cortices has been reported for recovered AN-BP participants, in comparison to controls (Bailer et al., 2004). A further study, however, found no difference in 5-HT binding potential between AN subgroups and controls, but increased 5-HT binding potential in the dorsal raphe and anteroventral striatum in recovered AN-R compared to recovered AN-BP participants; and decreased 5-HT binding potential in the anteroventral striatum in AN-R compared to recovered individuals with BN (Bailer, Frank, Henry, Price, Meltzer, Becker, et al., 2007).

A neurotransmitter system largely related to the serotonergic system which has also been implicated in the aetiology and course of AN is the dopaminergic system. Homovanillic acid (HVA), the major metabolite of DA in humans, has been found to be decreased in the CSF of individuals with AN in the ill state (W. H. Kaye, Ebert, Raleigh, et al., 1984). Two related studies have reported that HVA returns to normal levels following weight restoration (W. H. Kaye, Ebert, Gwirtsman, et al., 1984; W. H. Kaye, Ebert, Raleigh, et al., 1984). However, a more recent study undertaken by the same investigators examining the HVA levels in individuals recovered from AN
utilising more stringent criteria than purely weight restoration (including over one year of normal weight, regular menstrual cycles, no restricting eating patterns and no bingeing or purging) found that individuals recovered from AN-R had significantly lower CSF HVA than AN-BP, BN participants and healthy controls (W. H. Kaye, Frank, & McConaha, 1999).

In related work, G. K. Frank et al. (2005) used positron emission tomography (PET) imaging with radiogland $[^{11}C]$raclopride to assess DA D2/D3 receptor function in recovered AN individuals. The investigators reported significantly higher $[^{11}C]$raclopride binding potential in the antero-ventral striatum than control participants, providing support for the possibility that AN is associated with decreased intrasynaptic DA concentration or increased D2/D3 receptor density; the authors suggest this may contribute to the disturbed reward processing exhibited in AN. Another study using an amphetamine challenge and PET, found that recovered AN participants exhibited a positive association between endogenous DA release and anxiety in the dorsal caudate, possibly explaining why food-related DA release produces anxiety in AN but is pleasurable in healthy individuals (Bailer et al., 2012).

Additionally, AN has been associated with altered D2 receptor sensitivity demonstrated by significantly reduced growth hormone response to growth hormone releasing hormone administered with apomorphine, a selective D1 and D2 receptor agonist (Brambilla, Bellodi, Arancio, Ronchi, & Limonta, 2001). A study indirectly investigating dopaminergic function in AN also revealed a deficit in this group (A. D. Lawrence et al., 2003). Participants were administered a task which involved the learning of a series of two-alternative forced-choice visual discriminations. This is analogous to tasks which activate DA neurons in primates and is sensitive to neurotransmission, including L-dopa treatment in Parkinson’s disease. The AN group was found to show deficits in learning during the early stages of the task when DA activity should be at a maximum, providing indirect evidence for altered DA neurotransmission in AN.

Neuropeptides have also been of interest in AN as they are involved in the regulation of feeding behaviours. Abnormalities in the ill state of AN have been found for a variety of neuropeptides including opioid peptides, oxytocin, neuropeptide-Y
and leptin, though the differences observed appear to normalise after weight restoration suggesting a state rather than trait effect (for a review see Bailer & Kaye, 2003).

1.7.3.4.2.2 Regional cerebral blood flow

Functional neuroimaging is relatively recent technology which has allowed the indirect measurement of brain activity. Early functional studies utilised single-photon emission computed tomography (SPECT), which have shown hypo- and hyperperfusion at rest in a number of brain areas in the ill state of AN. Kuruoglu et al. (1985) reported hypoperfusion in frontal, parietal and frontotemporal areas, which normalised following weight restoration. Another study reported unilateral temporal lobe hypoperfusion which persisted in a subgroup who had a follow-up scan following weight restoration (Gordon, Lask, Bryant-Waugh, Christie, and Timimi, 1997). A more recent study by Chowdhury et al. (2003) revealed hypoperfusion in the temporal, parietal and frontal lobes, thalamus, and caudate nuclei. Other recent studies found hypoperfusion in the medial prefrontal cortex, the ACC (Takano et al., 2001), the posterior cingulate gyrus, the subcallosal gyrus, the midbrain (Yonezawa, Otagaki, Miyake, Okamoto, & Yamawaki, 2008), the anterior temporal lobe and caudate nuclei (Key, O'Brien, Gordon, Christie, & Lask, 2006), and hyperperfusion in the thalamus and the amygdala-hippocampus complex (Takano et al., 2001). Hypoperfusion specific to AN-R has also been found in frontal areas, mainly the ACC (Naruo et al., 2001), and hyperperfusion specific to AN-BP in the right hemisphere, including inferior and superior prefrontal, and parietal regions (Naruo et al., 2000). Changes in regional cerebral blood flow (rCBF) at rest have been reported by some to normalise following weight restoration and remission (Kuruoglu et al., 1985), though others have found persistent changes (Frampton, Watkins, Gordon, & Lask, 2011). One study reported that, in comparison with healthy controls, individuals with AN-R prior to treatment had lower cerebral blood flow in the ACC, right parietal lobe, insula and occipital lobes. Following treatment and weight gain, normalisation in a number of brain areas occurred, but decreased rCBF persisted in the ACC (S. Kojima et al., 2005). Another study by Matsumoto et al. (2006) found AN patients had increased rCBF post-treatment relative to pre-treatment in the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex, anterior and posterior cingulate and precuneus. A
more recent study by Komatsu et al. (2010) however, reported increased rCBF in the right posterior cingulate gyrus and bilateral parietal lobe following weight-recovery. Differences in rCBF have also been reported in AN relative to different conditions. Prior to eating a meal, AN participants have been found to show significantly decreased rCBF in the left parietal cortex in comparison to controls. Post-meal however, AN participants were found to not differ in rCBF relative to healthy controls or BN patients (Nozoe et al., 1995). Individuals with AN have also been found to show differences in rCBF when viewing stimuli of their own bodies. In a study by Beato-Fernández et al. (2009), healthy individuals, patients with BN and patients with AN viewed videos of themselves and landscapes. When viewing videos of one’s own body, increased rCBF of the left parietal and right superior frontal cortices was found in AN, whereas healthy controls showed decreased activation in these areas, suggesting a possible dysfunction in somatosensory integration in AN.

1.7.3.4.2.3 Glucose metabolism

Findings similar to those reported with the use of SPECT have also been found with PET. Individuals with AN have been shown to display global hypometabolism as well as relative hypometabolism of glucose in cortical regions, most significantly in the frontal and parietal cortices (Delvenne et al., 1997; Delvenne et al., 1995), which have been found to normalise with weight gain (Delvenne et al., 1996). The same authors also reported hypermetabolism in the inferior frontal cortex and basal ganglia (BG) when compared to controls, as well as increased glucose metabolism in the caudate and putamen when compared to participants with BN (Delvenne, Goldman, De Maertelaer, & Lotstra, 1999); whereas AN individuals in remission have been shown to display normal glucose metabolism in the brain (Delvenne et al., 1996; G. K. Frank et al., 2007; Herholz et al., 1987). Furthermore, individuals with AN have been shown to have greater rCBF within the bilateral medial temporal lobe in comparison to healthy controls (Gordon et al., 2001), an area heavily involved in memory processes (Squire & Zola-Morgan, 1991) and an area which has also been associated with increased blood flow in schizophrenia (Friston, Liddle, Frith, Hirsch, & Frackowiak, 1992). Additionally, the study by C. M. Gordon et al. (2001) reported increased occipital and temporo-occipital cortex activity of AN patients relative to controls when viewing images of high- compared to low-calorie
foods. These areas are related to the processing of visual information and increased activity of related visual processing areas have been found in individuals with specific phobias when presented with phobic stimuli (Wik et al., 1993).

1.7.3.4.2.4 Blood oxygen level dependent (BOLD) response

Changes in neural activity in response to different conditions that were initially explored with PET have typically been explored with functional magnetic resonance imaging (fMRI) since the technology became widely available. In the first fMRI study in AN, Ellison et al. (1998) presented individuals with images of high- and low-calorie drinks. The authors reported that the group of AN participants showed increased activity of the left insula, ACC and amygdala-hippocampal region in response to high- versus low-calorie drinks, relative to controls. In response to images of food and non-food items, Joos et al. (2011) found increased right amygdala activity and decreased posterior middle cingulate cortex activity in AN-R compared to controls, whereas, K. R. Kim, Ku, Lee, Lee, and Jung (2012) reported increased left anterior insula activity in AN, and significant interactions between the right insula and inferior frontal gyrus. However, the studies by K. R. Kim et al. (2012) and Joos et al. (2011) involved passive viewing of images. In a study undertaken by Brooks et al. (2011), the investigators asked participants to imagine they were eating the food in the images presented to them and were using the objects in the control images. Increased activity of the cerebellum, left visual cortex, right DLPFC and parietal lobe was reported in AN-R to food compared to non-food items, and in the bilateral cerebellum and SMA in AN-BP. However, this study only reported within-group comparisons for AN participants and did not present between-group comparisons with healthy controls. Utilising the same paradigm, a more recent study by this group which reported results compared to healthy individuals, increased right visual cortex activity and reduced bilateral cerebellar vermis activity was reported in AN when thinking about eating food (Brooks et al., 2012). When the investigators examined AN-R and AN-BP separately in comparison to healthy controls, increased right visual cortex and DLPFC activity, and reduced left cerebellar vermis and right insular activity was found when thinking about eating food in AN-R. Similar results were reported for the AN-BP group, though no increase in right DLPFC activity was found. When comparing the two AN subgroups to one another, the AN-R group showed increased
activity of the visual cortex, left parahippocampal gyrus and left ACC, suggesting a possible difference in the processing of food-related information between the two AN subgroups.

BOLD activity differences in response to images of food have also been found between patients currently ill with AN and weight-recovered patients. Holsen et al. (2012) presented ill AN, weight-recovered AN and healthy controls with images of food and non-food items before and after a meal. Pre-meal, the two patient groups showed reduced hypothalamus, amygdala and anterior insula activity when viewing images of high-calorie foods compared to controls. Additionally, the ill AN group also showed increased hippocampus and orbitofrontal cortex activity. Post-meal, the group with active illness persisted to show reduced amygdala and anterior insula activity, whereas the weight-recovered individuals did not. Other studies assessing AN participants in a hungry and satiated state have reported increased posterior cingulate (Gizewski et al., 2010), and inferior parietal and visual cortex activity (Santel, Baving, Krauel, Munte, & Rotte, 2006) in a hungry state when viewing food images. When satiated, increased activity of the left insula to food images has been reported in AN in comparison to controls (Gizewski et al., 2010). In relation to a hungry state however, increased occipital cortex activity has been reported in AN when viewing food images (Santel et al., 2006). Different neural responses in AN when hungry and satiated have also been investigated with the use of oral stimuli. In a task where participants were required to drink chocolate milk or water through a tube while undergoing fMRI, the group of AN-R participants showed increased right amygdala and left medial temporal gyrus activity relative to controls when drinking the flavoured milk (Vocks, Herpertz, Rosenberger, Senf, & Gizewski, 2011). Although groups did not differ in responses to the chocolate milk in the satiated condition, when comparing the hungry to the satiated condition the AN group displayed increased inferior temporal gyrus activity, which included the extrastriate body area, whereas the control group showed increased left insula activity. In a study by Wagner, Aizenstein, Mazurkewicz, et al. (2007), where participants were administered either a sucrose solution or water, the investigators reported reduced activation to both stimulus types in the insula, and ventral and dorsal striatum in AN. A similar finding was reported by T. A. Oberndorfer et al. (2013) who reported reduced right insula activity in AN to both sucrose and sucralse in a group of weight
recovered AN participants relative to healthy controls. Furthermore, differences in striatum and insula activity have also been reported in a study by Cowdrey, Park, Harmer, and McCabe (2011). In this study the investigators administered a pleasant chocolate taste or an aversive unpleasant taste coupled with the presentation of chocolate, mouldy strawberries or a grey control image, or a grey screen coupled with a tasteless liquid which acted as a control condition, to healthy individuals and individuals weight-recovered from AN-R. The weight-recovered AN group was found to show increased ventral striatum and cingulate cortex activity to the taste of chocolate, and increased activity of the cingulate, medial prefrontal and occipital cortices in response to the sight of chocolate. When presented with the mouldy strawberry picture however, no group differences were apparent, though increased activation of a number of areas was evident when the oral stimulus was administered alone or with the corresponding aversive image, including the ACC, DLPFC, lateral posterior insula, putamen and caudate.

Furthermore, in a series of studies undertaken by Uher and colleagues (Uher et al., 2003; Uher et al., 2004), the investigators presented participants with images of food and non-food items and asked them to think about how hungry the images made them; and emotional aversive and neutral images which required participants to think about how the images made them feel. In the food/non-food contrast, individuals with AN demonstrated more activity of the lingual gyrus and lower activity of the inferior parietal lobule and cerebellum when compared to controls (Uher et al., 2004); whereas individuals weight-recovered from AN showed increased prefrontal and ACC activity, and reduced inferior parietal activity in the same contrast compared to healthy individuals (Uher et al., 2003). Relative to individuals with a current diagnosis of AN-R, the weight-recovered group were found to show heightened activation of the dorsal ACC and the prefrontal cortex. In this earlier study, group differences were specific to food stimuli and no difference in activation was apparent for the emotional aversive stimuli for either AN-R or weight recovered AN compared to controls. In the later study however which contained a larger sample size, AN participants were found to show reduced right cerebellar activity but increased left cerebellar activity when viewing the emotional aversive images compared to healthy individuals. Individuals with AN have also been found to show differences in brain activation when presented with negative words related to interpersonal relationships. Specifically, AN has been
associated with increased left insula, and right superior temporal and inferior frontal gyri activation, relative to healthy controls (Miyake, Okamoto, Onoda, Shirao, & Yamawaki, 2012). In an earlier study, the same group investigated neural responses to negative body-image words (Miyake et al., 2010). AN-R was associated with more activity of the right amygdala and inferior parietal lobule, whereas AN-BP was associated with higher activity of the amygdala and left ventromedial prefrontal cortex, relative to a healthy comparison group. Response to negative body-image words have also been investigated in AN utilising an Emotional Stroop task consisting of fat, thin and neutral words, and words comprised of XXXXs (Redgrave et al., 2008). This study revealed increased activation at the junction of the left insula, and frontal and temporal lobes, and the left middle and medial frontal gyri to thin versus XXXX words in AN compared to controls; whereas the fat-XXXX contrast revealed lower activity of the DLPFC and parietal areas in comparison to controls. These findings suggest that individuals with AN process positive and negative body image words differently to healthy individuals, with increased activation to thin words and decreased activation to fat words in areas related to executive function.

Furthermore, body image in AN has also been explored by examining responses to images of human bodies. A recent study involving passive viewing of body images and images of chairs which acted as control condition, aimed to investigate the connectivity within the core network for body processing (Suchan et al., 2013). The findings of the study revealed a different network in AN during the processing of human bodies. In healthy controls, effective connectivity was found between the middle occipital gyrus and extrastriate body area, and the extrastriate body area and fusiform gyrus. In AN however, effective connectivity was evident between the middle occipital gyrus and fusiform body area, and the fusiform body area and the extrastriate body area. Furthermore, reduced connectivity between the fusiform body area and extrastriate body area was found in the group of AN patients. Differences in the extrastriate body area and fusiform body area function between AN and healthy individuals have also been reported in a study involving the presentation of underweight, overweight and normal weight female bodies. Uher et al. (2005) reported reduced activation of the occipitotemporal cortex (including the extrastriate body area), the fusiform gyrus and the parietal cortex in a group of AN participants to all body shapes, relative to both BN and healthy controls. This task required
participants to think about how acceptable the body or house (control image) would be for them. In a similar study utilising stimuli of computer-generated nude females depicting underweight, overweight and normal body weights, participants were asked to process the stimuli during two conditions: one which they were required to imagine how it would feel to be the body shape presented, and the other where they needed to estimate the body weight of the stimuli, which acted as the control condition (Fladung et al., 2010). Greater activity of the ventral striatum to normal weight compared to underweight stimuli was evident in healthy controls, whereas individuals with AN were found to show greater activity to underweight stimuli in the same contrast. However, groups were not found to differ in response to overweight stimuli. In another study, Friederich et al. (2010) presented participants with images from magazines of either slim idealised female bodies or interior home designs in which participants were asked to compare their body shape or room design with the presented image. Group comparisons revealed that in response to the body images, individuals with AN showed decreased activity of the rostral ACC and greater activity of the right insula and premotor cortex. In a recent study by Suda et al. (2013), the investigators presented individuals with AN and healthy individuals with images of ‘body checking’, such as images of measuring leg width with a measuring tape and pinching skin folds, and neutral active images such as using a computer or writing. The authors reported increased right parietal cortex activity in the AN group to the body checking images compared to the neutral images, and lower activity of the anteromedial prefrontal cortex and right fusiform gyrus relative to controls.

Rather than displaying images of other people’s bodies, several studies have focused on responses to images of one’s own body. Sachdev, Mondraty, Wen, and Gulliford (2008) found that in comparison to a group of healthy participants, AN participants showed less activity of the frontal gyri, insula, precuneus and occipital regions when processing own body images, but did not differ when processing non-self body images. Vocks, Busch, Grönemeyer, et al. (2010) reported higher amygdala activity in AN compared to BN and controls when viewing another woman’s body, and reduced inferior parietal lobule activity when viewing own body images compared to controls alone. In a related study, the same authors presented AN patients with own body stimuli before and after undergoing body image therapy and found increased pre- to post-treatment activity in the right middle temporal gyrus (including
the extrastriate body area); whereas decreased pre- to post-treatment activity in the left precuneus, posterior cingulate gyrus, fusiform gyrus, and right inferior and superior frontal gyri, parahippocampal gyrus, and bilateral inferior parietal lobule was reported in AN (Vocks, Busch, Schulte, et al., 2010). Furthermore, other studies have not only presented individuals with images of their own body, but also distorted images of their own body. Castellini et al. (2012) asked participants to passively view images of their own body undistorted, their own body digitally distorted, and control of images of houses. The authors reported that in comparison to healthy controls, individuals with AN showed increased inferior frontal gyrus activity when presented with overweight stimuli relative to normal weight stimuli, and greater activity of the middle temporal gyrus in the underweight-normal weight contrast. In another study with similarly distorted images, participants were asked to either rate how much the image corresponded to their real body, or how much it represented their ideal body (Mohr et al., 2010). In the ideal body condition, increased activity of the insula and middle frontal gyrus was found for thin images in comparison to thin images of the real body condition. Additionally, the AN group were found to show decreased precuneus activity for all body sizes in the real body condition compared to controls, and to the heavier images in the real body condition relative to the ideal body condition in comparison to healthy individuals. Furthermore, an early fMRI study in AN undertaken by Seeger, Braus, Ruf, Goldberger, and Schmidt (2002) presented distorted own body images of maximum subjective unacceptability to the participant, subjective unacceptability of another woman’s body and abstract images consisting of participants own body. This study reported that AN participants showed increased activity of the right amygdala, fusiform gyrus and brainstem to distorted own body images compared to distorted images of other bodies and the abstract images. However, this study was only comprised of three individuals with AN and three comparison participants. In a follow-on study by the same group of investigators, the same task was performed in a larger sample and was found to lead to increased inferior parietal lobule and prefrontal cortex activity in the same comparison mentioned above (Wagner, Ruf, Braus, & Schmidt, 2003).

Although the great majority of fMRI studies have presented individuals with disorder-relevant stimuli such as bodies and food, other aspects of the disorder have also been investigated. A number of cognitive tasks have been performed while
undergoing fMRI, including tasks of inhibition, working memory, visuospatial processing, cognitive flexibility and reward. During the completion of a stop-signal task, groups of AN participants and healthy controls demonstrated similar neural activity when the inhibitory demand was low. However, when the inhibitory demand was high, individuals with AN showed decreased prefrontal cortex activity in comparison to controls (T.A. Oberndorfer, Kaye, Simmons, Strigo, & Matthews, 2011). However, during a number n-back task, a task assessing working memory, individuals with AN were reported to show increased activation of temporal and parietal areas compared to controls. A subgroup of the same AN participants were retested following seven months of treatment and weight restoration and were found to show reduced activity in the ACC, and frontal and parietal regions compared to the results from the original test session. At follow-up, the AN patients no longer differed from the control group (Castro-Fornieles et al., 2010). However, in a more recent study by Lao-Kaim, Giampietro, Williams, Simmons, and Tchanturia (2013), the authors reported no difference in performance or brain activity between groups of AN participants and healthy controls on a letter n-back task, suggesting that verbal working memory may be intact in AN. During a visuospatial processing task, in which participants were required to identify a target shape within more complicated figures, the AN group not only performed poorer on the task but also showed greater fusiform gyrus activity, whereas controls showed greater precuneus activity (Fonville et al., 2013). These findings suggest that unlike healthy individuals who utilise visuospatial search strategies to complete such tasks, individuals with AN may utilise strategies related to object recognition. During a behavioural response shifting task, where participants were required to respond to and classify shapes as targets, non-targets or standard shapes, Zastrow et al. (2009) described that individuals with AN showed decreased bilateral thalamus, rostral cingulate, sensorimotor region and cerebellum activity to target trials, independent of performance. The AN group also showed reduced activity of the dorsal ACC and ventral putamen in the correct shift target trials, and reduced activity in the rostral ACC and dorsal and middle striatum in the correct maintain target trials, relative to controls. Incorrect trials relative to correct trials were associated with lower activity of the dorsal ACC which extended to the medial frontal gyrus in AN. Together, the findings by Zastrow et al. (2009) indicate that during tasks of behavioural response shifting, individuals with AN may have altered fronto-striatal-thalamic function. Additionally, during the Wisconsin Card Sort
Test (WCST), a task of behavioural response shifting and cognitive flexibility, individuals with AN are also found to show differences in neural response. In a study by Sato et al. (2013), the authors reported poorer performance on the task in AN, and lower right ventrolateral prefrontal cortex and bilateral parahippocampal cortex activity relative to healthy controls.

Differences in responses to stimuli related to reward have also been recently investigated in AN. In a study by G. K. W. Frank et al. (2012), participants performed a reward-conditioning task where they not only learned specific associations, but they would receive or be deprived of one of the two association stimuli therefore causing an unexpected violation of these learned associations. When an unexpected stimulus was received, AN participants had greater right ventral putamen activation compared to controls, and greater left orbitofrontal cortex activity in comparison to a sample of obese participants and the healthy control group combined. When a stimulus was unexpectedly deprived, AN participants showed reduced activation of the bilateral putamen and left orbitofrontal cortex compared to the two comparison groups. Additionally, in a study presenting a simple monetary reward task to individuals weight-recovered from AN and a healthy comparison group, the healthy controls were found to show increased left anterior ventral striatum activity for wins than for losses, whereas the patient group did not differ and had similar responses to both conditions, suggesting a possible difficulty in differentiating positive and negative feedback in AN (Wagner, Aizenstein, Venkatraman, et al., 2007).

A range of other BOLD studies have been undertaken in AN. One study aiming to assess emotion processing in AN presented individuals with happy and fearful human faces (Cowdrey, Harmer, Park, & McCabe, 2012). The study revealed no difference in neural response between groups. However, this result may be due to the fact that appropriate comparisons between conditions could not be made as a neutral control condition was not presented. A study investigating the processing of identity in AN found reduced precuneus, dorsal ACC and left middle frontal gyrus activity when presented with stimuli related to self-knowledge and perspective taking (McAdams & Krawczyk, 2014). Two recent studies have also looked at pain perception in AN. In the earlier study, Bär, Berger, Schwier, Wutzler, and Beissner (2012) administered a painful thermal stimulus to the right arm of participants and
found that AN participants had an increased heat pain threshold and increased right pons activity in comparison to controls. The later study undertaken by Strigo et al. (2013) investigated pain processing and anticipation in weight-recovered AN. The authors reported increased DLPFC and decreased posterior insula activity during pain stimulation in the AN group. During pain anticipation however, the AN group displayed greater right anterior insula, DLPFC and cingulate cortex activity, relative to controls, suggesting a potentially intensified stress response.

Recently, studies have begun to investigate functional connectivity in individuals with AN. During resting state scans of individuals weight-recovered from AN, increased temporal coherence has been reported between the default mode network functional connectivity map, and the right precuneus and the DLPFC/inferior frontal gyrus (Cowdrey, Filippini, et al., 2012). Decreased connectivity in the right middle frontal gyrus has also been reported for weight-recovered AN, and decreased connectivity of the left occipitotemporal junction within the ventral visual network (Favaro et al., 2012). Favaro et al. (2012) also reported increased connectivity in the left superior parietal cortex within the somatosensory network for individuals with AN. In another study, the same authors described increased prefrontal functional connectivity in individuals with AN who were Met-Met carriers of the COMT gene, compared to AN patients who were Val carriers of the gene (Favaro et al., 2013). In a more recent study by Amianto et al. (2013), the investigators reported intrinsic connectivity networks in the cerebellum in AN which were more restricted to vermián areas, and showed greater medial and less lateral connectivity in the cerebellum relative to healthy individuals. The AN group also demonstrated less cerebellar connectivity with the parietal lobe, but more cerebellar connectivity with the posterior cingulate cortex, bilateral temporal pole and insula. Furthermore, the anterior insula showed more connectivity in AN, in contrast to individuals with BN who showed hyperconnectivity with the posterior portion of the insula.

1.7.4 Aetiology conclusions

AN is a complex condition and although a variety of theories exist relating to the aetiology of AN, the cause of the disease remains unknown. Sociocultural, psychological and biological aspects may contribute to the condition, but no clear
aetiology has been established. A multifactorial approach incorporating the above factors may assist in providing a better understanding of the illness.

1.8 Current study

The factors involved in the cause and maintenance of AN remain very unclear therefore causing a hindrance in the improvement of current treatments or the development of new and more effective treatments. Many patients remain under- or unresponsive to treatment, leading to significant morbidity and mortality rates. By gaining a better understanding of how the brain functions differently in individuals with AN, more effective treatments may be developed in the future. Therefore, the aim of this study was to utilise a comprehensive battery of assessments including a range of cognitive assessments, eyetracking tasks and functional neuroimaging measures to gain a better understanding of the neurobiological and cognitive features of AN.
Chapter 2: Method

2.1 Ethics approval

The study was granted independent ethics approval by the Human Research Ethics committees at St Vincent’s Hospital (Human Research Ethics Committee A (HREC-A)) (057/12), Austin Health (Non Drug Study Advisory Committee (NDSAC)) (H2012/04646) and The Melbourne Clinic (The Melbourne Clinic Research Ethics Committee (TMC REC)) (235). In addition, the study received expedited ethics approval from Swinburne’s Human Research Ethics Committee (SUHREC) (2012/277) and was registered with The University of Melbourne Health Sciences Human Ethics Sub-Committee (HESC) (1239068), on the basis of the prior St Vincent’s Hospital review. Participants were also invited to have their data stored in a databank (Cognitive and Genetic Explanations of Mental Illnesses Bio-Databank (CAGEMIS)) under the approval received by the Human Research Ethics Committees of The Alfred Hospital and the Baker IDI Heart and Diabetes Institute (196/10). All of the institutions named above are located in Melbourne, Australia. Approval letters from each of the ethics committees are provided in Appendix B.

2.2 Participant recruitment

2.2.1 Recruitment procedure

A total of 31 healthy control and 30 AN participants were recruited for the study. Healthy control participants were recruited through public advertisements through the University of Melbourne (n=18) and Swinburne University of Technology (n=6), and through word of mouth (n=7). Participants with AN were recruited through the Body Image and Eating Disorders Treatment and Recovery Service (BETRS), a joint collaboration between the mental health departments of the Austin and St Vincent’s Hospitals. The BETRS inpatient service is provided through the Acute Psychiatry Unit at the Austin Hospital, and day patient and outpatient services are provided through St Vincent’s Hospital. Four AN participants were recruited through the BETRS inpatient service and three through the day patient service. Participants
with AN were also recruited through the inpatient (n=3) and day patient (n=1) eating disorder programs at the Melbourne Clinic. In addition, AN participants were also recruited through public advertisements on eating disorder support websites (n=1) and support groups on Facebook (n=1), through advertisements posted through the University of Melbourne (n=9), and through word of mouth (n=8). AN participants recruited through BETRS and the Melbourne Clinic had a current diagnosis of AN from their treating physician. AN participants recruited through other sources were required to have a diagnosis of AN by a psychologist or psychiatrist. Although confirmation of a diagnosis could not be established for these individuals, to be eligible to participate they had to meet DSM-IV criteria for AN as assessed by the Mini International Neuropsychiatric Interview (MINI), as was also required of patients recruited from the hospital sites.

Potential AN participants recruited through BETRS and The Melbourne Clinic were approached by their clinicians or by the researcher directly. The aims of the project were briefly explained as were the eligibility criteria and the time commitment required of participants. Interested patients had the option to have their contact details passed on to the researcher or to contact the researcher directly. Potential healthy control participants and participants with AN recruited through other sources were required to contact the researcher directly.

At first contact, the research was described in detail and potential participants were screened for eligibility to participate. The participant information and consent form (PICF) was emailed to participants and any questions or concerns welcomed prior to booking the three test sessions. Participants were informed that all three sessions would need to be undertaken within approximately one week and that a detailed screen would be undertaken in the first session which may prevent them from continuing with the remaining sessions. Therefore, at first contact, participants were booked in for their first session and were tentatively booked in for the remaining two sessions. The recruitment period began from May 2013 at BETRS, from January 2014 at the Melbourne Clinic, and from May 2013 for recruitment through advertisements. Recruitment concluded in mid-June 2014 at all recruitment sites.
2.2.2 Eligibility criteria

All participants were required to be right-handed females, over 16 years of age, English speaking, have no significant ocular pathology, no colour vision deficiency and normal visual acuity of at least 6/7.5 (or corrected to normal with glasses or contact lenses). Participants were also required to have no history or neurological condition or brain injury and have no psychotic conditions. As participants were undertaking a magnetic resonance imaging (MRI) scan as part of the study, for safety reasons they were required to not be pregnant, have no metallic pins or implants or any other metal that could not be removed. Due to slow recruitment of AN participants, exceptions were made for AN participants with irremovable facial or ear piercing (n=3) and irremovable dental plates (n=3) as although they had the potential to create an artifact in the MRI signal, they did not pose a safety issue. Control participants were also required to have no Axis I psychiatric disorders and no history of an eating disorder. All participants in the AN group were required to have a current diagnosis of AN.

2.2.3 Sample size

In total, 30 AN participants were recruited. Two participants recruited through public advertisements were at a healthy body weight, therefore not meeting the criteria for current AN, and did not continue following the screening process. One AN participant recruited from the day patient service at BETRS reported psychotic features and high suicidality when tested on the MINI. She also presented with high inattentiveness during the cognitive assessments in the first session. Due to these factors it was not considered appropriate to continue with the scanning sessions and her data was excluded. In addition, one AN participant recruited through word of mouth reported significant psychotic features and her sessions were not continued.

Thirty-one healthy control participants were recruited. One individual was excluded as she was taking antidepressant medication, though did not show depressive symptoms on the MINI or Montgomery-Asberg Depression Rating Scale (MADRS). One participant was excluded who was breastfeeding; one who reported substance abuse and BN as measured by the MINI; and one whose parents both had
schizophrenia. Of the four control participants excluded from this study, all were recruited through public advertisements at the University of Melbourne and Swinburne University of Technology.

Overall, 26 AN participants and 27 healthy control participants completed the study. Although all participants were booked in for all three sessions within one week, due to unexpected illness or unexpected work or study commitments, some participants had sessions rescheduled over a maximum of 11 days from the first session. However, due to scheduling restraints, a number of participants could not be rescheduled within this timeframe. Of the 27 control participants, two participants only completed the first session due to illness and study commitments, and one participant only completed the first and second sessions and did not complete the ‘long magnetoencephalography (MEG)’ session due to work commitments. Of the 26 AN participants, two participants only completed the first session due to treatment and study commitments. Therefore, 24 participants in each group completed all three sessions. The average number of days between session one and two was 2.83 (SD= 1.66) for AN participants and 2.13 (SD= 1.51) for control participants (F(1,46)= 2.39, p= 0.129). The average number of days between the first and third sessions was 5.42 days (SD=2.30) for AN participants and 6.08 (SD=1.93) for control participants (F(1,46)= 1.181, p= 0.283).

2.3 Materials

2.3.1 Neuropsychological assessments

Samples of the neuropsychological assessments are provided in Appendix C.

2.3.1.1 Clinical demographic record

Basic demographic information was collected including, age, gender, area of residency, marital status, occupation, and primary and secondary languages spoken. Educational and employment history was also attained, as was a brief medical history which included information about illness duration and treatment for the AN participants. Body areas of concern were also reported for all participants. All
participants also had their BMI measured, their colour vision assessed, and their visual acuity measured.

2.3.1.2 Edinburgh Handedness Inventory (EHI)

The Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) is a 22-item self-report measure used to assess right or left hand dominance. A cross is placed in the right or left hand column to indicate hand preference for each activity listed. If the preference is so strong that the other hand would never be used, two crosses are placed in the appropriate left or right hand column. In the case of indifference, a cross is placed in each column. The EHI is a valid and reliable measure of handedness (Raczkowski, Kalat, & Nebes, 1974; Ransil & Schachter, 1994).

2.3.1.3 Wechsler Test of Adult Reading (WTAR)

The Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) is a reading test composed of a list of 50 words that have atypical grapheme to phoneme translations. Participants are asked to pronounce each word aloud. The test allows a reliable and valid estimate of intellectual functioning prior to injury or cognitive decline (R. E. A. Green et al., 2008; Wechsler, 2001).

2.3.1.4 Mini International Neuropsychiatric Interview (MINI)

The MINI, version 5.0.0 (Sheehan et al., 1998), is a structured diagnostic interview for DSM-IV and the International Classification of Disease (ICD-10) major Axis I psychiatric disorders. Precise questions are asked requiring a yes or no answer, and examples are asked from the participant when necessary. The MINI is a reliable and valid measure of major Axis I psychiatric disorders (Sheehan et al., 1997; Sheehan et al., 1998).

2.3.1.5 Eating Disorder Examination Questionnaire (EDE-Q)

The Eating Disorder Examination Questionnaire (EDE-Q), version 6.0 (Fairburn, 2008), is a 28-item self-report measure of psychological constructs shown to be clinically relevant in individuals with eating disorders. The questionnaire asks
individuals to report on items in relation to the past 28 days. The questionnaire consists of four subscales: restraint, eating concern, shape concern and weight concern. Ratings for the relevant items for each subscale are summed and divided by the number of items in that subscale. A global score is obtained by summing the four subscale scores and dividing the total by the number of subscales (i.e. four). The EDE-Q is a reliable (Luce & Crowther, 1999) and valid measure of eating disorder psychopathology in the general population (Fairburn & Beglin, 1994; Mond, Hay, Rodgers, Owen, & Beumont, 2004) and in clinical populations of eating disordered individuals (Carter, Aimé, & Mills, 2001; Wolk, Loeb, & Walsh, 2005).

2.3.1.6 Figure Rating Scale (FRS)

The Figure Rating Scale (FRS) (Stunkard, Sørensen, & Schulsinger, 1983) is a 9-point rating scale of nine male and nine female schematic silhouettes ranging from thin to very obese, and is a reliable and valid measure of body image disturbance (J. K. Thompson & Altabe, 1991). Only the female silhouettes were presented to participants who were asked to indicate along the 9-point scale their ideal figure, the figure that best reflects how they think they look, the figure that best reflects how they feel most of the time, the figure they think is most preferred by men, and the figure they think is most preferred by women. Similarly to J. K. Thompson and Altabe (1991), discrepancy scores were calculated as follows: ideal – think; ideal – feel; ideal – preferred by men; ideal – preferred by women; think – feel; think – preferred by men; think – preferred by women; feel – preferred by men; feel – preferred by women; preferred by men – preferred by women.

2.3.1.7 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS (Montgomery & Asberg, 1979) is a ten-item diagnostic questionnaire used to measure the severity of depressive episodes, and is a reliable and valid measure of depressive episodes (Davidson, Turnbull, Strickland, Miller, & Graves, 1986). The timeframe for the scale is one week and symptoms are rated on a six-point scale, with defined anchor points at 0, 2, 4 and 6. A score of over 34 indicates a severe depressive episode, 20-34 a moderate depressive episode, 7-19 a
mild depressive episode, and a score under 7 indicates an absence of depressive symptoms.

2.3.1.8 Depression Anxiety Stress Scale (DASS)

The Depression Anxiety Stress Scale (DASS) (Lovibond & Lovibond, 1996) is a 42-item self-report instrument designed to measure the three related negative emotional states of depression, anxiety and tension/stress. The timeframe for the scale is one week and symptoms are rated on a four-point Likert scale ranging from ‘did not apply to me at all’ (0) to ‘applied to me very much, or most of the time’ (3). The severity ratings for the depression axis are as follows: normal= 0-9, mild= 10-13, moderate= 14-20, severe= 21-27 and extremely severe= 28+. The severity ratings for the anxiety scale are: normal= 0-7, mild= 8-9, moderate= 10-14, severe= 15-19 and extremely severe= 20+. The severity ratings for the stress scale are as follows: normal= 0-14, mild= 15-18, moderate= 19-25, severe= 26-33 and extremely severe= 34+. The DASS is a reliable and valid measure of depression, anxiety and tension/stress in clinical populations and the general population (Antony, Bieling, Cox, Enns, & Swinson, 1998).

2.3.1.9 Personality Diagnostic Questionnaire (PDQ-4)

The Personality Diagnostic Questionnaire (PDQ-4) (Hyler, 1994) is a 99-item true/false self-report questionnaire used to screen for DSM-IV Axis II personality disorders. If the threshold is met for any particular personality dimension, an additional series of questions are asked with the use of a Clinical Significance Scale. A total score of 50 or more suggests a substantial likelihood that a personality disturbance is present. The PDQ-4 is a reliable and valid measure of personality psychopathology (Hyler, Skodol, Keilman, Oldham, & Rosnick, 1990; Hyler, Skodol, Oldham, Kellman, & Doidge, 1992).

2.3.1.10 Toronto Alexithymia Scale (TAS-20)

The Toronto Alexithymia Scale (TAS-20) (Bagby, Parker, & Taylor, 1994) is a valid and reliable 20-item self-report measure of the alexithymia construct (Bagby et
al., 1994; J. D. A. Parker, Taylor, & Bagby, 2003). Items are responded to on a 5-point Likert scale ranging from ‘strongly disagree’ (1) to ‘strongly agree’ (5). A score of 61 and over indicates high alexithymia (alexithymia), whereas a score of 51 and under indicate low alexithymia (non-alexithymia). The TAS-20 can also be divided into three factors: difficulty identifying feelings, difficulty describing feelings and externally-oriented thinking.

2.3.1.11 Barratt Impulsiveness Scale (BIS-11)

The Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995) is a 30-item self-report measure of impulsive personality traits. Items are scored on a 4-point Likert scale ranging from ‘rarely/never’ (1) to ‘almost always/always’ (4). The scale yields three second-order factors: attentional, consisting of the first-order factors of attention and cognitive instability; motor, consisting of the first-order factors of motor and perseverance; and non-planning, comprised of the first-order factors of self-control and cognitive complexity. The BIS-11 is a reliable and valid measure of impulsivity (Stanford et al., 2009).

2.3.2 Apparatus and physical set-up

2.3.2.1 General equipment

BMI was measured with the use of a standard tape measure and a bathroom scale (Soehnle Slim Design Scale, model GSH63538) which measures body weight in 100g increments. Colour vision was assessed with Ishihara’s tests for colour deficiency (Ishihara, 2001), and visual acuity was measured with a 40cm Snellen visual acuity chart.

2.3.2.2 Management and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery

The MATRICS Consensus Cognitive Battery provides a brief evaluation of cognitive domains that are relevant to schizophrenia and related disorders. The MATRICS is a reliable and valid cognitive battery of tasks for use with patients with
schizophrenia (Nuechterlein et al., 2008). The battery was administered to participants as it is a comprehensive battery of cognitive tasks. Though the MATRICS was originally designed to assess cognitive domains most relevant to schizophrenia, it has since been applied to assess cognitive impairments in other psychiatric illnesses, including bipolar disorder (BD) (Van Rheenen & Rossell, 2014), posttraumatic stress disorder (J. L. Kaye et al., 2014) and MDD (Murrough et al., 2014). The MATRICS assesses seven cognitive domains with the use of 10 different tasks detailed in 4.4.2.1.

2.3.2.3 EyeLink1000

The EyeLink1000 (SR Research, Ontario, Canada) was used for all eyetracking recordings. The neuroimaging facility at Swinburne University of Technology has EyeLink1000 systems set up in both the MRI and MEG machines, and in an interview room for behavioural recordings. The EyeLink1000 is a remote view system with the potential for 2000Hz monocular and 1000Hz binocular recordings with adequate head support. The systems at Swinburne are set up as monocular systems with a sampling rate of 500Hz. At 500Hz, the EyeLink1000 has an average accuracy of 0.25° - 0.5° with a spatial resolution of 0.05° root-mean-squared (RMS).

The EyeLink1000 system’s saccade detection algorithm uses the following thresholds for the detection of saccades: a saccade velocity threshold $30^\circ$/sec, an acceleration threshold of $8000^\circ$/sec$^2$ and a motion threshold of $0.15^\circ$. These thresholds are recommended by SR Research for use in cognitive research as they reduce the number of microsaccades detected, reduce the number of false saccades detected due to low velocity thresholds and ensure the eye has moved significantly after the onset of a saccade. Fixations are not detected as such, but are classified as any sample that is not a saccade or a blink/eyetracker drop-out. SR Research’s analysis program, DataViewer, was used for eyetracking analyses utilising the above criteria in each chapter, bar Chapter 9 in which a custom-made program run under Matlab R2014a was used (Mathworks, Natick, MA, USA). Threshold criteria are explained in detail within this chapter.

In the MEG system, participants sat in the scanner with their head unsupported. In the MRI set-up, participants’ heads were supported by pads placed
around their head to prevent significant movement. In the behavioural set-up, movement was restricted with the use of a chinrest. Due to set-up constraints, the left eye was recorded in the MEG system and the right eye in both the MRI system and behavioural set-up. However, as the two eyes typically move in synchronisation and share the same movement characteristics, and we had no reason to believe otherwise in our groups, this was not considered a significant confound.

2.3.2.4 Behavioural eyetracking

The behavioural eyetracking tasks were conducted in an interview room with images presented on a 17” screen with a resolution of 1024x768, 90cm away from the participant who rested on a chinrest. A computer mouse situated in front of the participant allowed for participant responses during the tasks that required such responses.

2.3.2.5 Magnetic resonance imaging (MRI)

MRI scans were undertaken with the Siemens Tim Trio 3 tesla system with a 32 channel head coil. A 24” screen at the rear of the bore was viewed with the use of a mirror mounted to the head coil. Padding was placed around the participants head to minimise movement, and underneath the head so that all participants’ eyes were as close to the coil as possible to improve eyetracking and to ensure that everyone’s eyes were the same distance to the mirror and subsequently to the monitor (i.e. 10cm from eye to mirror and 115cm from mirror to monitor). A trigger from the MRI scanner through a serial port triggered the commencement of the eyetracking tasks. Participants held a button box in their right hand to navigate through instruction slides and to make responses during the tasks.

During each functional run of the active tasks, $T_2^*$-weighted images (1080 images per run of the emotional faces task, and 612 images per run of the prosaccade/antisaccade/no-go saccade task) depicting BOLD contrasts were acquired oblique to the commissural plain using an interleaved multiband sequence (multiband acceleration factor= 4, bandwidth= 25988 Hz/Px, repetition time (TR)= 710ms, echo time (TE)= 30ms, echo spacing= 0.51ms, flip angle= 52°, field of view= 222mm,
voxel resolution= 3x3x3mm, slice orientation= transversal, slice thickness= 3mm, number of slices= 44). During the resting state task, T2*-weighted images depicting BOLD contrasts were acquired continuously using an interleaved multiband sequence (multiband acceleration factor= 6, bandwidth= 1860 Hz/Px, TR= 870ms, TE= 30ms, echo spacing= 0.69ms, flip angle= 55°, field of view= 192mm, voxel resolution= 2x2x2mm, slice orientation= transversal, slice thickness= 2mm, number of slices= 66). Multiband acquisition sequences were derived from the Human Connectome Project (Moeller et al., 2010). Multiband acquisition sequences were utilised in both active and resting state tasks to increase power as a greater number of samples are collected within a significantly reduced repetition time, which was particularly beneficial for the prosaccade/antisaccade/no-go saccade task which consisted of very short trial times. A T1-weighted image was acquired sagitally for anatomical reference (bandwidth= 170 Hz/Px, TR= 1900ms, TE= 2.52ms, echo spacing= 7.5ms, flip angle= 9°, field of view= 256mm, voxel resolution= 1x1x1mm, slice orientation= sagittal, slice thickness= 1mm).

2.3.2.6 Magnetoencephalography (MEG)

MEG was recorded with the Elekta Neuromag TRIUX, equipped with 102 triple-sensor elements evenly distributed over the head and 306 independently sampled sensors configured in the helmet array. Images were presented on a rear-projected screen measuring 22”, 115cm in front of the participant. MEG recordings were undertaken during a fixation task and a prosaccade/antisaccade/no-go saccade task. The results of the prosaccade/antisaccade/no-go saccade task in the MEG are not presented in this thesis, nor are the MEG results for the fixation task. However, eyetracking results during the fixation task in the MEG are presented in Chapter 9.

2.4 Procedure

Participants were asked to complete three sessions at Swinburne University of Technology. At the beginning of the first session, the study was reintroduced again in detail and questions welcomed. Participants then completed the study PICF and the CAGEMIS databank PICF in the presence of an independent witness (see Appendix D). Participants also completed Swinburne’s MRI and MEG pre-scan checklist and consent forms (see Appendix D). A detailed screen was then undertaken to ensure that
participants met the eligibility criteria to participate and that they possessed no other characteristics that would likely be a potential confound (see 2.2.3). All participants were administered the MINI, which was used as a screening tool for Axis I psychiatric conditions in the control group and to indicate comorbid conditions in the patient group. Participants were then administered the MADRS and were asked to fill out a clinical demographic record. Participants were then administered the WTAR and MATRICS. All participants’ BMI were also recorded in the first session, but were not revealed to participants. Participants also undertook a short imaging scan, either MEG or MRI, to familiarise them with the scanning procedure and to reduce the overall scanning time in the other two sessions. The scan that participants completed in the first session was counterbalanced between participants. If the MRI scan was completed (‘short MRI’), participants first underwent an anatomical scan, then an ‘eyes open’ resting state scan (fixating on a white fixation cross on a black background), followed by a social processing task (which was used for another project), and a DWI scan which is not reported in this thesis. If the MEG was completed in the first session (‘short MEG’), the same social processing task was undertaken by participants (which was used for another project). Following the first session, participants were given a pack of questionnaires which they were asked to complete before their next session including the EDE-Q, FRS, DASS, PDQ-4, BIS-11 and TAS-20.

The second and third sessions were counterbalanced between participants and involved MEG and MRI scans. During the MRI session (‘long MRI’), participants completed three runs of a prosaccade/antisaccade/no-go (PAN) saccade task, followed by an anatomical scan, and two runs of an implicit emotional faces task. The order of tasks remained consistent between participants. The reason for this is that the PAN saccade task is more cognitively demanding than the faces task and performance is significantly affected by fatigue. Choosing to have the structural scan between the saccade and faces task enabled an additional rest period between active tasks. Eyetracking was performed during the two tasks. Following the scan, participants completed a battery of behavioural eye movement tasks which included an explicit emotional faces task, a memory-guided saccade task, a self-paced saccade task, an implicit biological motion task and an explicit biological motion task. Again, the order of tasks was the same for all participants.
During the MEG session (‘long MEG’), participants completed two eyetracking tasks: a fixation task which required participants to fixate on a white fixation cross on a black background (which also acted as a resting state MEG scan), and six runs of a PAN saccade task. If participants completed the ‘short MRI’ during the first session, they also completed the social processing task (used for another study) in the MEG at the end of this session. If participants completed the ‘short MEG’ in the first session, they also completed the ‘short MRI’ (as described above) following the PAN saccade task in the MEG during this session. Prior to the conclusion of the second session, participants who scored above the threshold for any personality disorder as measured by the PDQ-4 were administered the PDQ-4 Clinical Significance Scale.

The time commitment was approximately three hours for the first session, and between two and two and a half hours each for the second and third sessions, with breaks as required. All participants were reimbursed AUD$100 for their time and any expenses they may have incurred due to their participation. AN participants also received taxi vouchers to and from the testing venue. Participants who were inpatients at the time of testing were escorted in the taxi to and from the testing venue by the researcher.
Chapter 3: Participant Information

The following chapter describes general participant information to reduce repetition throughout the thesis. The results for the 24 AN and 24 control participants who completed all three sessions are reported.

3.1 Apriori power calculations

Participants were assigned to the AN or control group based on pre-existing AN. Target sample sizes were calculated with the use of G*Power 3.0.10. Utilising a large effect size of 0.60 and an alpha of 0.05, excellent statistical power of 0.96 would be achieved with a total of 40 participants. The target sample size was further supported by a study undertaken by Desmond and Glover (2002) who suggest a sample size of 12 for fMRI studies to achieve 80% power at the single voxel level for typical activations with a liberal alpha threshold of 0.05. Using a more conservative alpha of 0.002, a sample size of 21 is suggested.

3.2 Statistical analysis

Statistical analysis on behavioural data was carried out with IBM SPSS Statistics 21. Parametric and nonparametric analyses were undertaken as appropriate. Parametric analyses were carried out with analyses of variance (ANOVAs) and categorical analyses were undertaken with chi-square tests of independence. Continuous variables which violated the assumptions of an ANOVA were analysed with Mann-Whitney U tests. Specific statistical analyses are further described in each of the relevant chapters.

3.3 Demographic characteristics

All participants were female, aged between 16 and 44 years, spoke English as their primary language, and resided in Melbourne, Australia. Age did not significantly differ between groups (AN: M= 23.07, SD= 6.88; controls: M= 22.83, SD= 3.16; F(1,46)= 0.02, p= 0.878). Marital status also did not significantly differ between
groups with 91.67% of AN participants reporting their marital status as single, relative to 75% of healthy control participants ($\chi^2(2)= 2.69, p= 0.261$).

Control participants were found to have undertaken more years of fulltime education than AN participants, though barely reaching statistical significance at p < 0.05 (AN: M= 14.77, SD= 2.15; controls: M= 16.04, SD= 1.76; F(1,46)= 4.23, p= 0.045). As described in Figure 3.1, the majority of participants reported ‘currently studying’ as their highest level of education. All of the healthy control participants who were currently studying were studying at a tertiary level, whereas all but three AN participants who were currently studying were studying at a tertiary level. These three AN participants were still undertaking secondary education at the time of testing. A similar number of participants in each group had received a tertiary qualification. Unlike the control participants, several AN participants reported a trade qualification or secondary school as their highest level of formal education. Groups did not significantly differ in highest education level attained ($\chi^2(4)= 3.22, p= 0.522$).

Furthermore, current employment status did not differ between groups ($\chi^2(3)= 4.84, p= 0.184$) and is described in Figure 3.2. The majority of participants in both groups reported their employment status as students. A small number of participants in each group were in full-time employment, and a small percentage of AN participants were unemployed due to their medical condition.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.1.png}
\caption{Highest level of education reported by participants}
\end{figure}
3.4 Medical history

All AN participants had been externally diagnosed with AN by a psychologist or psychiatrist. One AN participant had also been formally diagnosed with BN. No AN participants had been diagnosed with BED or EDNOS. No control participants had been diagnosed with an eating disorder.

The average age of AN onset was 16.04 years (SD= 3.50), and the average illness duration was 6.67 years (SD= 7.66). Treatment duration was on average 3.65 years (SD= 2.75) at the time of testing. At the time of testing, the majority of AN participants were not receiving regular treatment in the form of inpatient or day patient care, but were receiving outpatient treatment with a private practitioner or were not receiving treatment/between treatment programs (Figure 3.3).
As would be expected, AN participants and controls significantly differed in BMI (AN: M= 16.52, SD= 1.14; controls: M= 22.55, SD= 3.59; F(1,46)= 61.57, p < 0.001, Cohen’s d= 2.26). Amenorrhea did not exclude individuals with AN from participating (as described below), and 20.8% were found to be currently cycling, with an additional 8.3% taking hormonal contraceptives and also cycling.

All control participants were required to be free of medication, excluding hormonal contraceptives, which 45.8% were taking. Of the 24 AN participants, all but six were taking some type of medication. The average number of different medications was 1.58 (SD= 1.25). A list of medications and the number of AN participants taking each medication type is reported in Table 3.1.
Table 3.1

*Number of anorexia nervosa participants taking different medications*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal contraceptive</td>
<td>3</td>
</tr>
<tr>
<td>SSRI</td>
<td>11</td>
</tr>
<tr>
<td>SNRI</td>
<td>3</td>
</tr>
<tr>
<td>NaSSA</td>
<td>1</td>
</tr>
<tr>
<td>Melatonergic antidepressant</td>
<td>2</td>
</tr>
<tr>
<td>Benzodiaepine</td>
<td>5</td>
</tr>
<tr>
<td>Cyclopyrrolane</td>
<td>1</td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>10</td>
</tr>
<tr>
<td>Cephalosporin antibiotic</td>
<td>1</td>
</tr>
<tr>
<td>Antifibrinolytic</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: SSRI= selective serotonin reuptake inhibitor; SNRI= selective norepinephrine reuptake inhibitor; NaSSA= noradrenergic and specific serotonergic antidepressant

Additionally, all participants were asked whether they had specific areas of body concern. All but one AN participant reported yes, relative to 20.83% of control participants reporting a specific area of body concern, and the groups significantly differed ($\chi^2(1)= 27.77, p < 0.001$). The frequency of reported areas of concern are detailed in Table 3.2. For those who endorsed specific areas of body concern, the average number of areas of concern was 5.45 (SD= 2.19) for AN participants, and 1.80 (SD= 1.30) for control participants.
Table 3.2

Number of participants expressing areas of body concern

<table>
<thead>
<tr>
<th>Area</th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Back</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Body hair</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Buttocks, hips, thighs</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Cheeks, cheekbones</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest, breasts</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Chin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ears</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eyes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Face (in general)</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Facial hair</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Feet</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Forehead</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitals</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hair</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hands/fingers</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Jaw</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Legs</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Mouth, lips, teeth</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nose</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Muscle tone (in general)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Shoulders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Waist, stomach</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa
3.5 Neuropsychological test battery

All participants were administered a battery of neuropsychological tests. The WTAR, MINI and MADRS were administered to all participants. The remaining assessments were taken home and returned by participants during their second session. The WTAR was used as a measure of premorbid intelligence and scores were not found to differ between groups (AN: M= 104.67, SD= 8.19; controls: M= 105.67, SD= 7.14; F(1,46)= 0.20, p= 0.654).

3.5.1 Clinical assessment

Axis I psychiatric disorders were explored with the MINI. As described in Chapter 2, control participants found to have an Axis I disorder with the use of the MINI were excluded from the study. Therefore, all of the 24 control participants who completed the study did not have any Axis I disorders. All AN participants met the criteria for AN, with the exception of the amenorrhea criterion. The study began with the use of the MINI for DSM-IV and for consistency was utilised throughout the study. As the amenorrhea criterion is no longer included in the diagnostic criteria of the DSM-5, participants were not required to meet this criterion. AN participants were also found to have a number of comorbid Axis I disorders, detailed in Table 3.3. The average number of Axis I disorders was 4.63 (SD= 2.65). The items used for this calculation are detailed in Table 3.3.
Table 3.3

*Number of anorexia nervosa participants meeting criteria for Axis I diagnoses as scored by the Mini International Neuropsychiatric Interview (MINI)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive episode (^a)</td>
<td>17</td>
</tr>
<tr>
<td>Current</td>
<td>17</td>
</tr>
<tr>
<td>With melancholic features</td>
<td>11</td>
</tr>
<tr>
<td>Recurrent</td>
<td>6</td>
</tr>
<tr>
<td>Dysthymia (^a)</td>
<td>14</td>
</tr>
<tr>
<td>Suicidality (^a)</td>
<td>18</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>High</td>
<td>6</td>
</tr>
<tr>
<td>(Hypo) Manic episode (^a)</td>
<td>4</td>
</tr>
<tr>
<td>Hypomaniac episode</td>
<td>2</td>
</tr>
<tr>
<td>Current</td>
<td>0</td>
</tr>
<tr>
<td>Past</td>
<td>2</td>
</tr>
<tr>
<td>Manic episode</td>
<td>2</td>
</tr>
<tr>
<td>Current</td>
<td>1</td>
</tr>
<tr>
<td>Past</td>
<td>2</td>
</tr>
<tr>
<td>Panic disorder</td>
<td></td>
</tr>
<tr>
<td>Lifetime panic disorder</td>
<td>10</td>
</tr>
<tr>
<td>Lifetime panic disorder with limited symptom attacks</td>
<td>6</td>
</tr>
<tr>
<td>Current panic disorder</td>
<td>3</td>
</tr>
<tr>
<td>Current agoraphobia</td>
<td>11</td>
</tr>
<tr>
<td>Current panic disorder without agoraphobia (^a)</td>
<td>1</td>
</tr>
<tr>
<td>Current panic disorder with agoraphobia (^a)</td>
<td>3</td>
</tr>
<tr>
<td>Agoraphobia without a history of panic disorder (^a)</td>
<td>7</td>
</tr>
<tr>
<td>Social anxiety disorder (^a)</td>
<td>8</td>
</tr>
<tr>
<td>Generalised</td>
<td>7</td>
</tr>
<tr>
<td>Non-generalised</td>
<td>1</td>
</tr>
<tr>
<td>Disorder</td>
<td>Frequency</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>12</td>
</tr>
<tr>
<td><em>Obsessions</em></td>
<td>11</td>
</tr>
<tr>
<td><em>Compulsions</em></td>
<td>14</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>4</td>
</tr>
<tr>
<td>Alcohol abuse and dependence</td>
<td>2</td>
</tr>
<tr>
<td><em>Dependence</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Abuse</em></td>
<td>0</td>
</tr>
<tr>
<td>Substance abuse and dependence</td>
<td>1</td>
</tr>
<tr>
<td><em>Dependence</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Abuse</em></td>
<td>0</td>
</tr>
<tr>
<td>Psychotic disorders and mood disorders with psychotic features</td>
<td>0</td>
</tr>
<tr>
<td><em>Mood disorder with psychotic features</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Lifetime</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Current</em></td>
<td>0</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>0</td>
</tr>
<tr>
<td><em>Current</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Lifetime</em></td>
<td>0</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>24</td>
</tr>
<tr>
<td><em>Binge eating/purging type</em></td>
<td>1</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>3</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>17</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: items marked *a* were used to calculate the average number of comorbid psychiatric illnesses in the anorexia nervosa group.
Axis II personality disorders were explored with the PDQ-4. The results are presented in Table 3.4. AN participants scored significantly higher on total PDQ score, as well as items related to schizoid, borderline, avoidant, dependent, obsessive compulsive, negativistic and depressive personality disorders. Whether the items reached clinical significance was also explored and the results are detailed in Table 3.5. AN participants were more likely than control participants to have a clinically significant personality disorder ($\chi^2$(1)= 24.13, p < 0.001). The average number of clinically significant personality disorders for the AN group was 2.46 (SD= 1.74) and 0.17 (SD= 0.38) for the control group (F(1,48)= 39.55, p < 0.001, Cohen’s d= 1.82).

Table 3.4

*Personality Diagnostic Questionnaire (PDQ-4) scores*

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th>U</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid</td>
<td>3.00</td>
<td>1.00</td>
<td>5.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoid</td>
<td>2.50</td>
<td>0.00</td>
<td>4.00</td>
<td>102.00</td>
<td>-3.93</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>2.00</td>
<td>1.00</td>
<td>5.00</td>
<td>228.50</td>
<td>-1.26</td>
</tr>
<tr>
<td>Histrionic</td>
<td>2.00</td>
<td>2.00</td>
<td>3.00</td>
<td>237.00</td>
<td>-1.09</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>1.00</td>
<td>2.00</td>
<td>5.00</td>
<td>215.00</td>
<td>-1.55</td>
</tr>
<tr>
<td>Borderline</td>
<td>4.50</td>
<td>1.00</td>
<td>3.00</td>
<td>36.00</td>
<td>-5.26</td>
</tr>
<tr>
<td>Antisocial</td>
<td>1.00</td>
<td>1.00</td>
<td>2.00</td>
<td>208.00</td>
<td>-1.73</td>
</tr>
<tr>
<td>Avoidant</td>
<td>6.00</td>
<td>2.00</td>
<td>4.00</td>
<td>38.50</td>
<td>-5.21</td>
</tr>
<tr>
<td>Dependent</td>
<td>4.00</td>
<td>1.00</td>
<td>3.00</td>
<td>46.00</td>
<td>-5.07</td>
</tr>
<tr>
<td>Obsessive compulsive</td>
<td>5.00</td>
<td>3.00</td>
<td>5.00</td>
<td>150.50</td>
<td>-2.88</td>
</tr>
<tr>
<td>Negativistic</td>
<td>2.00</td>
<td>1.00</td>
<td>4.00</td>
<td>143.00</td>
<td>-3.07</td>
</tr>
<tr>
<td>Depressive</td>
<td>5.50</td>
<td>2.50</td>
<td>7.00</td>
<td>50.00</td>
<td>-4.97</td>
</tr>
<tr>
<td>Total PDQ score</td>
<td>38.00</td>
<td>19.00</td>
<td>26.00</td>
<td>50.00</td>
<td>-4.91</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; PDQ= Personality Diagnostic Questionnaire
<table>
<thead>
<tr>
<th>Personality disorder</th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Schizoid</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Histrionic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Borderline</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Antisocial</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Avoidant</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Dependent</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Obsessive compulsive</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Negativistic</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Depressive</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa
Eating disorder symptomatology was investigated in all participants with the EDE-Q. AN participants scored significantly higher on all of the EDE-Q subscales and the global EDE-Q score (Table 3.6, Figure 3.4).

Table 3.6

_Eating Disorder Examination Questionnaire (EDE-Q) scores_

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Restraint</td>
<td>4.50</td>
<td>5.40</td>
</tr>
<tr>
<td>Eating concern</td>
<td>4.10</td>
<td>5.00</td>
</tr>
<tr>
<td>Shape concern</td>
<td>5.38</td>
<td>2.88</td>
</tr>
<tr>
<td>Weight concern</td>
<td>4.50</td>
<td>5.40</td>
</tr>
<tr>
<td>Global score</td>
<td>4.74</td>
<td>3.61</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa

_Figure 3.4. Eating Disorder Examination Questionnaire (EDE-Q) median scores_
Furthermore, body image was investigated with the FRS and results are presented in Table 3.7 and Figure 3.5. Ideal figures were significantly thinner in AN, and the figures participants’ felt they looked like were significantly larger in AN. The figures participants’ thought they looked like did not significantly differ between groups even though AN participants’ BMIs were significantly lower. Discrimination scores were also calculated for each of the subscales and are also presented in Table 3.7. AN participants’ ideal figures were significantly thinner than their reported think, feel and men prefer figures, relative to controls. AN participants’ feel figures were also significantly heavier than their think figures, compared to controls.

Table 3.7
Figure Rating Scale (FRS) scores

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Ideal</td>
<td>2.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Think</td>
<td>5.00</td>
<td>7.00</td>
</tr>
<tr>
<td>Feel</td>
<td>7.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Men prefer</td>
<td>4.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Women prefer</td>
<td>2.50</td>
<td>3.00</td>
</tr>
<tr>
<td>Ideal – think</td>
<td>-3.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Ideal – feel</td>
<td>-5.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Ideal – men prefer</td>
<td>-1.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Ideal – women prefer</td>
<td>0.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Think – feel</td>
<td>-2.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Think – men prefer</td>
<td>1.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Think – women prefer</td>
<td>2.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Feel – men prefer</td>
<td>4.00</td>
<td>9.00</td>
</tr>
<tr>
<td>Feel – women prefer</td>
<td>4.00</td>
<td>8.00</td>
</tr>
<tr>
<td>Men prefer – women</td>
<td>1.00</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa
To ascertain current depressive symptoms, the MADRS was administered to all participants and was found to significantly differ between groups (AN: M= 25.33, SD= 10.75; controls: M= 1.00, SD= 1.69; F(1,46)= 119.93, p < 0.001, Cohen’s d = 3.16). Of the 24 control participants, all but one were found to have normal levels of depression/absence of depressive symptoms. One control participant was found to have mild depression. All AN participants were found to have some level of depression, with 41.67% displaying mild symptoms, 33.33% moderate symptoms and 25% demonstrating severe depressive symptoms. The groups significantly differed (χ²(3)= 44.36, p < 0.001).

AN participants were also found to have significantly higher scores on the depression, anxiety and stress subscales of the DASS, relative to controls (Table 3.8). Severity ratings are presented in Figure 3.6, and were found to significantly differ between groups with AN participants reporting more severe symptoms on each of the subscales (depression: χ²(3)= 28.24, p < 0.001; anxiety: χ²(4)= 28.02, p < 0.001; stress χ²(4)= 32.11, p < 0.001).
### Table 3.8

**Depression Anxiety Stress Scale (DASS) scores**

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
<td>U</td>
<td>z</td>
</tr>
<tr>
<td>Depression</td>
<td>25.00</td>
<td>37.00</td>
<td>1.00</td>
<td>16.00</td>
<td>6.00</td>
<td>-5.85</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16.00</td>
<td>36.00</td>
<td>1.50</td>
<td>16.00</td>
<td>50.00</td>
<td>-4.93</td>
</tr>
<tr>
<td>Stress</td>
<td>26.50</td>
<td>41.00</td>
<td>3.00</td>
<td>17.00</td>
<td>32.00</td>
<td>-5.29</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa

---

**Figure 3.6.** Depression Anxiety Stress Scale (DASS) severity ratings

As a number of the tasks to be undertaken were related to impulsivity and emotion processing, the BIS-11 and TAS-20 were also administered to participants to examine whether these constructs influenced the findings. Impulsivity was investigated with the BIS-11, and the AN group were found to score higher on the attention and cognitive instability subscales of the attentional scale, and lower on the motor subscale of the motor scale (Table 3.9). Groups however did not significantly differ on overall BIS scores.
### Table 3.9

**Barratt Impulsiveness Scale (BIS-11) scores**

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td><strong>Attentional</strong></td>
<td>20.00</td>
<td>14.00</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>13.50</td>
<td>12.00</td>
</tr>
<tr>
<td><strong>Cognitive instability</strong></td>
<td>7.00</td>
<td>6.00</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>19.50</td>
<td>14.00</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>12.00</td>
<td>12.00</td>
</tr>
<tr>
<td><strong>Perseverance</strong></td>
<td>7.50</td>
<td>7.00</td>
</tr>
<tr>
<td><strong>Nonplanning</strong></td>
<td>22.50</td>
<td>18.00</td>
</tr>
<tr>
<td><strong>Self-control</strong></td>
<td>11.00</td>
<td>14.00</td>
</tr>
<tr>
<td><strong>Cognitive complexity</strong></td>
<td>11.50</td>
<td>9.00</td>
</tr>
<tr>
<td><strong>Total BIS score</strong></td>
<td>61.00</td>
<td>34.00</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; BIS= Barratt Impulsiveness Scale

The TAS-20 was administered to participants to investigate group differences on the alexithymia construct. AN participants were found to score significantly higher on each subscale of the TAS-20 (Table 3.10). Utilising empirically designed cut-off scores, the majority of AN participants were found show high alexithymia, compared to controls who demonstrated mainly low alexithymia scores (Table 3.11) \( (\chi^2(2)= 25.07, p < 0.001)\).
Table 3.10

*Toronto Alexithymia Scale (TAS-20) scores*

<table>
<thead>
<tr>
<th></th>
<th>AN Median</th>
<th>Range</th>
<th>AN Median</th>
<th>Range</th>
<th>U</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty identifying</td>
<td>22.00</td>
<td>23.00</td>
<td>11.00</td>
<td>15.00</td>
<td>43.50</td>
<td>-5.06</td>
<td>0.001</td>
</tr>
<tr>
<td>feelings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty describing</td>
<td>19.00</td>
<td>14.00</td>
<td>10.00</td>
<td>14.00</td>
<td>53.00</td>
<td>-4.86</td>
<td>0.001</td>
</tr>
<tr>
<td>feelings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Externally oriented thinking</td>
<td>19.50</td>
<td>13.00</td>
<td>18.00</td>
<td>22.00</td>
<td>184.50</td>
<td>-2.15</td>
<td>0.032</td>
</tr>
<tr>
<td>TAS score</td>
<td>62.50</td>
<td>31.00</td>
<td>41.00</td>
<td>41.00</td>
<td>39.50</td>
<td>-5.13</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; TAS= Toronto Alexithymia Scale

Table 3.11

*Number of participants with high, low and intermediate Toronto Alexithymia Scale (TAS-20) scores*

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>High alexithymia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Low alexithymia</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Intermediate alexithymia</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa

3.6 Summary

AN and healthy control groups were well matched for age, demographic characteristics and premorbid intelligence. Due to the recruitment procedure, all control participants were free of Axis I psychiatric disorders. A small number of control participants were found to have Axis II personality disorders, though the incidence of personality disorders was much greater in AN participants. The AN group were also found to have greater levels of state depression, anxiety and stress.
than healthy controls, and demonstrated significantly higher eating disorder symptomatology and body image concerns than control participants. As the nature of some of the tasks described in the following chapters can be related to behavioural impulsivity and the ability to process emotions, these constructs were briefly explored. Overall, impulsivity was not found to differ between groups, though AN participants showed more attentional impulsivity and less motor impulsivity than control participants. Processing of emotions within the self was also explored and AN participants were found to score higher on the alexithymia construct than controls, particularly in identifying and describing feelings within the self.

The findings of this chapter will be explored further in relation to the behavioural tasks described in the empirical chapters to follow.
Chapter 4: Cognition

Investigations of cognition in AN have revealed that while some aspects of cognition remain unaltered during the course of AN, others can differ dramatically from the norm during the acute state and during recovery. Intelligence quotient (IQ) scores are generally found not to differ in individuals with AN compared with healthy controls (Gillberg, Råstam, Wentz, & Gillberg, 2007; Steinglass, Walsh, & Stern, 2006). However, overall IQ scores combine performance on a number of different measures and do not address different aspects of cognition separately. The following section aims to summarise the key findings in a range of cognitive domains in AN.

4.1 Cognition in anorexia nervosa

4.1.1 Cognitive shifting and flexibility

Individuals with AN are often observed to have rigid thinking patterns and be opposed to change (Strober, 2004). Correspondingly, a common feature of AN is perfectionism, which has been identified as a significant risk factor for the illness, and is a feature found to persist following long-term recovery (Bastiani et al., 1995; Fairburn, Cooper, et al., 1999). Thus, cognitive assessments reported in the AN literature have often focused on tasks related to perfectionism and rigid thinking patterns, such as cognitive set shifting tasks (M. Wu et al., 2014). During tasks which require changes in behaviour in response to shifts in cognitive set, such as certain target detection tasks and the WCST, individuals with AN perform significantly poorer than healthy controls, displaying stereotyped behaviours with rigid approaches to changing rules (Fassino, Pieró, et al., 2002; McAnarney et al., 2011; Steinglass et al., 2006; Tchanturia, Anderluh, et al., 2004; Tchanturia, Serpell, Troop, & Treasure, 2001; Zastrow et al., 2009). Research undertaken by Zastrow et al. (2009) indicated that during behavioural response shifting, a group of individuals with AN had reduced activation of the ventral-anterior cingulate-striato-thalamic loop, an area involved in motivation related behaviour, relative to the control group. Additionally, the patient group demonstrated increased activation of fronto-parietal areas during behavioural response shifting, which may reflect effortful cognitive control during task performance. Discordant sister-pairs of individuals with and without AN have also
been reported to have more set-shifting difficulties than healthy individuals (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005), implying a possible genetic or familial contribution to the behaviour. Furthermore, recovered AN patients have been reported to continue displaying poorer performance, though to a lesser extent than when in the ill state, on tasks of cognitive shifting and flexibility (Tchanturia, Morris, et al., 2004), suggesting a trait rather than state effect.

Though other cognitive domains have also been investigated in AN, they have been of lesser focus and have produced largely inconsistent findings.

4.1.2 Speed of processing, psychomotor speed and reaction time

Individuals with AN in the ill state of the condition have been reported to show deficits in reaction time and psychomotor speed. Studies utilising finger tapping tasks have revealed slower reaction times and poorer overall performance in AN groups (M. W. Green, Elliman, Wakeling, & Rogers, 1996; Hatch et al., 2010b). Whether performance on this task improves following weight recovery remains unclear with some authors reporting improvements (Hatch et al., 2010b) and others who report continuing deficits (Bosanac et al., 2007). The effects of starvation have been implicated as a possible contributing factor to these results (M. W. Green et al., 1996). In addition, these findings have also been suggested to potentially involve the dopaminergic system and BG as they are involved in motor function (Bosanac et al., 2007). However, different types of reaction time tasks have suggested that individuals with AN may have superior psychomotor speed in comparison to healthy individuals. AN participants have been shown to demonstrate faster reaction times and psychomotor speed on drawing and copying tasks than healthy controls (G. L. M. Pieters et al., 2005; G. L. M. Pieters et al., 2003), which persists after weight recovery (G. L. M. Pieters et al., 2005). Therefore, from these studies it appears that individuals with AN may display enhanced psychomotor speed on simple visuomotor tasks, but poorer performance on pure motor tasks.
4.1.3 Problem solving and decision making

Relative to healthy individuals, individuals with AN have been found to be impaired on tasks assessing decision making (Brogan, Hevey, & Pignatti, 2010). A measure commonly used to assess decision making capabilities is a gambling task which assesses the ability to balance immediate rewards against long-term negative consequences. Individuals ill with AN have been found to display deficits in performing such tasks (Cavedini et al., 2004; Tchanturia et al., 2007). Additionally, AN patients who performed better on a decision making gambling task in the ill state have been found to have significantly greater improvement of nutritional status following treatment (Cavedini et al., 2006). Individuals with AN have also been found to be impaired on problem solving tasks including the Austin maze test, and the object assembly and block design subscales of the Wechsler Adult Intelligence Scale (WAIS) (Gillberg et al., 2010; Lauer, Gorzewski, Gerlinghoff, Backmund, & Zihl, 1999; Szmukler et al., 1992; Tokley & Kemps, 2007). Furthermore, AN participants post-treatment have been shown to have improved problem solving abilities (Lauer et al., 1999). In addition, individuals with AN have been reported to show deficits in strategic planning when completing tasks (Sherman et al., 2006). A factor likely to influence the problem solving and decision making deficits reported in groups of AN participants, is a preoccupation with detail that is often reported in individuals with AN (Tokley & Kemps, 2007).

4.1.4 Memory

Individuals with AN are often found to have deficits in memory storage and retrieval. Numerous studies have demonstrated impaired immediate and delayed verbal and non-verbal recall (M. W. Green et al., 1996; Mathias & Kent, 1998; Ohrmann et al., 2004; Seed, Dixon, McCluskey, & Young, 2000; Sherman et al., 2006), though other studies have reported no such deficit (Chui et al., 2008; Key et al., 2006; Nandrino, Doba, Lesne, Christophe, & Pezard, 2006). Following weight recovery, individuals with AN have been found to improve on measures of recall and perform at the same level as healthy controls (Jones, Duncan, Brouwers, & Mirsky, 1991; Kingston et al., 1996; Moser et al., 2003).
One component of memory that has been frequently shown to be affected in AN is working memory. The concept of working memory can be further divided into three components, the episodic buffer, phonological loop and visuospatial sketchpad. A study by Kemps, Tiggemann, Wade, Ben-Tovim, and Breyer (2006) investigated whether different components of working memory are affected in AN. AN participants were not impaired on recall of object names, a measure assessing the phonological loop component of working memory. They were however found to perform poorly on the location of objects, the visuospatial component of working memory; and the combined recall of objects and locations, a central executive deficit in working memory. At long-term follow-up, Gillberg et al. (2010) indicated that those recovered from AN had poorer working memory ability than controls, as measured by the working memory index of the WAIS. However, a study by Bosanac et al. (2007) found no differences in working memory, specifically the phonological loop and visuospatial sketchpad components, in the ill or recovered states of AN. A recent fMRI study by Castro-Fornieles et al. (2010) found while there were no differences in task performance between groups of individuals with AN and healthy controls, the AN group demonstrated significantly increased activity in the temporal and parietal areas, particularly the superior temporal gyrus, while performing a working memory task. A subgroup of patients were reassessed following seven months of treatment and weight recovery and were found to have decreased activation in these areas while performing the task, and activations did not differ in comparison to controls. It was suggested that additional effort may need to be employed by individuals with AN in the ill state to perform at a normal level, which may not be required in the weight-recovered state. Additionally, individuals in the ill state of AN have been reported to show deficits in inhibition of irrelevant information during a recall task, which significantly improves with weight restoration (Hatch et al., 2010b).

4.1.5 Inhibition and impulsivity

High levels of perfectionism have consistently been reported for individuals with AN (Bastiani et al., 1995; Halmi et al., 2000; Srinivasagam et al., 1995), and a particular component of perfectionism that appears to be elevated in individuals with AN is a concern over making mistakes (Bulik et al., 2003). Self-report studies have often indicated that individuals with AN are less impulsive than healthy individuals.
(G. K. L. Butler & Montgomery, 2005; Claes, Vandereycken, & Vertommen, 2002; W. H. Kaye, Bastiani, & Moss, 1995; Rosval et al., 2006). G. L. M. Pieters et al. (2007) found that in addition to scoring highly on perfectionism and controlled response style measures, AN participants made significantly fewer errors than controls on a speeded choice-reaction task, suggesting reduced impulsivity. However, several other behavioural studies have reported no difference in impulsivity in AN compared to healthy individuals, though, a number of studies have reported increased impulsivity in this group. A study by Southgate, Tchanturia, and Treasure (2008) indicated that a group of individuals with AN did not differ on impulsiveness from controls on the matching familiar figures test, but were found to be more efficient in their responses evident by superior accuracy and shorter response times. However, when distinguishing AN by the presence or absence of binge-purge behaviours, individuals with AN-BP have been found to be more impulsive than individuals AN-R and healthy controls on performance on this task (Toner, Garfinkel, & Garner, 1987). On a go/no-go task, a task of inhibition and impulse control, individuals recovered from AN have been found to not differ on performance in comparison to healthy controls (T.A. Oberndorfer et al., 2011). The recovered patient group did, however, show reduced medial prefrontal cortex activation in comparison to controls as inhibition trials became more difficult, but did not differ from controls when the trials were easier. These results suggest a demand-specific modulation of inhibitory control circuitry in individuals recovered from AN. However, other go/no-go studies and other impulse control paradigms in individuals ill with AN have demonstrated significantly higher impulsivity in comparison to healthy individuals, evident through more errors of commission and shorter response latencies, suggesting a speed-accuracy trade-off in AN, in favour of speed (G. K. L. Butler & Montgomery, 2005; Hatch et al., 2010b).

4.1.6 Visuospatial processing and visual learning

A number of recent studies have reported that individuals with AN display disturbances in a range of visual processing tasks (Gillberg et al., 2007; Jones et al., 1991; Kingston et al., 1996). Although improvements in visuospatial processing have been reported following weight recovery (Jones et al., 1991; Kingston et al., 1996), a more recent investigation reported persistent problems at long term follow-up
(Gillberg et al., 2007). Furthermore, significant difficulties in visual discrimination learning, a dopaminergic function, have been reported in AN in comparison to healthy controls (A. D. Lawrence et al., 2003). As dopamine lesions lead to anorexia in animals and the dopaminergic system is involved in reward, the researchers suggest that these results may provide further evidence for the role of dopaminergic system in the psychopathology of AN. During tasks of visual learning however, in which visual reproduction of geometric shapes is required, individuals with AN have been reported to not differ in performance to healthy individuals (Chui et al., 2008; Key et al., 2006). Intact performance on tasks such as the Rey-Osterrieth Complex Figure task in AN (Andrés-Perpiña et al., 2011; Kingston et al., 1996), further supports the findings of intact visual learning in AN.

4.1.7 Attention/vigilance and attentional bias

Individuals suffering from AN are commonly found to be impaired on measures of attention (Bosanac et al., 2007; Jones et al., 1991; Kingston et al., 1996; Lauer et al., 1999; Seed et al., 2000; Szmukler et al., 1992). Although some investigations report improvements with recovery (Jones et al., 1991; Lauer et al., 1999; Szmukler et al., 1992), others report that attentional problems continue to exist (Kingston et al., 1996). Individuals with AN are also found to show differences in attentional bias. A common task used to assess attentional bias to different stimuli is a variant of the classic Stroop task, the Emotional Stroop task, where participants are required to ignore the semantic content of the word and report the colour of the ink. Research has consistently indicated that words of emotional significance take longer to process than neutral words, and the effect has been demonstrated for a number of disorder-relevant stimuli in a variety of illnesses (see J. M. G. Williams, Mathews, & MacLeod, 1996 for a review). Although findings for the classic Stroop task are inconsistent in the AN literature (Ferro et al., 2005; Steinglass et al., 2006), numerous studies have demonstrated an Emotional Stroop effect among this group. Two different types of stimuli are often utilised to assess attentional bias in eating disordered individuals: stimuli related to food and eating, and stimuli related to body shape and weight. Individuals with AN have been found to be significantly slower at naming the colour of both food-related and body-related words than healthy individuals (D. I. Ben-Tovim & Walker, 1991; D. I. Ben-Tovim, Walker, Fok, & Yap,
1989; Long, Hinton, & Gillespie, 1994; Perpiñá, Hemsley, Treasure, & De Silva, 1993). Furthermore, in a study by Redgrave et al. (2008) the researchers presented an Emotional Stroop task consisting of fat, thin, and neutral words, and words made of XXXXs, to AN participants and healthy controls during fMRI. The AN group had increased reaction times in the fat and thin conditions, and demonstrated greater activation in the left insula, frontal and temporal cortices, and the left middle and medial frontal gyri than controls on the thin versus XXXX stimuli contrast. In the fat versus XXXX stimuli contrast, control participants displayed greater activation in the left DLPFC and right parietal areas in comparison to the AN group. The authors suggested that these results may be related to different mechanisms underlying attentional bias in AN which differ under conditions of positive or negative valence.

4.1.8 Social cognition

Although individuals with AN often demonstrate an impairment in social functioning (Tchanturia et al., 2013), whether this deficit is related to poor social cognitive abilities is unclear. Little research has been undertaken in the area of social cognition in AN, though the limited studies have reported poorer performance on the Reading the Mind in the Eyes (RME) task, where participants are presented with a set of eyes and are required to indicate from a list of words what the person is thinking or feeling (Harrison, Sullivan, Tchanturia, & Treasure, 2009; T. A. Russell, Schmidt, Doherty, Young, & Tchanturia, 2009), and a cartoon task developed by Happé, Winner, and Brownell (1998) which assesses theory of mind (T. A. Russell et al., 2009). Adenzato, Todisco, and Ardito (2012) and Tchanturia, Anderluh, et al. (2004) reported comparable performance between AN and healthy control participants in the RME and cartoon tasks respectively. In the Reading the Mind in the Voice (RMV) task, individuals with AN have demonstrated poorer performance than recovered AN and healthy control individuals (Oldershaw, Hambrook, Tchanturia, Treasure, & Schmidt, 2010). The same study also reported poorer performance in AN participants than recovered AN participants in the Reading the Mind in the Films (RMF) task. Furthermore, across the RME, RMV and RMF, individuals with AN showed poorer performance for negative emotions relative to recovered patients and healthy participants, and poorer performance for positive emotions than the control group. The recovered AN group, however, performed similarly to the healthy control group.
Social cognition in AN has recently also been studied with the use of functional neuroimaging. In this study, Schulte-Rüther, Mainz, Fink, Herpertz-Dahlmann, and Konrad (2012) administered a theory of mind task in which shapes were presented in a ‘social’ (suggesting contingent interactions) or ‘non-social’ (circling figures or figures that performed physical movements) manner. The patient group was tested at admission to hospital and at discharge following weight recovery and were required to indicate whether they thought the figures ‘were friends’. Relative to controls and irrespective of time point, the AN group demonstrated reduced middle and anterior temporal cortex, and prefrontal cortex activity to the social relative to the non-social stimuli, suggesting a neural contribution to the social cognitive profile in AN.

4.2 Cognition in anorexia nervosa: conclusions

The literature assessing different cognitive domains in AN has thus far been rather limited, and the findings to date are often inconsistent. As AN is often associated with highly perfectionistic traits, investigations into cognitive performance in AN have often focused on tasks related to perfectionism and rigid thinking patterns, such as cognitive set shifting tasks (M. Wu et al., 2014). Individuals with AN have been found to perform significantly more poorly than healthy individuals during tasks of cognitive set shifting such as the WCST and certain target detection tasks, displaying stereotyped behaviours with rigid approaches to changing rules (McAnarney et al., 2011; Steinglass et al., 2006; Zastrow et al., 2009). Unlike has been undertaken in other psychiatric illnesses, however, there is a paucity of research employing more comprehensive assessments of cognitive profile in AN. Studies of cognition in AN have tended to use a range of cognitive assessments rather than utilising a standard cognitive battery, and have consequently reported conflicting findings (e.g. Chui et al., 2008; Gillberg et al., 2010; Gillberg et al., 2007; Jones et al., 1991; Kingston et al., 1996; Lauer et al., 1999; Mathias & Kent, 1998; Ohrmann et al., 2004; Szmukler et al., 1992; S. B. N. Thompson, 1993). Although cognitive batteries have been compiled in past research to assess cognition in AN (e.g. Jones et al., 1991; Kingston et al., 1996), a standardised cognitive battery has rarely been used (e.g. Hatch et al., 2010b). Therefore, the use of a standard neurocognitive battery, such as the Measurement and Treatment Research to Improve Cognition in
Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al., 2008), would be advantageous and would also allow for direct comparisons to be drawn between AN and other clinical populations. The MATRICS was originally designed to assess cognitive domains most relevant to schizophrenia and related disorders, but has since been applied to assess cognitive impairments in other psychiatric illnesses, including bipolar disorder (BD) (Van Rheenen & Rossell, 2014), posttraumatic stress disorder (J. L. Kaye et al., 2014) and MDD (Murrough et al., 2014).

4.3 Current study aims and hypotheses

The aim of this study was to utilise a comprehensive battery of tasks to investigate cognitive performance in AN. The MATRICS was administered to participants assessing the seven cognitive domains of speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition. Though the cognitive findings in AN to date are largely inconsistent, several studies have reported poorer cognitive performance in a range of cognitive domains. Therefore, it was hypothesised that individuals with AN would show poorer performance on tasks assessing each of the cognitive domains, except the tasks assessing speed of processing and visual learning, where the literature has tended to report intact performance to date. We further completed exploratory analyses of performance on each of the tasks in AN given that the MATRICS was originally designed to examine cognitive profile in people with schizophrenia, who are reported to show substantial cognitive problems. Individuals with AN were not expected to show such extreme deficits, and thus may only show impairment at the individual task level rather than at the level of cognitive domains overall.

4.4 Method

4.4.1 Participants

Twenty-six individuals with AN and 27 healthy control individuals completed the cognitive battery. Clinical and demographic characteristics for the additional two AN and three control participants who did not complete the entire study but completed the MATRICS are included in Appendix E.
4.4.2 Materials

4.4.2.1 Cognitive battery

The MATRICS Consensus Cognitive Battery was administered to participants as it is a comprehensive battery of cognitive tasks. The MATRICS assesses seven cognitive domains with the use of 10 different tasks (see Appendix C).

4.4.2.1.1 Speed of processing

Speed of processing is assessed with the Brief Assessment of Cognition in Schizophrenia: Symbol Coding (BACS: SC) task, Category Fluency: Animal Naming (Fluency) task and the Trail Making Test: Part A (TMT-A). The BACS: SC task is a paper-and-pencil test which involves using a key to write digits that correspond to nonsense symbols. The key consists of nine nonsense symbols labelled a number from 1 to 9. Below the key, nonsense symbols are presented in a random order. The participant is required to match and report as many nonsense symbols as they can in 90 seconds working from left to right without skipping any symbols. The raw score is achieved by simply counting the number of correctly matched symbols. The maximum number of correct responses is 110. Participants also begin with a practice trial of 10 nonsense symbols.

The fluency task requires participants to orally report as many animals as they can in 60 seconds. The number of animals reported constitutes the raw score.

Finally, the TMT-A is a paper-and-pencil test which requires participants to draw a line connecting consecutive numbers from 1 to 25 irregularly placed on a sheet of paper as quickly as possible. The task is discontinued after 300 seconds. The raw score is equivalent to the amount of time in seconds required to complete the task. The task also begins with a practice trial containing numbers of 1-8.

4.4.2.1.2 Attention/vigilance

Attention/vigilance is tested with the Continuous Performance Test – Identical Pairs (CPT-IP), a computer-based task of sustained attention in which numbers are
flashed on the screen for 50ms and participants are required to click the mouse when the same number appears consecutively. The CPT-IP task was presented on a 17.3” laptop, with external mouse. Prior to the commencement of the task, participants complete a short practice trial. The task begins with a two-digit condition, followed by 3- and 4-digit conditions. Each condition consists of 150 trials in which the total number of possible hits is 30, the total number of possible false alarms is also 30, and total number of possible random responses is 90. The number of hits, false alarms and random responses are reported as a proportion of the total number possible for that response type, and the mean and standard deviation of reaction time (ms) for each response type is reported. The primary summary scores for the 2-, 3- and 4-digit subtests are reported, as is the overall summary score, which represent the ability to discriminate identical pairs from nearly identical pairs.

4.4.2.1.3 Working memory

Nonverbal working memory is assessed with the Wechsler Memory Scale (WMS®-III): Spatial Span. Verbal working memory is assessed with the Letter-Number Span (LNS) task. The Spatial Span task is a visual analogue to the digit span test. The Spatial Span task involves the use of a Spatial Span Board which features 10 cubes. In the ‘forward’ subtest, the administrator taps the cubes in a specified sequence at a rate of one cube per second and the respondent is required to tap the blocks in the same sequence. The ‘forward’ subtest consists of eight items, each with two trials. The first item begins with a sequence of two blocks. Each subsequent item consists of one extra block in the sequence, therefore reaching a nine-block sequence at item eight. Participants are awarded one point for each complete correct sequence reproduced and no points if an error is made or all of the correct cubes are not tapped. The test is discontinued once the respondent fails to correctly reproduce both trials in an item. The ‘backward’ subtest is then administered in the same manner except participants are now required to reproduce the sequence in the reverse order. The maximum number of correct responses overall is 32, 16 for each of the forward and backward sections.

The LNS is a task of verbal working memory which requires the mental reordering of orally presented lists of intermixed letters and numbers. In this task, a
list of letters and numbers is read out to respondents. The respondent is required to mentally reorder the sequence and verbally report the sequence beginning with the numbers from smallest to largest, followed by the letters in alphabetical order. The task consists of six trials, each containing four items. The first trial begins with a 2-symbol sequence. Each subsequent trial has an additional symbol leading to a 7-symbol sequence by the final trial (trial 6). A score of one is awarded for each correct response and a score of zero for each incorrect response. The task is discontinued once all four items on a trial are incorrect. The total number of correct responses is 24. The task also begins with a practice trial.

4.4.2.1.4 Verbal learning

Verbal learning is tested with the Hopkins Verbal Learning Test – Revised (HVLT-R™). A list of 12 words from three semantic categories (four-legged animals, precious stones and human dwellings) are read out to respondents at a rate of one word every two seconds. Respondents are then required to report as many words as they can remember, in any order. The words are then read out a second time and participants are required to again report as many words as they can remember in any order, including words they reported in the previous trial. The word list is then read out a third time, and participants are once again required to report as many words as they can remember in any order, including words they reported in the previous trials. A score of one is awarded for each correctly reported word for each trial. A delayed recall trial is then administered following a period of 20-25 minutes in which participants are undertaking other cognitive tasks. The respondent is not instructed about a delayed memory component following the third trial, and is required to report as many words as they can remember without the word list being read out to them again. A delayed recall score is obtained, and a retention score is calculated by dividing the score for trial 4 (delayed recall) by the higher score of trials 2 and 3, multiplied by 100. A longer list of 24 words is then read out to participants containing the original 12 words, as well as six semantically-related words and six semantically-unrelated words, to assess delayed recognition. The respondent is required to report whether the word read out was on the original list of words or not. The number of true-positives, semantically-related false positives and semantically-unrelated false
positive errors is reported. A recognition discrimination index score is calculated by the total number of true positives minus the total number of false positives.

4.4.2.1.5 Visual learning

Visual learning is assessed with the Brief Visuospatial Memory Test – Revised (BVMT-R™). In this task, six geometric figures are presented for 10 seconds to participants. Participants are required to draw each figure exactly as it appeared and its correct location on the page after the 10 second presentation. Following trial 1, the respondent’s booklet is turned to a clean page and trial 2 is administered, followed by trial 3. Trials 2 and 3 involve the same procedure as trial 1. Each of the six shapes in each trial receives one point for accuracy and one point for correct placement. Although not a component of the MATRICS, following a period of 20-25 minutes in which participants are completing other cognitive tasks, the participants were asked to draw the figures again from memory. The delayed trial was scored in the same way as trials 1-3, and a retention score was calculated by dividing the score for trial 4 (delayed recall) by the higher score of trials 2 and 3, multiplied by 100. Form 1 of the test was used for all participants.

4.4.2.1.6 Reasoning and problem solving

Reasoning and problem solving is assessed with the Neuropsychological Assessment Battery (NAB®): Mazes task. In this task, a set of seven mazes of increasing difficulty is administered to participants. Participants are required to work through each maze as quickly as possible. The score received for each maze is determined by the speed in which it is completed. The maximum score for the first three mazes is two points each, and five points each for the remaining four mazes. A maze is discontinued if the respondent reaches the maximum amount of time allowed for that maze. A maximum score of 26 is achievable.

4.4.2.1.7 Social cognition

Social cognition is evaluated with the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™): Managing Emotions. The task consists of two
subtests, the Emotion Management task which measures the ability to incorporate one’s own emotions into decision making; and the Social Management task which measures the individual’s ability to incorporate emotions into decision making that involves other people. The tasks involve the respondent rating the effectiveness of alternative actions or responses in achieving a certain result in situations where an individual must regulate their emotions. Participants are presented with eight different scenarios. In each scenario a list of three to four actions/responses are presented. The participant is required to report how effective they think each action is in relation to that scenario on a Likert scale ranging from very ineffective (1) to very effective (5). The task is traditionally presented orally to participants, but was presented as a paper-pencil questionnaire for convenience. The score for each action is entered into the scoring program to produce raw and standard scores for the two subtests and an overall Managing Emotions Score.

4.4.2.1.8 Additional tasks

To achieve an even more comprehensive cognitive battery, participants also completed the Trail Making Test: Part B (TMT-B) and a digit span task, which were included under the speed of processing and working memory domains, respectively (but did not contribute to the cognitive domain scores calculated by the MATRICS scoring program). TMT-B is a paper-and-pencil test which requires participants to draw a line connecting consecutive numbers and letters in ascending order by alternating from number to letter (i.e., 1-A-2-B-3-C, and so on.). Numbers from 1-12 and letters from A-L are irregularly placed on a sheet of paper and participants are required to complete the task as quickly as possible. The raw score is equivalent to the amount of time in seconds required to complete the task. The task also begins with a practice trial containing numbers of 1-4 and letters A-D. A derived difference score is also calculated (TMT-B – TMT-A) allowing for the executive component of attentional switching to be isolated from processing speed effects. A ratio score is also computed by dividing the TMT-B score by the TMT-A score.

A digit span task was administered in the same manner as the Spatial Span task. Sequences of single digit numbers were verbally presented to participants at a rate of one digit per second. Participants were then required to verbally report the
sequence in the same order. The ‘forward’ subtest consists of eight items, each with two trials. The first item begins with a sequence of two digits. Each subsequent item consists of one extra digit in the sequence, therefore reaching a nine-digit sequence at item eight. Participants are awarded one point for each complete correct sequence reported and no points if an error is made. The test is discontinued once the respondent fails to correctly report both trials in an item. The ‘backward’ subtest is then administered in the same manner except participants are now required to report the sequence in the reverse order. The maximum number of correct responses overall is 32, 16 for each of the forward and backward sections.

4.4.2.2 MATRICS Consensus Cognitive Battery (MCCB) scoring

The following scores from the above tests are entered into the MATRICS Consensus Cognitive Battery (MCCB) scoring program: TMT-A raw score, BACS: SC raw score, HVLT-R™ trials 1-3 raw scores (summed by the program), WMS III®: Spatial Span total raw score, LNS raw score, NAB® Mazes raw score, BVMT-R™ trials 1-3 raw scores (summed by the program), Fluency raw score, MSCIET™ Managing Emotions standard score, and the d’ scores for trials 1-3 of the CPT-IP (averaged by the program). A t-score and a percentile score are calculated for each task. A t-score and a percentile score are also calculated for each cognitive domain. The scores were not corrected for age, gender or education level by the program, but as discussed in Chapter 3, groups were matched on these characteristics.

4.4.2.3 Statistical analysis

A multivariate analysis of variance (MANOVA) was conducted on the seven cognitive domain scores across groups. One way ANOVAs were used on each of the task variables to compare group performance, with alpha set at 0.01 to account for multiple comparisons.

4.4.3 Procedure

The cognitive tasks were administered during the first session. Each task was explained to participants and questions welcomed prior to their commencement. The order of tasks was as follows: TMT-A, TMT-B, BACS: SC, HVLT-R™, WMS III®:
Spatial Span, digit span, LNS, NAB® Mazes, BVMTR™, Fluency, MSECIT™ Managing Emotions, CPT-IP. The delayed component of the HVLT-R™ was administered 20-25 minutes following its initial administration, typically following the LNS. The delayed component of the BVMT-R™ was administered after 20-25 minutes, typically following the CPT-IP. The administration of the cognitive task took between 60-90 minutes to complete, with breaks as required.

4.5 Results

The following section describes the results from the cognitive assessments. Following normality checking and the removal of outliers, a MANOVA was carried out on the data and the results are presented separately for each cognitive domain. The results of the MANOVA did not reveal a significant group difference in cognitive domain scores (F(1,45)= 0.73, p= 0.649). The results from the one way ANOVAs for each task variable are presented in the sections below.

4.5.1 Speed of processing

As described in Table 4.1, group analyses revealed that AN and healthy control participants did not differ on the overall speed of processing domain, or on any of the speed of processing tasks individually.
Table 4.1

*Speed of processing domain scores*

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th></th>
<th></th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>BACS: SC</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>63.23</td>
<td>9.80</td>
<td>68.11</td>
<td>9.19</td>
<td>3.50</td>
<td>0.067</td>
<td>0.51</td>
</tr>
<tr>
<td>T-score</td>
<td>55.00</td>
<td>9.29</td>
<td>59.56</td>
<td>8.79</td>
<td>3.37</td>
<td>0.072</td>
<td>0.50</td>
</tr>
<tr>
<td>Percentile score</td>
<td>63.72</td>
<td>26.27</td>
<td>76.97</td>
<td>23.09</td>
<td>3.82</td>
<td>0.056</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>28.19</td>
<td>6.43</td>
<td>27.19</td>
<td>5.54</td>
<td>0.37</td>
<td>0.544</td>
<td>0.17</td>
</tr>
<tr>
<td>T-score</td>
<td>58.54</td>
<td>11.78</td>
<td>56.85</td>
<td>10.23</td>
<td>0.31</td>
<td>0.580</td>
<td>0.15</td>
</tr>
<tr>
<td>Percentile score</td>
<td>71.13</td>
<td>30.30</td>
<td>69.44</td>
<td>29.33</td>
<td>0.04</td>
<td>0.838</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>TMT-A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw score</td>
<td>23.62</td>
<td>5.75</td>
<td>21.30</td>
<td>4.83</td>
<td>2.54</td>
<td>0.117</td>
<td>0.44</td>
</tr>
<tr>
<td>T-score</td>
<td>53.50</td>
<td>8.18</td>
<td>56.56</td>
<td>7.71</td>
<td>1.96</td>
<td>0.168</td>
<td>0.39</td>
</tr>
<tr>
<td>Percentile score</td>
<td>59.86</td>
<td>24.16</td>
<td>69.25</td>
<td>20.27</td>
<td>2.36</td>
<td>0.131</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>TMT-B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT derived</td>
<td>40.09</td>
<td>12.72</td>
<td>38.07</td>
<td>11.21</td>
<td>0.38</td>
<td>0.543</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>TMT derived difference score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT ratio score</td>
<td>1.76</td>
<td>0.57</td>
<td>1.85</td>
<td>0.58</td>
<td>0.30</td>
<td>0.587</td>
<td>0.16</td>
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<td><strong>Domain score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T-score</td>
<td>57.42</td>
<td>9.75</td>
<td>59.85</td>
<td>7.80</td>
<td>1.01</td>
<td>0.320</td>
<td>0.28</td>
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<tr>
<td>Percentile score</td>
<td>70.47</td>
<td>27.20</td>
<td>78.26</td>
<td>19.44</td>
<td>1.45</td>
<td>0.235</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Note: *a* signifies scores used to calculate the speed of processing domain score; TMT-A and TMT-B scores are reported in seconds; AN= anorexia nervosa; BACS: SC= Brief Assessment of Cognition in Schizophrenia: Symbol Coding; Fluency= Category Fluency: Animal Naming; TMT-A= Trail Making Task Part A; TMT-B= Trail Making Task Part B; Derived difference score= TMT-B – TMT-A; Ratio score= TMT-B/TMT-A
4.5.2 Attention/vigilance

Groups were not found to differ on overall performance on the CPT-IP task, but AN participants were found to have increased average reaction times for false alarm responses in three-digit component of the task \((F(1,51)= 11.37, \ p < 0.001,\) Cohen’s \(d= 0.93\)), and the task overall \((F(1,51)= 12.80, \ p < 0.001,\) Cohen’s \(d= 0.98\)). A trend for increased reaction times of false alarm responses for the two-digit component was also apparent \((F(1,51)= 5.324, \ p= 0.025,\) Cohen’s \(d= 0.63\)) (Table 4.2).
Table 4.2
Attention/vigilance domain scores

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td><strong>CPT-IP</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 digit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hits proportion</td>
<td>0.97</td>
<td>0.05</td>
<td>0.98</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>Hits reaction time M</td>
<td>510.13</td>
<td>58.04</td>
<td>490.51</td>
<td>52.45</td>
<td>1.67</td>
</tr>
<tr>
<td>Hits reaction time SD</td>
<td>112.85</td>
<td>40.13</td>
<td>93.43</td>
<td>28.27</td>
<td>4.17</td>
</tr>
<tr>
<td>False alarms proportion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False alarms reaction time M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False alarms reaction time SD</td>
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</tr>
<tr>
<td>Random responses proportion</td>
<td></td>
<td></td>
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<td>Random responses proportion</td>
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<tr>
<td>d’</td>
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Table 4.2 cont’d

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<td><strong>Overall</strong></td>
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<td>0.09</td>
<td>0.06</td>
<td>1.04</td>
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<td>147.39</td>
<td>369.98</td>
<td>133.55</td>
<td>12.80</td>
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<td>False alarms reaction time SD</td>
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<td>36.02</td>
<td>53.85</td>
<td>32.24</td>
<td>3.98</td>
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<tr>
<td>Random responses proportion</td>
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<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>T-Score</td>
<td>43.42</td>
<td>8.08</td>
<td>46.85</td>
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<td>2.27</td>
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<tr>
<td>Percentile score</td>
<td>30.84</td>
<td>22.34</td>
<td>41.41</td>
<td>24.22</td>
<td>2.73</td>
</tr>
</tbody>
</table>

Note: a signifies scores used to calculate the attention/vigilance domain score; reaction times are reported in milliseconds; AN= anorexia nervosa; CPT-IP= Continuous Performance Test – Identical Pairs
4.5.3 Working memory

AN and control groups were not found to differ on the overall working memory domain score, nor the working memory tasks individually. A trend for AN participants to show poorer performance on the backward component of the WMS®-III: Spatial Span task was found (F(1,51)= 5.88, p = 0.019, Cohen’s d= 0.67) (Table 4.3).

Table 4.3

Working memory domain scores

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<td>M</td>
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<td>WMS®-III: Spatial Span</td>
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<td>Forward raw score</td>
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<td>Backward raw score</td>
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<td>1.80</td>
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<tr>
<td>Total raw score a</td>
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<tr>
<td>T-score</td>
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<td>29.51</td>
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<tr>
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<td>T-score</td>
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<tr>
<td>Digit Span</td>
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<tr>
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<td>2.14</td>
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<tr>
<td>Backward raw score</td>
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<td>1.83</td>
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<td>Total raw score</td>
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<td>3.30</td>
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<td>T-score</td>
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<td>9.68</td>
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<td>Percentile score</td>
<td>66.72</td>
<td>27.32</td>
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</table>

Note: a signifies scores used to calculate the working memory domain score; AN= anorexia nervosa; WMS®-III: Spatial Span= Wechsler Memory Scale: Spatial Span; LNS= Letter Number Span
4.5.4 Verbal learning

AN and control groups did not differ on any components of the verbal learning task, or overall domain score (Table 4.4).

Table 4.4

Verbal learning domain scores

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<th>Controls</th>
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<tr>
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<tr>
<td>Trial 1 recall score</td>
<td>8.42</td>
<td>8.22</td>
<td>1.84</td>
<td>1.25</td>
<td>0.22</td>
<td>0.643</td>
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<td>0.13</td>
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<td>Trial 2 recall score</td>
<td>10.35</td>
<td>9.89</td>
<td>1.50</td>
<td>1.69</td>
<td>1.08</td>
<td>0.303</td>
<td>0.29</td>
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<td>Trial 3 recall score</td>
<td>10.62</td>
<td>10.33</td>
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<td>1.75</td>
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<td>0.539</td>
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<td>3.82</td>
<td>1.48</td>
<td>0.229</td>
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<td>Number of true positives</td>
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<td>Number of semantically-related false positives</td>
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<td>0.63</td>
<td>0.85</td>
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<td>0.01</td>
<td>0.927</td>
<td>0.02</td>
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<tr>
<td>Number of semantically-unrelated false positives</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Total number of false positive errors</td>
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<td>0.85</td>
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<td>Total true positives - total false positives</td>
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<td>T-score</td>
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Note: *a* signifies scores used to calculate the verbal learning domain score; AN= anorexia nervosa; HVLT-R™= Hopkins Verbal Learning Test – Revised
4.5.5 Visual learning

AN and control participants were not found to differ on any of the visual learning task components or the visual learning domain score (Table 4.5).

Table 4.5

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<td>SD</td>
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<td>9.77</td>
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Note: \textsuperscript{a} signifies scores used to calculate the visual learning domain score; AN= anorexia nervosa; BVMT-R\textsuperscript{TM}= Brief Visuospatial Memory Test – Revised
4.5.6 Reasoning and problem solving

As described in Table 4.6, groups did not differ on reasoning and problem solving.

Table 4.6
*Reasoning and problem solving domain scores*

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<th></th>
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</tr>
<tr>
<td>T-score</td>
<td>55.15</td>
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<td>58.11</td>
<td>7.11</td>
<td>1.95</td>
<td>0.169</td>
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<td>65.20</td>
<td>26.41</td>
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<td>21.40</td>
<td>2.08</td>
<td>0.156</td>
<td>0.40</td>
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</table>

Note: a signifies scores used to calculate the reasoning and problem solving domain score; AN= anorexia nervosa; NAB®: Mazes= Neuropsychological Assessment Battery Mazes task
4.5.7 Social cognition

AN and control participants did not differ on social cognition scores (Table 4.7).

Table 4.7

<table>
<thead>
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<th>Social cognition domain scores</th>
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<th>Cohen’s d</th>
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<td>SD</td>
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<td>SD</td>
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<td>0.106</td>
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<td>0.10</td>
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</tr>
<tr>
<td>Raw score</td>
<td>0.42</td>
<td>0.04</td>
<td>0.40</td>
<td>0.07</td>
<td>0.99</td>
<td>0.323</td>
</tr>
<tr>
<td>Standard score ^a</td>
<td>96.98</td>
<td>5.92</td>
<td>95.41</td>
<td>9.57</td>
<td>0.51</td>
<td>0.477</td>
</tr>
<tr>
<td>Domain score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-score</td>
<td>49.42</td>
<td>6.93</td>
<td>48.07</td>
<td>10.86</td>
<td>0.29</td>
<td>0.594</td>
</tr>
<tr>
<td>Percentile score</td>
<td>47.98</td>
<td>23.91</td>
<td>46.42</td>
<td>31.05</td>
<td>0.04</td>
<td>0.839</td>
</tr>
</tbody>
</table>

Note: ^a signifies scores used to calculate the social cognition domain score; AN= anorexia nervosa; MSCEIT™: Managing Emotions= Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions
4.5.8 Overall cognition

Groups did not differ on overall MATRICS scores (Table 4.8).

<table>
<thead>
<tr>
<th>Overall composite domain score</th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>MATRICS overall composite score</td>
<td>54.31</td>
<td>7.97</td>
</tr>
<tr>
<td>T-score</td>
<td>63.35</td>
<td>24.97</td>
</tr>
<tr>
<td>Percentile score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; MATRICS= Management and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery

4.6 Discussion

The aim of this study was to explore cognitive performance in AN. The AN group were hypothesised to show poorer performance on tasks assessing each of the cognitive domains, except the tasks assessing speed of processing and visual learning. Analyses revealed largely non-significant group differences overall, and in each of the cognitive domains. The findings for each cognitive domain are discussed separately below.

4.6.1 Speed of processing

As hypothesised, performance on the speed of processing domain and each of the tasks comprising the domain were not found to significantly differ between AN participants and controls. Poorer performance on both the TMT-A and –B tasks has been reported in AN by several investigators (Jones et al., 1991; Kingston et al., 1996; Nikendei et al., 2011; Szmukler et al., 1992; Tchanturia, Anderluh, et al., 2004), though others have failed to find any significant group differences (Andrés-Perpiña et
al., 2011; Mathias & Kent, 1998; Steinglass et al., 2006). Furthermore, one study reported poorer performance on TMT-B but not TMT-A (S. B. N. Thompson, 1993). Following treatment, TMT-A performance has been found to improve (Lauer et al., 1999), though poorer TMT-B performance has been found in weight-recovered AN relative to controls, with weight-recovered individuals not differing in performance to underweight patients with AN-R (Nikendei et al., 2011). Findings with the use of digit symbol tasks appear to be more consistent, with performance in AN not typically differing to healthy individuals (Andrés-Perpiña et al., 2011; Key et al., 2006; Mathias & Kent, 1998; Szmukler et al., 1992). One study, however, found poorer symbol coding performance in underweight AN which improved with re-feeding (Kingston et al., 1996), whereas another study reported superior performance in AN in the underweight and weight-restored states relative to healthy individuals (G. Pieters et al., 2004). Furthermore, intact fluency task performance has been consistently found in AN (Andrés-Perpiña et al., 2011; Hatch et al., 2010b; Mathias & Kent, 1998; Tchanturia, Anderluh, et al., 2004).

4.6.2 Attention/vigilance

The CPT-IP task was found to result in one significant finding. Individuals with AN were found to not differ to controls in the proportion of correct hits, false alarms or random responses. Groups also did not differ in reaction times to correct hits. Reaction time on false alarm trials did differ between groups, with significantly slower reaction times on the three-digit component, and a trend for increased reaction times on the two-digit component of the task. However, this finding is somewhat limited as only a small proportion of false alarms were elicited in each group. A lack of significant group differences has also been reported in a small number of studies examining CPT-IP performance in AN (Bradley et al., 1997; Jones et al., 1991). During a sustained attention task similar to the CPT-IP, the rapid visual information processing task, AN participants have been found to show poorer performance in relation to the proportion of hits and false alarms, but did not differ in reaction times to healthy controls (Fowler et al., 2006).
4.6.3 Working memory

The cognitive battery administered included three tasks of working memory: a spatial span task, an LNS task and a digit span task. The lack of significant differences between group on the LNS and digit span tasks are consistent with previous studies that have also reported intact performance on letter-number span (Gillberg et al., 2010) and digit span tasks in AN (Andrés-Perpiña et al., 2011; Gillberg et al., 2010; Key et al., 2006). Furthermore, a recent study by Hatch et al. (2010b) reported no group differences in the forward component of the digit span task, but superior performance in AN during the backward component. At weight recovery, AN participants were found to perform better than healthy individuals in both the forward and backward components of the task. The findings of typical working memory performance in AN in the current study are contrary to a number of other reports of poorer working memory in AN utilising different tasks (e.g. M. W. Green et al., 1996; Sherman et al., 2006).

Although AN and control participants did not differ in overall performance on the spatial span task, a trend for AN participants to perform poorer on the backward component of the task relative to controls was found. A study by Fowler et al. (2006) also reported intact overall spatial span performance in AN, but did not report whether AN and healthy individuals differed in the forward or backward components of the task. The result of the present study differ to that reported in neurodegenerative disorders such as Alzheimer’s disease and that of normal age-related decline, which result in poorer performance in both components of the task (Carlesimo, Fadda, Lorusso, & Caltagirone, 1994; Hester, Kinsella, & Ong, 2004). The forward component is thought to represent the capacity of the visuospatial sketchpad, whereas the backward component of this task is thought to represent a measure of executive function as it requires additional manipulation within temporary storage (Hester et al., 2004), suggesting that individuals with AN have specific working memory difficulties when the cognitive demand is high. This deficit appears to be specific to visuospatial working memory as LNS and digit span performance was intact in this cohort. Working memory deficits specific to visuospatial working memory have also been reported by Kemps et al. (2006), who found AN participants were poorer at recalling object locations, but did not differ in the recall of object names compared to healthy
individuals. Poorer capacity to manipulate and process visuospatial material may also be related to the specific visuospatial processing deficits experienced in AN, in which patients overestimate the size of their own body (Tovée, Emery, & Cohen–Tovée, 2000).

4.6.4 Verbal learning

Related to working memory are tasks of verbal learning. AN participants were not found to significantly differ from control participants on any aspect of the HLVT-R task in this study. Utilising the same task, Chui et al. (2008) also reported intact verbal learning performance in AN. Intact immediate and delayed verbal learning performance has also been demonstrated with the use of similar verbal learning tasks in the underweight state and at weight-recovery (Andrés-Perpiña et al., 2011; Hatch et al., 2010b; Lauer et al., 1999; Mathias & Kent, 1998; Steinglass et al., 2006; Szmukler et al., 1992), though others have reported poorer immediate and delayed recall in underweight (M. W. Green et al., 1996; Nikendei et al., 2011; Ohrmann et al., 2004) and weight-recovered AN (Nikendei et al., 2011).

4.6.5 Visual learning

As hypothesised, participants with AN were also not found to demonstrate any deficits on the BVMT-R™. Using similar tasks of visual reproduction, studies by Chui et al. (2008) and Key et al. (2006) also found no deficit in immediate or delayed reproduction of geometric shapes in AN. Performance on the Rey-Osterrieth Complex Figure task, which utilises similar visuospatial memory abilities, has also been found not to differ between AN and healthy individuals (Andrés-Perpiña et al., 2011; Kingston et al., 1996), though other studies has reported poorer performance in AN (Mathias & Kent, 1998; Stedal, Rose, Frampton, Landrø, & Lask, 2012). As a distortion in the way one’s physical appearance is perceived exists in AN, visuospatial processing deficits may exist in the condition. However, the results from this study and previous research suggest that visuospatial memory of simple stimuli remains intact in AN.
4.6.6 Reasoning and problem solving

The mazes task also requires visuospatial processing to an extent. Similarly to performance on the other cognitive tasks, AN participants were not found to differ from controls. Intact maze performance has also been reported in the underweight state of AN (Hatch et al., 2010b; Kingston et al., 1996; Mathias & Kent, 1998), and superior performance in the weight-recovered state relative to controls (Hatch et al., 2010b). A study by Szmukler et al. (1992) has however reported poorer performance in AN on the Austin maze test. Additionally, AN participants have been reported to show deficits in other tasks assessing problem solving abilities such as object assembly and block design tasks (Gillberg et al., 2007; Tokley & Kemps, 2007).

4.6.7 Social cognition

Social cognition in AN is scarcely studied, despite apparent problems with social functioning in AN (Tchanturia et al., 2013). In the only other study utilising an emotional intelligence task in AN, Hambrook, Brown, and Tchanturia (2012) also used the MSCEIT and administered the entire task to groups of AN and control participants. Similarly to the findings of the current study, AN participants were not found to differ from control participants on the managing emotions branch of the MSCEIT. Additionally, Hambrook et al. (2012) reported similar performance to that of controls for the other branches, namely, perceiving emotions, using emotions and understanding emotions. The AN group were, however, found to have significantly lower total MSCEIT scores than control participants, suggesting poorer overall emotional intelligence in AN.

4.6.8 Summary and conclusions

Overall, the results from this study suggest intact cognitive performance in AN on the majority of the measures studied, despite significantly low BMIs and the potential long- and short-term effects of starvation. The only cognitive measure which differed between AN and control groups was visuospatial working memory, evident by a trend for poorer performance on the backward component of the spatial span task in the AN group. This result supports the notion that individuals with AN may possess
specific visuospatial processing deficits which influence the evaluation of their own body size and shape, though, this potential relationship would need to be specifically investigated with a sensitive measure of body image distortion.

Contrary to expectations, individuals with AN did not differ in performance to healthy individuals on any overall cognitive domain. Though the AN group were found to make false alarm responses of longer reaction time than the control group, this finding is limited due to the small number of false alarm responses for either group, thereby not allowing accurate statistical analyses to be undertaken. The existing research utilising the same or similar tasks is particularly inconsistent with many studies reporting no cognitive deficits, while others report significantly poorer cognitive performance in AN. The inconsistency in findings may be largely related to differences in methodology, particularly the participants examined. Malnutrition certainly affects cognitive function as reported in studies of induced starvation (Keys, Brozek, & Henschel, 1950a, 1950b). Studies in AN patients often recruit individuals currently undergoing inpatient treatment as they are often easily accessible to researchers. The primary role of most inpatient treatment services is medical stabilisation. Therefore, patients admitted to such services are typically very physically unwell. The majority of patients in this study were outpatients or were not receiving treatment at the time of testing. Furthermore, the few inpatients that were recruited were required to be medically stable due to the large time commitment of the study and because testing was not undertaken within the hospital of inpatient care. Despite all patients recruited for this study being medically stable, their BMIs were significantly below normal and their eating disorder symptomatology significantly high, suggesting that they were in an acute phase of the illness but were physically well enough to function. Therefore, the sample recruited is a significant strength of this study, especially as they were age, gender and IQ matched to the healthy control cohort, resulting in a homogenous sample which is often not achieved in research in AN.

The study is however not without its limitations. The MATRICS is a standard cognitive battery originally compiled to assess the areas of cognition most relevant to schizophrenia and related disorders. Therefore, cognitions often associated with AN, such as cognitive set shifting (Fassino, Pieró, et al., 2002; McAnarney et al., 2011;
Steinglass et al., 2006; Tchanturia, Anderluh, et al., 2004; Tchanturia et al., 2001; Zastrow et al., 2009), were not investigated. As the aim of the study was to investigate general cognition in AN, and the size of the existing cognitive battery and the number of other tasks to be undertaken as part of this study was already lengthy, an additional cognitive set shifting task was not considered feasible. Future research in AN would benefit from including set shifting tasks. Although the MATRICS provides a comprehensive profile of basic cognitive tasks, a battery also including tasks related to the specific cognitive traits commonly associated with AN, and tasks allowing more detailed exploration of executive function would be beneficial in future research.

The findings of this study suggest a cognitive profile in AN different to that of other psychiatric illnesses, such as schizophrenia, BD and MDD, which are all associated with significant cognitive deficits (Heinrichs & Zakzanis, 1998; Sweeney, Kmiec, & Kupfer, 2000). Similar findings to the current study have however been reported in OCD. Intact performance on a range of cognitive tasks have been reported in OCD, and although poorer performance on tasks of spatial working memory have been found in this group (Purcell, Maruff, Kyrios, & Pantelis, 1998), deficits in spatial span performance have not been reported (Krishna et al., 2011; Purcell et al., 1998). Similarly, poor visuospatial working memory has also been reported in body dysmorphic disorder (BDD), another psychiatric illness within the OCD-spectrum with prominent body image disturbance (Deckersbach et al., 2000; Dunai, Labuschagne, Castle, Kyrios, & Rossell, 2010), though poorer performance on tasks of verbal working memory and executive function have also been reported in BDD (Deckersbach et al., 2000; Hanes, 1998). However, unlike the current study, the spatial span task components in these studies were not separated to better investigate visuospatial working memory. The deficits in visuospatial working memory and otherwise intact cognitive performance in OCD illustrates the overlap in clinical presentation that is often reported in AN, and may provide support for the long-proposed hypothesis that AN and OCD share overlapping psychopathology (Halmi et al., 2003; Holden, 1990; W. H. Kaye et al., 1992).

Overall, visuospatial working memory was the only cognitive measure that groups were found to differ on in this study. This finding may be related to AN
patients’ difficulties in evaluating their bodies, but would require further investigation. As cognitive functioning in general appears to remain largely unaltered in AN, it may suggest that the limited cognitive deficits observed may arise from quite restricted brain regions which may also be involved in the psychopathology of AN. With the use of a variety of tasks, the following chapters aimed to explore the functioning of a range of cortical and subcortical brain regions in AN, with a particular focus on visuospatial processing.
Chapter 5: Eye Movements

The visual system is a complex biological system which processes information gathered from visible light to build a representation of the surrounding environment. Light enters the eye via the cornea and through the pupil, onto the retina situated at the back of the eye. The retina is connected to the optic nerve which sends neural signals to the brain. The fovea describes the region of the retina which has the greatest visual resolution. The eyes move to locate stimuli of interest onto this area and keep them there with the use of four different types of eye movements: saccadic, smooth pursuit, vergence and slow stabilising eye movements (Dodge, 1903). Slow stabilising eye movements, namely the vestibular-ocular reflex and the optokinetic reflex, are reflexive movements which act to help hold gaze stationary. Smooth pursuit refers to slow eye movements (<100°/second) which are used to track moving targets. Vergence describes when the eyes converge or diverge when a target moves toward or away from the individual, respectively; whereas saccades are the fast jerky eye movements, typically followed by a period of fixation, that redirect gaze. As humans we use a ‘saccade and fixate’ strategy when viewing our surroundings (Liversedge, Gilchrist, & Everling, 2011), making approximately three to four saccades every second of our waking lives (Ludwig, Gilchrist, McSorley, & Baddeley, 2005).

5.1 Saccade characteristics

Saccadic eye movements are stereotypical and tend to have a characteristic temporal profile. In normal viewing, most saccades do not exceed an amplitude of 15 degrees (Bahill, Adler, & Stark, 1975). For targets that are further in the periphery, the head is involved in redirecting the image onto the fovea (Bahill, Adler, et al., 1975). Accurate saccades can be made in less than 100 milliseconds, with both eyes moving in the same direction with the same amplitude. Saccades begin when the eye is stable, quickly accelerating to a peak velocity followed by a rapid deceleration which then quickly returns to a stable position. The peak velocity and the duration of a saccade are closely related to the amplitude, a relationship that has been termed the main sequence (Bahill, Clark, & Stark, 1975). In laboratory based experiments a number of saccade characteristics are typically examined including the gain or accuracy, latency
and peak velocity, and less frequently the duration of saccades. Gain refers to the accuracy of a saccade onto a target and is calculated by dividing the saccadic amplitude by the target step amplitude. Latency describes the time from stimulus onset to the initiation of a saccades (saccadic reaction time), whereas the duration of a saccade refers to the duration from the beginning to the end of a saccade. Finally, peak velocity refers to the fastest point of a saccade quoted in degrees per second (Liversedge et al., 2011).

5.2 Saccade tasks

A range of tasks based in the laboratory are typically carried out to examine the various saccade characteristics in different populations. Included among these tasks, and which will be the focus of this review, are the prosaccade, antisaccade, go/no-go saccade, memory-guided saccade and self-paced saccade tasks. In the prosaccade task a stimulus is presented and participants make a saccade toward this target (Hallett & Lightstone, 1976). The saccade that is generated is termed a prosaccade or a reflexive saccade, though the later term has caused controversy as it is not by definition a reflexive action. The antisaccade task is a little more complicated. Participants are required to fixate on a central fixation stimulus and a target is presented in the periphery. Participants are required to suppress a prosaccade to the presented stimulus and instead make a saccade to the mirror image of the stimulus, the same distance from the centre but in the opposite direction (Hallett, 1978). A task with similarities to the antisaccade task, in that suppression of a prosaccade is required, is the go/no-go task. In the saccade variant of this task, participants fixate on a central stimulus which will change in one of two ways indicating that a saccade should be made to a peripherally presented stimulus (go) or to remain fixated on the central stimulus and not make a saccade toward the peripheral stimulus (no-go) (Van't Ent & Apkarian, 1999). The memory-guided saccade task (also known as the oculomotor delayed response task) requires participants to fixate on a central stimulus while a target is briefly presented in the periphery. Participants are required to maintain fixation on the central stimulus and produce a saccade to the remembered location following a short delay (C. Pierrot-Deseilligny, S. Rivaud, B. Gaymard, & Y. Agid, 1991). The self-paced saccade task requires repetitive, self-initiated refixations between two stimuli (Abel & Douglas, 2007).
5.3 Physiology of saccadic eye movements

Each eye is controlled by six extraocular muscles. Horizontal eye movements are controlled by the medial and lateral rectus muscles, whereas vertical eye movements are controlled by the superior and inferior rectus muscles, in addition to the superior and inferior oblique muscles. The muscles are innervated by three groups of motor neurons located in the brainstem: the lateral rectus muscles by the abducens nerve, the inferior and superior oblique muscles by the trochlear nerve, and the medial, inferior and superior recti muscles by the oculomotor nerve (Liversedge et al., 2011). The neuronal firing pattern required to produce a saccade is referred to as the pulse-step model. The pulse component involves the sudden increase in neuronal firing level which brings the eyes on target, followed by the step component which involves returning the firing level to a new baseline and holding the eyes in position (Troost, 1983). To produce a saccade, a motor neuron must generate a burst or pulse signal. Specifically, saccadic eye movements are generated in the brainstem with horizontal saccades generated by neurons in the paramedian pontine reticular formation (Keller, 1974), and vertical saccades by neurons in the mesencephalic reticular formation (pulse component) (Buttner-Ennever & Buttner, 1978; Buttner, Buttner-Ennever, & Henn, 1977). For horizontal saccades, the signal then projects to an integrative network including the nucleus prepositus hypoglossi, vestibular nucleus and cerebellum, whereas the signal for vertical saccades project to neurons in the interstitial nucleus of Cajal and the vestibular nucleus (step component) (Sparks, 2002). Additionally, a number of other subcortical and cortical brain areas are involved in the production of saccades including the superior colliculus (SC), BG, thalamus, parietal cortex and frontal cortex.

5.3.1 Subcortical areas

The SC, an area deep within the brain, plays an important role in the generation of saccades. The caudal SC is involved in driving saccades, whereas the rostral SC is involved in maintaining fixation between eye movements (Munoz & Wurtz, 1993a, 1993b, 1995). Neurons in the intermediate SC optimally discharge in relation to saccades of different amplitudes and directions forming an orderly map across the SC, with the largest saccade represented in the caudal SC and the smallest
in the rostral SC (D. A. Robinson, 1972; Schiller & Stryker, 1972). The intermediate SC receives projections from areas in all four cortices including areas such as the frontal eye field (FEF) (Bruce, Goldberg, Bushnell, & Stanton, 1985; Sommer & Wurtz, 2000), supplementary eye fields (SEF) (Shook, Schlag-Rey, & Schlag, 1990), DLPFC (Selemon & Goldman-Rakic, 1988) and the lateral intraparietal lobule (area LIP) (Clower, West, Lynch, & Strick, 2001; Lynch, Graybiel, & Lobeck, 1985). The intermediate SC also receives subcortical projections from the cerebellum, brainstem and BG (Edwards, Ginsburgh, Henkel, & Stein, 1979; Hikosaka, Takikawa, & Kawagoe, 2000). The SC projects to the areas involved in horizontal and vertical saccade premotor circuitry, the paramedian pontine reticular formation and the rostral interstitial nucleus of the medial longitudinal fasciculus (Sparks, 2002). The intermediate SC has also been found to project to the FEF, a projection which relays an internal copy, or corollary discharge, of the saccadic motor command to the cortex prior to the onset of a movement, providing a warning of an impending eye movement. It has been suggested that this projection is responsible for maintaining a stable view of the world in spite of the rapid eye movements humans continually make (Sommer & Wurtz, 2008). There is also evidence to suggest that the SC is involved in encoding information related to reward during reinforcement learning through projections to the substantia nigra pars compacta which carries transient visual activity to the BG dopaminergic system (Comoli et al., 2003).

The BG play an important role in voluntary saccadic eye movements. Most structures of the BG project exclusively to other BG structures, though two output nuclei exist, the globus pallidus internal segment and the substantia nigra pars reticulata, which primarily target the SC, thalamus and pedunculopontine tegmental nucleus (Skinner, Kinjo, Henderson, & Garcia-Rill, 1990). Through the pedunculopontine tegmental nucleus, the BG are involved in spinal cord processing, whereas through thalamic targets the BG play a role in cognitive, motor and sensory cortical information processing (Middleton & Strick, 2000a, 2000b). The main input nucleus of the BG is the striatum which is made up of two components, the caudate and putamen, which together receive inputs from virtually the entire cerebral cortex. Inputs from regions of the prefrontal cortex including the DLPFC, dorsomedial frontal cortex, FEFs and SEFs, and regions of the parietal cortex are of particular importance for saccadic eye movements (Liversedge et al., 2011). Striatal signalling is modulated
by DA input from neurons in the substantia nigra pars compacta, though the ventral striatum also receives DA inputs largely from the ventral tegmental area (VTA).

As mentioned above, the BG project to the thalamus among other areas. The thalamus acts as a link between subcortical structures and the cerebral cortex. All subcortical signals that are sent to the cortex are relayed by neurons in the thalamus. Different nuclei in the thalamus receive inputs from different subcortical areas including the brainstem, BG and cerebellum, and send outputs to the areas of the cortex related to eye movements including the FEF, SEF and lateral prefrontal cortex, which may play a role in regulating the cortical processing for the planning of voluntary eye movements (Liversedge et al., 2011). The thalamus is thought to play at least three roles in the control of eye movements. It is involved in the monitoring of self-generated movements, the planning and generation of volitional or voluntary saccades, and it plays a role in visuospatial attention, which directly guides eye movements (Liversedge et al., 2011). It has been suggested that the thalamus, particularly the internal medullary lamina complex, may be involved in the planning of self-paced saccades as corollary discharge signals may be transmitted for eye movements (Schlag & Schlag-Rey, 1986). The role of the thalamus has also been examined in relation to memory-guided saccades. As the thalamus connects with the prefrontal cortex, it may be involved in prefrontal processes including executive functions such as decision making and working memory. In a study undertaken by Tanibuchi and Goldman-Rakic (2003), the authors reported increased activation during a memory-guided saccade task in the mediodorsal nucleus of the thalamus, suggesting a role of this area in such tasks.

5.3.2 Cortical areas

Though not considered to play a key role in the preparation and production of eye movements, the parietal cortex is involved in visuospatial attention, enhancing sensory guidance and sending projections to regions involved in saccade production (for a review see Andersen, Snyder, Bradley, & Xing, 1997; Bisley & Goldberg, 2003). The parietal eye fields are however involved in triggering prosaccades during gap paradigms (C. H. Pierrot-Deseilligny, S. Rivaud, B. Gaymard, & Y. Agid, 1991). In addition, the posterior parietal cortex, area LIP in particular, sends projections to
areas of oculomotor control, namely the SC and FEF (Andersen, Asanuma, Essick, & Siegel, 1990; Ferraina, Paré, & Wurtz, 2002; Lynch et al., 1985). The posterior parietal cortex also shares reciprocal connections with the prefrontal cortex and has been found to have similar neuronal activation with the prefrontal cortex during memory-guided saccade tasks (Chafee & Goldman-Rakic, 1998, 2000; Gnadt & Andersen, 1988).

The prefrontal cortex is a highly interconnected area which receives inputs from all sensory systems and sends outputs to all sensory and motor systems (see Fuster, 2008 for a review). The prefrontal cortex has been found to play an important role in learning responses associated to different cues. In a study undertaken by Asaad, Rainer, and Miller (1998), the investigators trained monkeys to make specific saccadic responses, either saccade left or right, to different cues. The authors reported that the cues and associated saccadic responses were represented in a group of individual prefrontal neurons. The prefrontal cortex is also responsible for executive functions such as working memory and inhibition of inappropriate responses, including saccades (Roberts, Hager, & Heron, 1994). Human prefrontal cortex lesion studies have reported significantly increased error rates on the antisaccade task (Ploner, Gaymard, Rivaud-Péchoux, & Pierrot-Deseilligny, 2005). Animal studies have located a group of prefrontal neurons that are selective for the suppression of saccades in monkeys (Hasegawa, Peterson, & Goldberg, 2004). A more specific area of the prefrontal cortex, the DLPFC, plays an important role in the control of saccadic eye movements as it has connections with area LIP, the FEF, SC and brainstem oculomotor structures (Liversedge et al., 2011). Additionally, the DLPFC is involved in a number of processes related to saccadic eye movements including spatial working memory, and decisional and inhibitory processes (Pierrot-Deseilligny, Mílea, & Müri, 2004). In a series of studies undertaken by Funahashi and colleagues (Funahashi, Bruce, & Goldman-Rakic, 1989, 1990, 1991, 1993), neurons in the DLPFC were found to show phasic modulations in activity time-locked to the onset of visual stimuli and saccades, and sustained activity during the delay period of a memory-guided saccade task. These studies emphasise the importance of this area in undertaking such tasks.
An area of the prefrontal cortex which also plays a role in saccadic eye movements is the SEF which sends direct projections to essentially all cortical and subcortical areas involved in oculomotor control (Huerta & Kaas, 1990). Though the area is connected with oculomotor circuitry, it does not play a role in the initiation of saccades. Rather, it plays a role in monitoring the context and consequences of eye movements, such as in the go/no-go saccade and antisaccade tasks (Schlag-Rey, Amador, Sanchez, & Schlag, 1997; Stuphorn, Taylor, & Schall, 2000). An area closely related to the SEF which is highly involved in the generation of saccades is the FEF, an area regarded as the main cortical eye field in primates. The FEF is reciprocally connected with contralateral areas of the prefrontal cortex, and with the parietal, temporal and occipital cortices. It receives inputs from subcortical areas of the brain including the SC and the substantia nigra pars compacta, and sends projections to the SC, caudate nucleus, ventromedial putamen and brainstem regions (see Liversedge et al., 2011 for a review). Early studies reported that activation of the FEF occurred following rather than preceding spontaneous saccades, causing doubts as to whether the FEF plays a role in the generation of saccades (Bizzi, 1968; Bizzi & Schiller, 1970). However, more recent studies have demonstrated that the firing of FEF neurons is indeed presaccadic (Bruce & Goldberg, 1985; Bruce et al., 1985; M. E. Goldberg & Bushnell, 1981). Human lesion studies have further reinforced the importance of the FEF in the generation of saccades demonstrated by impaired performance on saccadic tasks in individuals with FEF lesions (Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994). The FEF has also been found to be involved in responses to changes in preparatory set. In a study undertaken by Everling and Munoz (2000), the researchers identified a group of FEF neurons that directly project to the SC and respond differently to variations in preparatory set of prosaccades or antisaccades. Though FEF neurons were found to discharge for both prosaccades and antisaccades, the level of presaccadic activity before the peripheral stimulus appeared was higher for prosaccade trials than antisaccade trials. The investigators suggested that the differences observed in preparatory activity reflect the different preparatory sets required to perform the different types of saccades.

The cerebellum has also been implicated in the control of saccadic eye movements. Areas of the cerebellum, particularly the vermis, flocculus and paraflocculus, are involved in saccadic gain, or the accuracy of saccades onto a target
(Glasauer, 2003; F. R. Robinson & Fuchs, 2001). Although the cerebellum plays a role in the control of saccades, its primary involvement is in vestibular and related optokinetic reflexes (Liversedge et al., 2011). It is however also involved in gaze maintenance (Glasauer, 2003), and dysfunction of the cerebellum can lead to difficulties in fixation stability and intrusive saccades such as square wave jerks (SWJs) (Hotson, 1982).

5.3.3 Physiology conclusions

The great majority of our understanding regarding the physiology of eye movements comes from animal studies, particularly neuronal studies in different species of monkeys. Due to ethical limitations, such studies cannot be carried out in human participants. Therefore, how well these animal models represent the human saccadic system is uncertain. Human studies in the past have focused on individuals with brain lesions, though with advances in neuroimaging technology we may gain a better understanding of the oculomotor structures involved in saccadic eye movements in humans.

5.4 Saccade research in humans

As our current understanding of saccade generation is superior for horizontal saccades than vertical saccades, horizontal saccade tasks are typically utilised in research paradigms. A number of eye movement characteristics are often measured in these tasks including latency, amplitude/gain, peak velocity, and accuracy or error rate.

5.4.1 Reflexive saccade tasks

As previously discussed, reflexive saccade tasks, or prosaccade tasks, are the most basic saccade task which simply require the direction of gaze onto a single onset stimulus. They are generally described as exogenously generated saccades and are almost always faster than endogenously generated saccades, or goal-directed saccades to a non-visible stimulus at the saccade destination, such as antisaccades or memory-guided saccades (Godijn & Theeuwes, 2002; Walker, Walker, Husain, & Kennard,
Though attempts have been made to characterise normal ranges of saccadic parameters such as latency, gain and peak velocity, saccade dynamics appear to be heavily influenced by age. The latencies of prosaccades has been found to be shorter in young adults aged 18-35 years (reported average latencies of approximately 230ms) compared to infants and children up to 18 years (reports of over 400ms and up to 300ms respectively), and older adults aged over 60 years (reports of over 260ms) for saccades up to 30° (Abel, Troost, & Dell'Osso, 1983; Fukushima, Hatta, & Fukushima, 2000; Irving, Steinbach, Lillakas, Babu, & Hutchings, 2006; Munoz, Broughton, Goldring, & Armstrong, 1998; Salman et al., 2006; Yang, Bucci, & Kapoula, 2002). Gain however appears to be somewhat less influenced by age than latency. Infants tend to greatly undershoot the target, with gains as low as 0.5 (Aslin & Salapatek, 1975). By the age of one, saccadic gain substantially improves and tends to approach similar values of adults. Saccades larger than 10° tend to become increasingly hypometric as age increases, going from close to one at age ten to as low as 0.6 in those over 80 years of age (Irving et al., 2006; Salman et al., 2006). For saccades smaller than 10° however, individuals aged below 30 years have been reported to display more hypermetric saccades than those above 30 years (Irving et al., 2006). The effect of age on peak saccadic velocity is still not entirely clear. Typical saccades in healthy adults are exceptionally fast, reaching hundreds of degrees per second and lasting only tens of milliseconds. For all ages, saccadic velocity increases as the magnitude of the saccade increases, but approaches a saturation limit for larger saccades known as the asymptotic peak velocity, or the fastest saccade achievable by an individual (Bahill, Clark, et al., 1975). Various studies have reported lower peak saccadic velocity in infancy, childhood and in those over 60 years of age compared to adults (Abel et al., 1983; Hainline, Turkel, Abramov, Lemerise, & Harris, 1984; Irving et al., 2006; Warabi, Kase, & Kato, 1984), though other studies have failed to report these findings or have reported the opposite effects (Fioravanti, Inchingolo, Pensiero, & Spanio, 1995; Fukushima et al., 2000; Garbutt, Harwood, & Harris, 2006; Munoz et al., 1998).

5.4.2 Volitionally controlled saccade tasks

A number of volitionally controlled saccade tasks exist, including the antisaccade, memory-guided saccade, go/no-go saccade and self-paced saccade tasks.
As described earlier, the antisaccade task requires the suppression of a prosaccade to a peripherally presented stimulus and the initiation of a volitionally controlled saccade in the opposite direction (Hallett, 1978). Despite the apparent simplicity of the task, most individuals will make a small number of errors. An error on the antisaccade task is defined as looking in the direction of the presented stimulus rather than the opposite way. Error rates on the antisaccade task vary across laboratories and studies, but an error rate of approximately 20% has been estimated for healthy individuals (Evdokimidis et al., 2002; Reuter & Kathmann, 2004). Several studies also distinguish between corrected and uncorrected errors (e.g. Crawford et al., 2005; Phillipou, Douglas, Krieser, Ayton, & Abel, 2014). An uncorrected error involves making a saccade to the peripheral stimulus and not correcting the mistake by looking in the opposite direction. A corrected error involves a saccade to the peripheral stimulus which is followed by a saccade to the correct location in the opposite direction. The typical latency for this ‘correction’ saccade is around 130ms following the incorrect saccade (Evdokimidis et al., 2002; Massen, 2004; Tatler & Hutton, 2007). Correct antisaccades tend to have latencies about 100-150ms longer than prosaccades, though antisaccade errors tend to have slightly shorter latencies than prosaccades (Everling & Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004). Antisaccade error rate and latency, however, appear to be influenced by the experimental design employed. Interleaved designs, where the presentation of antisaccade and prosaccade trials are both presented in the same run, produce increased latencies and error rates in comparison to blocked designs which involve the presentation of one condition in each run (Ethridge, Brahmbhatt, Gao, Mcdowell, & Clementz, 2009). Correct antisaccades also have peak velocities approximately 30% slower than prosaccades and correct antisaccades tend to be more hypometric than prosaccades (for reviews see Everling & Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004). Similarly to prosaccade performance, antisaccade performance is also affected by age with increased latencies and error rates in the elderly (Abel & Douglas, 2007; K. M. Butler, Zacks, & Henderson, 1999; C. Klein, Fischer, Hartnegg, Heiss, & Roth, 2000; Olincy, Ross, Youngd, & Freedman, 1997; Sweeney, Rosano, Berman, & Luna, 2001).

Though the go/no-go saccade task is much less widely used than the antisaccade task, it is a useful research tool that is gaining increasing interest. Unlike
the antisaccade task, which requires the inhibition of a reflexive response and the
initiation of a voluntary response, the go/no-go task requires either the inhibition of a
response or the initiation of a response depending on the cue presented. Similarly to
the antisaccade task, the latency of incorrect no-go trials is significantly shorter than
correct saccades on the go trials (Van't Ent & Apkarian, 1999). In a study utilising an
interleaved PAN saccade task undertaken by Brown, Goltz, Vilis, Ford, and Everling
(2006), the number of correct no-go trials was found to be significantly higher than
that of antisaccade trials, but did not significantly differ to number of correct
prosaccade trials.

The memory-guided saccade task is another widely used volitional eye
movement task. In this task, participants are required to maintain fixation while a
stimulus is peripherally presented, and hold the location of this stimulus in memory
until they receive a cue to saccade toward the remembered location. Errors on the task
are typically defined as premature responses, such as breaking fixation and looking at
the peripheral stimulus, or responses that are made before the response cue.
Directional errors are also sometimes reported but are much less frequent than
anticipatory errors. Anticipatory errors on the task have been reported to constitute an
average of approximately 6-18% of responses in adults (Brown et al., 2004;
Medendorp et al., 2007; C. Pierrot-Deseilligny et al., 1991), with an increase in error
rate in the elderly (Abel & Douglas, 2007). Memory-guided saccades also have
significantly longer latencies than visually-guided prosaccades (Mitchell, Macrae, &
Gilchrist, 2002; Özyurt, Rutschmann, & Greenlee, 2006). Age effects are also evident
by the increase in latency of correct memory-guided saccades ranging from an
average of approximately 250ms to 350ms in young and elderly participants,
respectively (Abel & Douglas, 2007). Performance on the self-paced saccade task,
which requires constant refixations from one stimulus to another, has also been shown
to be influenced by age, with young adults making an average of 69.50 saccades and
the elderly making an average of 52.15 saccades in a 30 second time frame (Abel &
5.4.3 Neuroimaging

Early studies investigating the function of the healthy human brain often utilised EEG, including early research into the generation and control of saccades. Although EEG offers good temporal resolution, it lacks adequate spatial resolution resulting in difficulties in interpreting areas of brain function. Modern research into the production of saccadic eye movements tends to employ technologies such as PET and fMRI which allow for more direct localisation of activity.

5.4.3.1 Positron emission tomography (PET)

PET studies have revealed rCBF increases in a number of areas of the human brain associated with saccadic eye movements. Visually guided prosaccades have been found to activate the FEF, SMA, striate and extrastriate cortices, posterior parietal and posterior temporal cortices, posterior thalamus, and cerebellum (Anderson et al., 1994; P. T. Fox, 1985; Sweeney et al., 1996). Antisaccades have been found to show increased activations in the FEF, SMA, DLPFC, posterior parietal cortex, thalamus and putamen, and decreased activation in the ventromedial prefrontal cortex and the ventral ACC, in comparison to prosaccades (O'Driscoll et al., 1995; Sweeney et al., 1996). Memory-guided saccades show increased activation in the FEF, SMA, DLPFC and posterior parietal cortex (Anderson et al., 1994; Sweeney et al., 1996). PET has also been used to investigate self-paced saccadic eye movements revealing significant rCBF elevations in the SMA, fusiform and lingual gyri, insula, cingulate cortex, BG and thalamus (Petit et al., 1993). These findings suggest that the basal ganglia-thalamocortical loop, which is involved in skeletal movements, may also play a role in saccadic eye movements.

5.4.3.2 Functional magnetic resonance imaging (fMRI)

Since the development of fMRI it is typically preferred in eye movement studies over other functional neuroimaging techniques such as PET, as it has far superior temporal resolution. fMRI studies have revealed enhanced activity during prosaccades, in relation to fixation and rest trials, in the FEF, SEF, posterior parietal cortex, precuneus, insula, anterior and posterior cingulate cortices, and striate and
prestriate cortices (Berman et al., 1999; Luna et al., 1998; Matsuda et al., 2004; Perry & Zeki, 2000; Petit, Clark, Ingeholm, & Haxby, 1997; Rosano et al., 2002). Antisaccades have been associated with increased activation in the FEF, SEF and inferior parietal lobule in comparison to prosaccades (Cornelissen et al., 2002; Dyckman, Camchong, Clementz, & McDowell, 2007; Ettinger et al., 2008), and in the SEF, prefrontal cortex, cuneus, precuneus, striatum, thalamus and intraparietal sulcus in comparison to trials of fixation (Brown, Vilis, & Everling, 2007; Dyckman et al., 2007). Similar findings by Matsuda et al. (2004) led to the suggestion of an involvement of the fronto-parietal and fronto-striato-thalamo-cortical circuits in the production of antisaccades. Furthermore, differences in BOLD activation have been reported for correct and incorrect antisaccades. Ford, Goltz, Brown, and Everling (2005) described that during the instruction period of an interleaved prosaccade/antisaccade task, when the stimulus indicating whether a prosaccade or an antisaccade will be required in the upcoming trial, correct antisaccades resulted in more activation of the DLPFC, ACC and presupplementary eye fields compared to antisaccade errors. Additionally, the investigators found that during this time, correct antisaccades were associated with enhanced activation of frontal and parietal cortical areas in comparison to prosaccades. During the response time however, correct and incorrect antisaccades were not associated with increased activation in any areas compared to prosaccades, but antisaccade errors showed more activation in the ACC in comparison to correct antisaccades. Similarly, DeSouza, Menon, and Everling (2003) reported differences in BOLD activation between instruction and response periods on an interleaved prosaccade and antisaccade task. Antisaccade instruction periods were associated with increased FEF and DLPFC activations in comparison to the instruction period of prosaccades. The researchers, however, reported no signal differences between the two tasks during the response periods, suggesting that changes in BOLD activity were restricted to the preparatory period of the task rather than the physical response of eye movements. Instruction-related differences were however not found in an interleaved PAN saccade study undertaken by Brown et al. (2006). This study did report differences in activation during the response periods of the different trials though. Antisaccades were associated with stronger activation in the FEF, SEF, ACC, precuneus and intraparietal sulcus compared to prosaccade and no-go responses. Prosaccades and no-go saccades demonstrated similar activation patterns for these areas, though no-go responses exhibited increased activation of the
superior frontal sulcus, right supramarginal gyrus and posterior cingulate sulcus in comparison to prosaccade responses. The discrepancy in findings between the studies by DeSouza et al. (2003) and Ford et al. (2005), and Brown et al. (2006) likely reflects differences in methodology between studies, and may be related to the extended preparatory and response period epochs in the earlier two studies compared to that of Brown et al. (2006).

Though less frequently studied with the use of functional imaging, memory-guided and self-paced saccade tasks when carried out with fMRI have provided important information about the possible brain areas involved in these types of tasks. In a blocked design, Özyurt et al. (2006) observed increased activation of the right inferior frontal gyrus, left inferior FEF, posterior parietal cortex and right posterior temporal gyrus during memory-guided saccades compared to prosaccades. Brown et al. (2004) employed an event-related design and compared memory-guided saccades against prosaccades across stimulus presentation, delay time, and response time. Greater activity was observed for memory-guided saccades compared to prosaccades during the delay time in the right posterior inferior frontal gyrus, right medial FEF, bilateral SEF, right rostral and ventral intraparietal sulcus, and greater activation in the right precentral gyrus, right rostral intraparietal sulcus during the response time, indicating that different cortical areas are involved in the different components of the task. Self-paced saccades have been reported to display increased activation of the SEF compared to rest conditions (Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999), but less activation in the FEF, parietal eye field, lateral occipital region, precuneus, and angular and cingulate gyri in comparison to prosaccades (Schraa-Tam et al., 2009). Though self-paced and memory-guided saccade tasks have been used in functional imaging studies, they are not typically utilised as they require responses which are not logically comparable to other tasks such as prosaccade tasks.

5.4.4 Saccade research: conclusions

Though some variability exists between studies, most likely due to differences in experimental paradigms, the characteristics of saccades are rather well defined. Changes with age are well documented and emphasise the point that age should be controlled for in studies assessing saccade dynamics. Furthermore, the development
of advanced neuroimaging technologies has allowed for a more thorough understanding of the brain areas involved in the production of saccades in humans.

5.5 Saccades and cognition

Saccadic eye movements provide a great deal of information about cognitive processes and are often used to assess differences in cognitive function in a variety of populations including neurologically impaired and psychiatric populations. Each of the different saccade tasks, including prosaccade, antisaccade, go/no-go saccade, memory-guided saccade and self-paced saccade tasks, allow the investigation of a variety of cognitive processes.

5.5.1 Prosaccades

The prosaccade task is the simplest saccade task since it merely requires a visually-guided saccade to a sudden onset peripheral stimulus. A cue presented in the periphery presumably captures our attention in an effortless and automatic manner resulting in a prosaccade to the stimulus (Roberts et al., 1994). A close relationship exists between saccadic eye movements and attention. Saccades, interspersed with fixations, act to direct the fovea onto areas of interest in a scene (Hutton, 2008). Though minimal effort is required to perform prosaccades, performance on a prosaccade task requires some attention, and the neural systems involved in attentional shift overlap with areas involved in oculomotor control including the FEF, SEF, ACC, anterior insula, inferior parietal lobule, precentral, superior temporal and intraparietal sulci, extrastriate cortex, putamen and cerebellum (Beauchamp, Petit, Ellmore, Ingeholm, & Haxby, 2001; Corbetta et al., 1998; Nobre, Gitelman, Dias, & Mesulam, 2000; Perry & Zeki, 2000). The effect of cognitive load provides an example of how attention can affect performance on saccade tasks. In a study by Stuyven, Van der Goten, Vandierendonck, Claeyys, and Crevits (2000), participants completed a random time interval generation task, a task which loads on executive processes, while performing prosaccade and antisaccade tasks. Although interference effects were more pronounced in the antisaccade task, they were also apparent in the prosaccade task, evident by increased saccadic latencies. Some have suggested that saccadic latency may be regarded as a decision time in which an individual considers
where to look and if it is worth looking there considering the current goals (Carpenter, 2001; Hutton, 2008).

Saccadic latency is also affected by the method of trial presentation. Three manipulations of saccade tasks are commonly employed: step, overlap and gap trials. In step trials, the target onset coincides with the offset of the central fixation stimulus. Overlap trials involve the onset of the stimulus while the fixation stimulus remains visible. In contrast, the offset of the fixation stimulus precedes the onset of the target stimulus in gap trials. Typically, gap and overlap durations of 200ms are utilised, but can vary between studies (see Hutton, 2008 for a review). In comparison to step trials, prosaccade latencies are significantly increased in overlap trials, and reduced in gap trials which can lead to very short latency saccades, or ‘express saccades’, with latencies of around 120ms (B. Fischer, Gezeck, & Hartnegg, 1997; B. Fischer & Ramsperger, 1984). Some have suggested that these may occur as a result of attentional processes. In gap trials, attention may be disengaged before the presentation of the target resulting in faster saccade onsets. In overlap trials, attention remains engaged on the fixation point and saccades are inhibited leading to slower latencies (B. Fischer & Weber, 1993). Other attentional influences such as the presentation of cues and distracters can also affect performance on the prosaccade task. Correctly cueing the location of an upcoming stimulus results in reduced saccadic latency, whereas invalid cues and distracters increase the latency of prosaccades to the target (Cavegn, 1996; Theeuwes, Kramer, Hahn, & Irwin, 1998; Walker, Deubel, Schneider, & Findlay, 1997; Walker, Kentridge, & Findlay, 1995; Walker et al., 2000).

5.5.2 Antisaccades

The antisaccade task is widely used in a variety of populations and provides information on a number of cognitive processes. The task is volitionally controlled and involves the suppression of a saccade to a peripherally presented stimulus, and the initiation of a saccade to the mirror image of the stimulus presented in the periphery. Correct antisaccades are typically hypometric, a finding thought to be related to poor coordinate transformations of spatial representations (Krappmann, 1998). The latency of correct antisaccades tends to be longer than that of prosaccades (Everling &
Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004), which is argued to occur as a result of the time consuming task of inhibiting the automatic response to make a prosaccade (Olk & Kingstone, 2003). Everling and Fischer (1998) suggest that antisaccades take longer to initiate because they require two distinct sub-processes, inhibition of a reflexive saccade and the ability to generate a saccade in the opposite direction. Errors on the task are thought to reflect a failure of inhibitory control mediated by frontal areas of the brain, demonstrated by less activation of the frontal areas during antisaccade errors than correct antisaccade responses (Curtis & D'esposito, 2003; Ford et al., 2005).

More recent explanations of antisaccade performance also emphasise the importance of three overlapping areas of cognition in performing the task: working memory, goal activation and attentional focus (Hutton & Ettinger, 2006). Goal directed behaviour relies on maintaining task relevant information in mind while ignoring task-irrelevant information, i.e. working memory. For example, when individuals are required to perform a task loading on working memory processes while undertaking an antisaccade task, increased error rates and antisaccade latencies result (Mitchell et al., 2002; Roberts et al., 1994). Attentional focus is also closely linked to working memory. For instance, increased attention needs to be oriented towards specific spatial locations to allow them to be held in working memory (Awh, Jonides, & Reuter-Lorenz, 1998). Similarly to prosaccades, performance on the antisaccade task is also influenced by gap and overlap conditions, demonstrated by increased error rates and decreased correct antisaccade latencies, approximately 25ms faster in gap compared to overlap conditions (B. Fischer & Weber, 1997). However, unlike the prosaccade task, distraction has been found to result in decreased rather than increased latencies on the antisaccade task (Kristjansson, Chen, & Nakayama, 2001). The authors suggest that performing a concurrent attentionally demanding task, in this case a discrimination task, interferes with the reflexive prosaccade to the target allowing the initiation of the correct antisaccade to occur more quickly. An additional difference to the prosaccade task is that cueing to the correct location for an antisaccade to be made results in increased latencies and errors (Weber, 1998). The authors explain this counterintuitive finding as a result of the cue acting as a trigger to produce an antisaccade which leads to an attentional shift in the opposite direction.
Errors on the antisaccade task provide insight into a number of cognitive processes. The majority of antisaccade errors are corrected by looking in the opposite direction following a saccade to the target, but approximately 28-50% of antisaccade errors are not recognised by individuals, and these errors tend to be smaller in amplitude and more quickly corrected than when individuals are aware of the error (Mokler & Fischer, 1999; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; A. J. G. Taylor & Hutton, 2011). In a review of the cognitive control of saccades by Hutton (2008), the author suggests that an incorrect antisaccade response may be simultaneously activated with a correct response, but the faster incorrect prosaccade reaches threshold first, with the correct saccade following shortly after. Therefore, corrected antisaccade errors may constitute two different types of errors which may represent different cognitive processes. Additionally, a small proportion of errors on the antisaccade task are often not corrected. Following an erroneous prosaccade to the peripheral stimulus, some individuals have difficulties in generating the correct response (Everling & Fischer, 1998; Hutton & Ettinger, 2006). Patients with Alzheimer’s disease and frontal lobe damage fail to correct a large proportion of antisaccade errors (Abel, Unverzagt, & Yee, 2002; Crawford et al., 2005; Guitton, Buchtel, & Douglas, 1985). These findings are suggested to occur as a result of frontal lobe deficits and reflect a reduction in cognitive capacity, particularly attentional focus (Bowling, Hindman, & Donnelly, 2012). Further evidence comes from findings that young children make a significant proportion of uncorrected antisaccade errors. This improves with age, and presumably corresponds to brain maturation, particularly maturation of the DLPFC (B. Fischer, Biscaldi, & Gezeck, 1997).

An issue that is often overlooked in the literature is that performance on the antisaccade task varies depending on the method of stimulus presentation. Stimuli are generally presented in two ways, either in blocked or interleaved conditions. In a systematic review by Ethridge et al. (2009), the authors suggest that the cognitive requirements for undertaking blocked and interleaved tasks differ. Blocked conditions result in faster latencies and a higher proportion of correct responses than interleaved conditions, suggesting that interleaved tasks are more difficult to perform. Additionally, switching between trials of prosaccades and antisaccades results in higher error rates than when the same trial type is repeated (A. K. C. Lee, Hääläinen, Dyckman, Barton, & Manoach, 2011). Furthermore, performance on
saccadic eye movement tasks can be affected by intertrial effects. Increased errors and latencies are observed in both antisaccade and prosaccade trials that follow an antisaccade trial, suggesting the possibility of persistent inhibition of the saccadic response system (Barton, Raoof, Jameel, & Manoach, 2006; A. K. C. Lee et al., 2011; Manoach, 2007). These findings emphasise the importance of choosing appropriate designs and controlling for the order of trial presentation.

5.5.3 Go/no-go saccades

The go component of the go/no-go task essentially represents a prosaccade response, whereas the no-go component requires similar cognitive processes to the antisaccade task as it requires the inhibition of a motor response, but unlike the antisaccade task it does not require the volitional action of generating a different motor response (Brown et al., 2006). Therefore, the task allows for the investigation of inhibitory performance regardless of the ability to perform a volitional saccade. Similarly to antisaccade trials, a no-go trial leads to increased saccadic latency in the following trial (Barton et al., 2006). No-go trials are also found to increase errors in the following trial, which is more evident in succeeding prosaccade than antisaccade trials (Barton et al., 2006). These findings provide further support for the possibility of persistent inhibition of the saccadic response system.

5.5.4 Memory-guided saccades

As the name suggests, memory-guided saccade tasks are often used as an assessment of visual memory. The task is typically performed with a short delay between the presentation of the target to be remembered and the execution of a memory-guided saccade, therefore assessing short-term or working memory (Hutton, 2008). Memory-guided saccades tend to be hypometric suggesting poor coordinate transformations of spatial representations between sensory input and motor output (Gnadt, 1991; Krappmann, 1998). Memory-guided saccades also have increased latencies in comparison to prosaccades (Mitchell et al., 2002; Özyurt et al., 2006), suggesting increased cognitive demand during the memory-guided task. The task is not only a measure of working memory, but can also be used to assess inhibition and attentional control. A memory-guided trial requires the suppression of a saccade to a
peripherally presented stimulus and the maintenance of fixation onto a central target until it is time to make the memory-guided saccade (Abel & Douglas, 2007). Two types of inhibitory errors can result during this task, a failure to suppress an unwanted reflexive saccade during target presentation and a failure to inhibit a planned saccade to the remembered location (Abel & Douglas, 2007). These findings suggest that the different error types may result from distinctly different processes, possibly due to a failure of impulse control in the former error type and goal neglect in the later error type.

5.5.5 Self-paced saccades

The self-paced saccade task is considered to be an almost entirely volitional task as no cues are presented to guide the constant refixation from one target to the other (Abel & Douglas, 2007). Results from neuroimaging (Grosbras et al., 1999; Schraa-Tam et al., 2009), ageing (Abel & Douglas, 2007) and neurodegenerative studies (Abel, 2009) suggest a role of frontal functioning in producing self-paced saccades, though the cognitive properties of the task are rarely discussed. In a study investigating saccadic eye movements in post-concussion syndrome, Heitger et al. (2009) reported fewer self-paced saccades in the post-concussion syndrome group. The authors suggest that poorer performance on this task may reflect a difficulty in disengaging attention and switching visual attention. I. M. Williams et al. (1997) found a similar result in a sample of severe traumatic brain injury (TBI) patients. TBI participants made fewer self-paced saccades than age-matched controls. Poorer performance on the task was correlated with neuropsychological tests requiring rapid visual scanning, which may reflect speed of information processing.

5.6 Clinical populations

Saccadic eye movement tasks have been widely used with a variety of clinical populations as they provide valuable information about cognitive and neural functioning. Among the clinical groups which saccade tasks have proven useful include those with neurological deficits such as frontal lobe lesions (e.g. Guitton et al., 1985), TBI (e.g. Heitger et al., 2004; I. M. Williams et al., 1997), Huntington’s disease (e.g Lasker, 1987), Alzheimer’s disease (e.g. Crawford et al., 2005),
Parkinson’s disease (e.g. White, Saint-Cyr, Tomlinson, & Sharpe, 1983) and multiple sclerosis (e.g. Fielding, Kilpatrick, Millist, & White, 2009). Saccadic eye movement tasks have also been extensively assessed in a range of psychiatric illnesses.

5.6.1 Schizophrenia

Schizophrenia is by far the most studied psychiatric illness in the saccadic eye movement literature. The illness is characterised by two or more of the following symptoms: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour and negative symptoms (affective flattening, alogia or avolition) (American Psychiatric Association, 2013). The functioning of the saccadic system has been studied in schizophrenia patients for over a hundred years (Diefendorf & Dodge, 1908). Individuals with the illness typically perform normally on standard prosaccade tasks (step trials), demonstrated by preserved latencies and gains (Clementz, McDowell, & Zisook, 1994; Fukushima et al., 1988; Fukushima, Fukushima, Morita, & Yamashita, 1990; Fukushima, Morita, et al., 1990; C. Klein, Heinks, Andresen, Berg, & Moritz, 2000; Landgraf, Amado, Bourdel, Leonardi, & Krebs, 2008; Levin, Holzman, Rothenberg, & Lipton, 1981; Maruff, Danckert, Pantelis, & Currie, 1998; Raemaekers et al., 2002). Levin et al. (1981) reported normal velocity, gain and latency of prosaccades among schizophrenia patients, but increased latency for targets greater than 10° in comparison to healthy controls. Though differences in prosaccade gain are often reported to not differ from healthy individuals, Nieman et al. (2000) observed lower prosaccade gain in schizophrenia patients. Hutton et al. (1998) reported no difference on prosaccade latency or gain between drug-naïve, antipsychotic-treated and control groups. The treated patients were however taking a variety of antipsychotic medications, resulting in interpretation of this finding being difficult. Nieman et al. (2000) however compared patients taking risperidone or olanzapine with healthy controls. No difference in prosaccade latency between schizophrenia patients and controls was reported, consistent with other studies, though latencies were prolonged for patients taking risperidone compared to those using olanzapine. Another factor which can influence saccadic performance in this population is the type of paradigm used, whether step, overlap or gap, as described previously in healthy populations. In a study by Clementz (1996) utilising the gap paradigm, the investigator reported more express saccades in both schizophrenia
patients and controls using a gap interval of 200ms rather than 0ms, 100ms, 300ms or 400ms. The sample of schizophrenia patients made a higher percentage of express saccades than controls. A similar result was reported by C. Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Millist, and White (2008) who found that individuals with schizophrenia with high or low negative symptom scores both made more express saccades in a gap paradigm than controls. As lesions of the SC result in the inability to generate express saccades (Schiller, Sandell, & Maunsell, 1987), these findings suggest adequate functioning of the SC. Lesions of the DLPFC however, result in an increased rate of express saccades (D. Braun, Weber, Mergner, & Schulte-Mönting, 1992). Therefore, the finding of increased express saccades in individuals with schizophrenia may suggest a dysfunction of the DLPFC.

The prefrontal cortex, in particular the DLPFC, is highly involved in the control of cognitive processes (see E. K. Miller & Cohen, 2001 for a review), and individuals with schizophrenia have been found to demonstrate disturbances in a number of cognitive domains (for a review, see Heinrichs & Zakzanis, 1998). Individuals with schizophrenia have also been found to show reduced rCBF in the DLPFC at rest (Weinberger, Berman, & Zec, 1986). Patients with schizophrenia also perform poorly on the WCST (see Heinrichs & Zakzanis, 1998 for a review), a task assessing frontal lobe function (A. L. Robinson, Heaton, Lehman, & Stilson, 1980). Healthy individuals show an increase in DLPFC rCBF during this task, whereas individuals with schizophrenia do not show such an increase (Weinberger et al., 1986). Volitional saccade tasks, which are cognitively demanding, are particularly disturbed among individuals with schizophrenia. In a 2006 review by Hutton and Ettinger, the authors described that up until the review’s publication, no study had failed to report increased antisaccade errors in patients with schizophrenia. Error rates have been reported to constitute approximately 25-70% of antisaccade responses in schizophrenia patients, significantly higher than healthy individuals who make an estimated 20-25% antisaccade errors (e.g. Brenner, McDowell, Cadenhead, & Clementz, 2001; Brownstein et al., 2003; Clementz et al., 1994; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995b; Curtis, Calkins, Grove, Feil, & Iacono, 2001; Ettinger et al., 2004; Fukushima et al., 1988; Fukushima, Fukushima, et al., 1990; Fukushima, Morita, et al., 1990; Gooding & Tallent, 2001; M. S. H. Harris, Reilly, Thase, Keshavan, & Sweeney, 2009; Karoumi, Ventre-Dominey, Vighetto,
Dalery, & d'Amato, 1998; Katsanis, Kortenkamp, Iacono, & Grove, 1997; C. Klein, T. Heinks, et al., 2000; Levy, Mendell, & Holzman, 2004; Maruff et al., 1998; McDowell & Clementz, 1997; Raemaekers et al., 2002; Reuter & Kathmann, 2004; Sereno & Holzman, 1995; Tien, Ross, Pearlson, & Strauss, 1996). Additionally, individuals with schizophrenia are often reported to have increased antisaccade latencies on correct responses (e.g. Fukushima et al., 1988; Fukushima, Morita, et al., 1990; M. S. H. Harris et al., 2009; Karoumi et al., 1998; C. Klein, T. Heinks, et al., 2000; Maruff et al., 1998; Raemaekers et al., 2002; Sereno & Holzman, 1995). Together these results suggest that individuals with schizophrenia are impaired in their ability to perform this cognitively demanding task, apparent by increased erroneous responses and longer response times when responding correctly. Although patients with schizophrenia make more antisaccade errors, they nevertheless correct these errors on almost all occasions, similarly to healthy individuals (Crawford et al., 1995b; Levy et al., 2004). This suggests that patients with schizophrenia understand the requirement of the task, but have difficulty in executing the correct response. These findings however appear to be influenced by anti-psychotic medication, in a similar way that prosaccades are affected. When samples of drug-naïve and drug-treated schizophrenia patients are compared separately to healthy controls, both schizophrenia groups have increased errors, but only drug-naïve patients display longer antisaccade latencies than controls (Crawford, Haeger, Kennard, Reveley, & Henderson, 1995a; Hutton et al., 1998; Müller, Riedel, Eggert, & Straube, 1999).

Additionally, individuals with schizophrenia are also found to have reduced antisaccade gains in comparison to healthy controls, suggesting a disturbance in reproducing spatial representations (Ettinger et al., 2004; Karoumi et al., 1998). As described earlier, the antisaccade task assesses executive functions, processes dominated by the prefrontal cortex. Antisaccade task performance in schizophrenia has been found to correlate with performance on executive tasks such as the Stroop task (Levy et al., 2004), and tasks assessing working memory (Hutton et al., 2004; Nieman et al., 2000). In particular, antisaccade errors have been found to correlate with WCST performance in schizophrenia patients (Crawford et al., 1995a; Karoumi et al., 1998; Rosse, Schwartz, Kim, & Deutsch, 1993; Tien et al., 1996). Performance on the WCST has also been found to correlate with anticipatory saccade errors on the memory-guided saccade task (Crawford et al., 1995a; Park, 1997).
Individuals with schizophrenia also demonstrate impaired performance on the memory-guided saccade task in comparison to healthy individuals in a number of ways. Schizophrenia patients make more anticipatory errors (Brenner et al., 2001; Camchong, Dyckman, Chapman, Yanasak, & McDowell, 2006; Fukushima, Fukushima, et al., 1990; Landgraf et al., 2008; McDowell et al., 2001; Müller et al., 1999; Park, 1997; Park & Holzman, 1992, 1993; Ross, Harris, Olincy, & Radant, 2000), have longer saccadic latencies (Brenner et al., 2001; Camchong et al., 2006; Fukushima, Fukushima, et al., 1990; Karoumi et al., 1998; Müller et al., 1999; Park & Holzman, 1992, 1993; Ross et al., 2000), and produce saccades that are more hypometric than healthy controls (Brenner et al., 2001; Everling, Krappmann, Preuss, Brand, & Flohr, 1996; Karoumi et al., 1998; McDowell et al., 2001). Schizophrenia patients have also been reported to display more fixation losses during fixation trials of interleaved prosaccade and antisaccade tasks (Barton, Pandita, Thakkar, Goff, & Manoach, 2008), and increased errors on no-go saccade tasks (Fukushima, Fukushima, et al., 1990; Landgraf et al., 2008; Raemaekers et al., 2002). Furthermore, performance on a self-paced task has been reported to differ in schizophrenia patients. In a task requiring participants to make 10° saccades at rate of one per second, individuals with schizophrenia showed increased intraindividual variability of intersaccadic intervals, relative to healthy controls (Gurvich, Fitzgerald, Georgiou-Karistianis, & White, 2008).

Biological relatives of individuals with schizophrenia are also reported to display impairments on saccadic eye movement tasks. First-degree relatives have been found to demonstrate decreased errors on the antisaccade task compared to patients, but increased antisaccade errors in comparison to healthy individuals (see Calkins, Curtis, Iacono, & Grove, 2004 for a meta-analysis). Biological relatives have also been found to display increased memory-guided saccade errors (anticipations) compared to healthy controls, at a similar rate to schizophrenia patients (Landgraf et al., 2008). First-degree relatives of individuals with schizophrenia have also been found to display similar functional neuroimaging results as their patient relatives (Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; Keshavan et al., 2002; Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2006).
Functional neuroimaging studies exploring the neural correlates of different saccade paradigms have in the past been limited to patients with schizophrenia (Hutton & Ettinger, 2006). However, a limited number of studies in other psychiatric illnesses have emerged in recent years. As individuals with schizophrenia are typically found to have intact prosaccade performance, it is perhaps not surprising that they also display normal BOLD contrasts associated with prosaccades in comparison to fixation trials in the FEF, SEF, parietal and cingulate cortices (Keedy, Ebens, Keshavan, & Sweeney, 2006; McDowell et al., 2002). Deficits in antisaccade performance are however consistently found in individuals with schizophrenia, which is also reflected in activation differences relative to healthy controls. In an EEG study undertaken by C. Klein, T. Heinks, et al. (2000), individuals with schizophrenia were found to show reduced contingent negative variation compared to healthy controls prior to antisaccades. Electrophysiological saccade studies in schizophrenia are however limited as contemporary research has tended to focus on source localisation with the use of fMRI. In comparison to blocks of fixation trials, blocks of antisaccade trials have been found to produce decreased BOLD activity in the FEF and SEF (Camchong et al., 2008), and no significant activations in the frontal gyrus, inferior parietal lobule, and the bilateral lentiform nucleus and thalamus (Tu, Yang, Kuo, Hsieh, & Su, 2006). In comparison to blocks of prosaccade trials, antisaccade trials have not been found to result in increased activity of the DLPFC as found in healthy controls (McDowell et al., 2002). Unlike healthy individuals, when antisaccade and no-go saccade trials are together compared to prosaccade trials, schizophrenia patients fail to activate the striatum (Raemaekers et al., 2002). The striatum is part of the inhibitory pathway and a failure to activate this area in schizophrenia may help explain the increased rate of inhibitory errors in these individuals. Additionally, when antisaccade and no-go saccade trials are compared to prosaccade trials, activation difference in the FEF and SEF in relation to healthy controls have not been reported (McDowell et al., 2002; Raemaekers et al., 2002). Memory-guided saccade tasks result in decreased BOLD activity in the FEF, SEF, DLPFC, and parietal and cingulate cortices in schizophrenia relative to controls, in comparison to trials of prosaccades (Keedy et al., 2006). In relation to fixation trials, memory-guided trials result in decreased FEF, SEF, inferior parietal lobule, cuneus and precuneus activity, and a failure to activate the DLPFC, insula, thalamus and BG, relative to healthy individuals (Camchong et al., 2008; Camchong et al., 2006). Furthermore, in relation
to healthy controls, first-degree relatives of schizophrenia patients have been reported to display decreased activity during the memory-guided saccade task in comparison to prosaccade trials in the DLPFC and inferior parietal lobule (Keshavan et al., 2002); and the middle occipital gyrus, insula, ACC, cuneus and prefrontal cortex, on both memory-guided and antisaccade trials in comparison to fixation trials (Canchong et al., 2008).

5.6.2 Personality characteristics and disorders

Not only are individuals with schizophrenia and their biological relatives reported to demonstrate deficits in saccadic task performance, but individuals scoring high on measures of schizotypy are also found to display poorer performance on saccadic eye movement tasks. Schizotypy describes personality characteristics, cognitions and experiences which are similar to schizotypal personality disorder and schizophrenia, but which are less severe (Aichert, Williams, Möller, Kumari, & Ettinger, 2012). Higher schizotypy scores have been associated with poorer spatial accuracy on prosaccade tasks (Ettinger, et al., 2005), as well as increased antisaccade errors, but normal correct and incorrect antisaccade latencies (Aichert et al., 2012; Cadenhead, Light, Geyer, McDowell, & Braff, 2002; Ettinger et al., 2005; Gooding, Shea, & Matts, 2005; O'Driscoll, Lenzenweger, & Holzman, 1998); though increased rates of antisaccade errors are not always found (Brenner et al., 2001; C. H. Klein, Brügner, Foerster, Müller, & Schweickhardt, 2000). Furthermore, Brenner et al. (2001) reported that individuals scoring high on schizotypy had a lower rate of antisaccade errors than schizophrenia patients. Similarly to schizophrenia, high schizotypy has been found to result in reduced BOLD activity during antisaccades in the putamen, thalamus, visual cortex and cerebellum, and reduced activity in the SEF, posterior intraparietal sulcus and visual cortex during prosaccades (Aichert et al., 2012).

Other personality constructs have also been studied in relation to saccadic eye movements, but the research is rather limited. In comparison to highly introverted individuals, highly extraverted individuals have been found to make more antisaccade errors, but latency for correct and erroneous responses remains unaffected, similarly to findings in the schizotypal literature (Nguyen, Mattingley, & Abel, 2008).
Antisocial personality disorder has been associated with longer prosaccade latencies (Ceballos & Bauer, 2004), whereas borderline personality disorder has been associated with greater antisaccade errors than seen in healthy individuals (Grootens et al., 2008). Although borderline personality disorder has been linked to a greater rate of antisaccade errors than healthy individuals, individuals with the disorder make fewer errors than schizophrenia patients (Grootens et al., 2008). Furthermore, individuals with borderline personality disorder and psychotic-like symptoms make more erroneous responses on the antisaccade task than those without psychotic symptoms (Grootens et al., 2008). One study however found no difference in antisaccade performance in borderline personality disorder in comparison to healthy controls, despite the finding that individuals with borderline personality disorder self-reported more impulsivity (Jacob et al., 2010).

5.6.3 Mood disorders

Mood disorders are also regularly studied in the saccadic eye movement literature, in particular, BD and MDD. Performance on saccadic eye movement tasks in BD is regularly compared to performance in schizophrenia patients as the two illnesses are thought to share a common genetic vulnerability, though, performance of BD patients is also regularly compared to healthy individuals. An early study in manic-depressive patients reported normal prosaccade gain, latencies and velocities, but increased latencies for targets greater than 10° in comparison to controls (Levin et al., 1981). A more recent study however reported lower prosaccade gains in BD and MDD patients, relative to healthy individuals (Curtis et al., 2001). Furthermore, in a recent study by Velasques et al. (2012), the investigators divided their BD group into depressive and manic, and found that the manic group had slower prosaccade latencies than both the depressive group and healthy controls. On the antisaccade task, individuals with BD have consistently been reported to display more errors than healthy individuals (Curtis et al., 2001; Gooding & Tallent, 2001; M. S. H. Harris et al., 2009; Katsanis et al., 1997; Sereno & Holzman, 1995; Tien et al., 1996), but fewer errors than individuals with schizophrenia (Curtis et al., 2001; Gooding & Tallent, 2001). Similarly to findings in the schizophrenia literature, increased antisaccade errors have been found to be related to WCST performance in BD (Tien et al., 1996). The findings for memory-guided saccades in BD are somewhat limited. In a series of
studies, Park and Holzman reported fewer memory-guided saccade errors for BD participants in comparison to controls (Park & Holzman, 1992), but no difference in error rate between BD patients and controls in their following study, though BD patients were found to make fewer errors than schizophrenia patients (Park & Holzman, 1993). The authors also reported longer saccadic latencies in BD patients, though faster than schizophrenia patients, in their earlier paper (Park & Holzman, 1992), but no latency difference in their subsequent study (Park & Holzman, 1993).

The findings in MDD are also somewhat inconsistent. Prosaccade latency has been found to be increased by some (Mahlberg, Steinacher, Mackert, & Flechtner, 2001), but to not differ from healthy controls by others (Sweeney, Strojwas, Mann, & Thase, 1998). In a study comparing melancholic and non-melancholic MDD, the authors observed increased prosaccade latencies and peak velocities at larger amplitudes in individuals with melancholic MDD compared to non-melancholic MDD (C. Winograd-Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2006a). The researchers also reported that non-melancholic MDD performed similarly to healthy controls on the prosaccade task, but had increased peak saccadic velocities at larger amplitudes. Another study however, that did not differentiate between melancholic features, reported no difference in peak velocity between MDD and controls (Sweeney et al., 1998). Individuals with MDD without psychotic features have also been found to produce more hypometric prosaccades than MDD with psychotic features, schizophrenia, BD patients and healthy controls (M. S. H. Harris et al., 2009). MDD with psychotic features is also associated with a higher rate of antisaccade errors than MDD without psychotic features and healthy individuals (M. S. H. Harris et al., 2009). In a study combining MDD with and without psychotic features, the investigators reported increased antisaccade errors compared to healthy individuals, though both groups were found to almost always correct these erroneous responses (Sweeney et al., 1998). Furthermore, the same study reported that MDD did not differ from controls on antisaccade gain, latency or peak velocity, but did display increased saccade durations. Similar findings were also reported by the same authors for memory-guided saccades which revealed no difference between MDD and healthy individuals for memory-guided saccadic gain, latency or peak velocity, but longer saccade durations (Sweeney et al., 1998). Self-paced saccade performance has also
been found to not differ between MDD and controls (C. Winograd-Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2006b).

5.6.4 Anxiety disorders

Research investigating the effects of anxiety on saccadic eye movements has revealed increased antisaccade latencies in highly anxious individuals in comparison to individuals with low anxiety (Ansari & Derakshan, 2011a, 2011b; Derakshan, Ansari, Hansard, Shoker, & Eysenck, 2009), but no difference in antisaccade error rate or prosaccade performance (Ansari & Derakshan, 2011b; Cornwell, Mueller, Kaplan, Grillon, & Ernst, 2012; Derakshan et al., 2009; Reinholdt-Dunne et al., 2012). Relative to low-anxiety individuals, highly anxious individuals have also been found to show greater levels of contingent negative variation in frontal areas prior to antisaccades compared to prosaccades, suggesting that highly anxious individuals may require a greater level of cognitive effort to correctly perform antisaccades (Ansari & Derakshan, 2011a). In an antisaccade task utilising faces of different emotions as target stimuli, highly anxious individuals were found to display longer correction latencies when making erroneous responses to angry faces (Reinholdt-Dunne et al., 2012). Additionally, Cornwell et al. (2012) designed a task to induce anxiety by asking individuals to perform an interleaved prosaccade and antisaccade task in ‘threat’ (threat of minor electric shock) and ‘safe’ conditions, and found no difference in prosaccade performance or antisaccade error rate in the two conditions, though antisaccade errors had shorter latencies in the threat than safe condition. Furthermore, MEG source analyses indicated increased theta power in the right ventrolateral prefrontal cortex and SC during prosaccades and correct antisaccades. Additionally, in comparison to the safe condition, the threat condition reduced beta desynchronisation in the inferior parietal cortices during antisaccade preparation, but increased beta desynchronisation during prosaccade preparation. These results suggest a greater readiness to produce antisaccades during safe conditions and prosaccades during threat conditions. However, individuals clinically diagnosed with generalised anxiety disorder have been reported to have equal antisaccade performance to healthy controls, but increased antisaccade latency when a threat is present (Jazbec, McClure, Hardin, Pine, & Ernst, 2005). Though only limited research exists in the eye
movement literature in clinically diagnosed generalised anxiety disorder, other anxiety disorders, such as OCD, have had far more research interest.

Individuals with OCD have consistently been found to display normal prosaccade latency, gain and peak velocity (Maruff, Purcell, Tyler, Pantelis, & Currie, 1999; Rosenberg, Averbach, et al., 1997; Spengler et al., 2006; Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992; van der Wee et al., 2006). One study did however find slowed peak saccadic velocities in individuals with OCD, which was found to slow further as the distance between the target and the central fixation point increased (Rosenberg, Dick, O'Hearn, & Sweeney, 1997). The findings related to antisaccade performance are however rather inconsistent. Several studies have reported no difference between OCD and healthy controls on antisaccade errors (Kloft, Kischkel, Kathmann, & Reuter, 2011; Maruff et al., 1999; McDowell & Clementz, 1997; Spengler et al., 2006; van der Wee et al., 2006) or latency (Kloft et al., 2011; Rosenberg, Averbach, et al., 1997; Spengler et al., 2006). Other studies have however reported both increased antisaccade latency (Maruff et al., 1999; McDowell & Clementz, 1997; van der Wee et al., 2006) and errors (Lennertz et al., 2012; Rosenberg, Averbach, et al., 1997; Tien et al., 1992), particularly for targets of smaller amplitude (Rosenberg, Averbach, et al., 1997; Rosenberg, Dick, et al., 1997). Furthermore, first-degree relatives of individuals with OCD have been reported to have an increased rate of antisaccade errors in comparison to healthy individuals, which did not differ from their relatives with OCD (Lennertz et al., 2012). Additionally, patients with OCD have been found to not differ in error rate on a no-go saccade task (van der Wee et al., 2006), but to make more suppression errors when the target was close to the central fixation point on a memory-guided task (Rosenberg, Averbach, et al., 1997).

5.6.5 Childhood-onset disorders

A range of disorders which are typically first diagnosed in childhood are associated with impairments in saccadic eye movement function, including Tourette’s Syndrome (TS), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). TS is characterised by physical and vocal tics (American Psychiatric Association, 2013), and is thought to be a disorder of the frontal-striatal circuits or BG
As these areas are implicated in the production of saccadic eye movements, recent research has utilised these tasks to investigate potential deficits in these areas in individuals with TS. However, findings have been inconsistent. Although prosaccade peak velocity has been consistently found to not differ between TS and controls (LeVasseur, Flanagan, Riopelle, & Munoz, 2001; A. Straube, Mennicken, Riedel, Eggert, & Mülller, 1997), latency has been reported by some to be increased in TS (LeVasseur et al., 2001; Munoz, LeVasseur, & Flanagan, 2002), and to not differ from healthy controls by others (A. Straube et al., 1997). Prosaccadic gain has also been found to be lower in TS by one study (LeVasseur et al., 2001), but to not differ between TS and healthy individuals in another investigation (A. Straube et al., 1997). Several studies have also reported a decreased proportion of express saccades during gap trials in TS (LeVasseur et al., 2001; Munoz et al., 2002), though one study reported no difference in express saccade rate (A. Straube et al., 1997). The findings for antisaccade performance in TS have, however, been somewhat more consistent than prosaccade performance, particularly for antisaccade latency which is found to be increased in TS relative to healthy controls (Dursun, Burke, & Reveley, 2000; Farber, Clementz, Lam, & Swerdlow, 1996; Mueller, Jackson, Dhalla, Datsopoulos, & Hollis, 2006; A. Straube et al., 1997). Additionally, individuals with TS have regularly been reported to not differ from healthy individuals in rate of antisaccade errors (Jackson, Mueller, Hambleton, & Hollis, 2007; LeVasseur et al., 2001; Munoz et al., 2002; A. Straube et al., 1997), though some investigations have reported an increased error rate (Dursun et al., 2000; Farber, Swerdlow, & Clementz, 1999). However, on an interleaved prosaccade and antisaccade task, individuals with TS were found to make fewer errors than healthy controls on ‘switch’ trials where one trial was followed by the another type of trial (prosaccade or antisaccade), and did not differ on ‘repetition’ trials (e.g. prosaccade followed by a prosaccade) (Mueller et al., 2006). The authors described this result as possibly reflecting a generalised suppression of reflexive behaviour as a result of chronic suppression of tics. Furthermore, individuals with TS have been reported to display normal error rates and latencies on a no-go and a memory-guided saccade task, respectively (Farber et al., 1999; A. Straube et al., 1997).

ADHD is the most commonly diagnosed mental illness in children, and is characterised by symptoms of inattention and/or hyperactivity-impulsivity (American
Psychiatric Association, 2013). The condition can be categorised into three subtypes, predominantly inattentive, predominantly hyperactive-impulsive and the combined type. As the condition is characterised by difficulties in attention and impulsivity, volitional saccade tasks have been of particular interest in the condition as they assess these parameters. Individuals with ADHD have typically been found to demonstrate longer antisaccade latencies (Carr, Henderson, & Nigg, 2010; C. H. Klein, Raschke, & Brandenbusch, 2003; Munoz, Armstrong, Hampton, & Moore, 2003), but not in all studies (Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Nigg, Butler, Huang-Pollock, & Henderson, 2002; O’Driscoll et al., 2005). Each of the ADHD subtypes have also been reported to make more antisaccade errors (Carr et al., 2010; Feifel et al., 2004; Goto et al., 2010; C. H. Klein et al., 2003; Loe, Feldman, Yasui, & Luna, 2009; Mahone, Mostofsky, Lasker, Zee, & Denckla, 2009; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz et al., 2003; Nigg et al., 2002; O’Driscoll et al., 2005), and to correct fewer of these errors than healthy controls (C. H. Klein et al., 2003). Furthermore, individuals with ADHD have been found to make more errors on the no-go saccade task (Castellanos et al., 2000; Loe et al., 2009; Mahone et al., 2009), though one study reported no difference in no-go saccade performance relative to healthy individuals (Feifel et al., 2004). Individuals with ADHD have also been reported to display poorer performance on memory-guided saccade tasks, evident by increased inhibitory errors (Castellanos et al., 2000; Goto et al., 2010; Loe et al., 2009; Mahone et al., 2009; Mostofsky et al., 2001; Rommelse et al., 2008; Ross et al., 2000) and increased latencies for correct responses (Castellanos et al., 2000; Goto et al., 2010; Loe et al., 2009). Spatial accuracy, or gain, of memory-guided saccades has been reported to be intact in ADHD (Loe et al., 2009; Ross et al., 2000). Intact prosaccade gain, latency and peak velocity has also been found in individuals with ADHD (Carr et al., 2010; Feifel et al., 2004; Hanisch, Radach, Holtkamp, Herpertz-Dahlmann, & Konrad, 2006; Loe et al., 2009; Mostofsky et al., 2001; Munoz et al., 2003; O’Driscoll et al., 2005), though latency is often found to be more variable than in healthy controls (Mostofsky et al., 2001; Munoz et al., 2003).

ASD is a pervasive developmental disorder characterised by impairments in social interaction and communication, and restricted repetitive and stereotyped patterns of behaviour and interests (American Psychiatric Association, 2013). Similarly to ADHD, individuals with ASD demonstrate intact gain, latency and peak
velocity of prosaccades (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007; Minshew, Luna, & Sweeney, 1999; Mosconi et al., 2009; van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001). ASD is also associated with an intact rate of express saccades in gap trials (Kawakubo et al., 2007), but also with a smaller gap effect (the difference in latency between gap and overlap trials) than healthy individuals (van der Geest et al., 2001). Individuals with ASD have also been reported to produce more incorrect responses on the antisaccade task than individuals without the condition (Agam, Joseph, Barton, & Manoach, 2010; M. C. Goldberg et al., 2002; Luna et al., 2007; Minshew et al., 1999; Mosconi et al., 2009; Thakkar et al., 2008), as have first-degree relatives of individuals with ASD in comparison to healthy controls (Mosconi et al., 2010). Latency and peak velocity of antisaccades in ASD have been reported to not differ from healthy individuals (M. C. Goldberg et al., 2002; Minshew et al., 1999; Mosconi et al., 2009), though, one study found that children, but not adults, with ASD had faster antisaccade latencies than age-matched controls (Luna et al., 2007). This study also reported increased memory-guided saccade latencies in adults with ASD, but not children, and poorer accuracy (gain) in both ASD groups relative to controls. Memory-guided saccadic gain has been reported to be increased in ASD by the same authors in a previous study (Luna et al., 2002), though others have failed to report a difference from healthy individuals (M. C. Goldberg et al., 2002). Additionally, individuals with ASD have been found to make more inhibitory errors on the memory-guided saccade task than healthy individuals (M. C. Goldberg et al., 2002; Minshew et al., 1999).

Recent research has utilised functional neuroimaging in combination with saccade tasks to gain a better understanding of ASD. However, the number of studies is limited to only a few and the findings are not consistent. In an event-related potential (ERP) study, Kawakubo et al. (2007) reported higher presaccadic positivity at 100-70ms before prosaccade onset for the ASD group compared to controls in an overlap task, which significantly correlated with severity of clinical symptoms. In relation to BOLD activity, one study reported no activation difference between ASD and controls (Luna et al., 2002), whereas another reported reduced activity bilaterally in the FEF, SEF, posterior parietal cortex and cerebellum, and greater activity bilaterally in the DLPFC, medial thalamus, caudate nucleus and right dentate nucleus (Takarae, Minshew, Luna, & Sweeney, 2007). In comparison to healthy individuals,
the production of antisaccades in individuals with ASD has been found to result in decreased FEF and dorsal ACC activity (Agam et al., 2010). When observing correct and error responses separately on the antisaccade task, ASD participants demonstrated greater bilateral rostral ACC activation to correct responses and greater activation in another more anterior perlingual rostral ACC region in the left hemisphere to errors; which was not evident in the healthy control group (Thakkar et al., 2008). Additionally, during a memory-guided saccade task, in comparison to a prosaccade task, individuals with ASD have been found to display significantly less activation in the DLPFC and posterior cingulate cortex compared to healthy controls, and relatedly showed poorer behavioural performance on the task (Luna et al., 2002).

5.6.6 Eating disorders

To date, no studies have utilised saccadic eye movement tasks in samples of AN or BN patients. In the only smooth pursuit eye movement study undertaken in individuals with AN, in which unpredictable step-ramp stimuli were utilised, AN patients were found to have lower gains and make more anticipatory errors than healthy controls (Pallanti, Quercioli, Zaccara, Ramacciotti, & Arnetoli, 1998). A search of the literature revealed that no research has been undertaken in AN or BN investigating any type of saccadic eye movement task including prosaccade, antisaccade, no-go saccade, memory-guided saccade or self-paced saccade tasks.

5.6.7 Saccade research in clinical populations: conclusions

The research related to saccadic eye movements in psychiatric populations has provided great insight into the brain mechanisms involved in these illnesses. As the different saccade paradigms utilise known brain circuits, it allows us to explore whether these areas of the brain are functioning appropriately. The areas of the brain involved in saccadic eye movements are also involved in aspects of cognition known to be affected in psychiatric illnesses, and may assist in our understanding of the cognitive problems experienced by individuals with mental illness. To date, no research has been undertaken examining saccadic eye movements in AN. Therefore, the current review of the saccadic eye movement literature in psychiatric illnesses was provided to allow for comparison with other potentially related mental illnesses and to
ascertain whether any commonalities may exist. Examining saccadic eye movements performance in AN will not only allow for the investigation of similarities in reported performance of other conditions, but also has the potential of indicating brain areas of possible dysfunction in AN.

5.7 Current study aims and hypotheses

The aim of the current study was to investigate whether performance on a range of saccadic eye movement tasks differs between individuals with AN and healthy individuals. Participants were required to undertake a self-paced saccade and a memory-guided saccade task while undergoing eyetracking, and an interleaved PAN saccade task while undertaking concurrent fMRI and eyetracking. The following hypotheses were formulated with reference to the saccadic literature in related psychiatric illnesses (particularly OCD as the two conditions share similar symptomatology), prior findings of poorer visuospatial processing in AN, and the previously reported differences in cognitive performance and dysfunctions of related brain areas in AN.

As AN is associated with structural brain differences, the self-paced task was performed as an exploratory task to investigate whether these structural changes resulted in similar findings as in neurodegenerative disorders and closed head injury. Performance on the self-paced saccade task was not expected to be greatly influenced by malnourishment in AN, and performance on the task was expected to remain intact. Performance on the memory-guided saccade task was expected to be poorer in AN participants. It was hypothesised that individuals with AN would show poorer performance on the memory-guided saccade task, evident by an increased rate of inhibitory errors, and increased latency and reduced gain of correct responses. It was hypothesised that during the PAN saccade task, AN participants would show increased errors on the antisaccade and no-go saccade components of the task, and show increased saccadic latency and reduced gain of correct antisaccade responses. Prosaccades were expected to remain intact, as was peak saccadic velocity for all the tasks. Furthermore, error rates on the PAN saccade and memory-guided saccade tasks were expected to positively correlate with self-reported impulsivity as measured by the BIS-11, whereas latency of correct responses on these tasks was expected to negatively correlate with impulsivity. Specifically related to the fMRI task, the AN
group were hypothesised to show reduced activity in the FEF, SEF, ACC and DLPFC during correct antisaccade response periods, compared to correct prosaccade and no-go response periods, but to not differ from healthy individuals during preparatory (cue) periods.

5.8 Method

5.8.1 Participants

Twenty-four individuals with AN and 25 healthy control participants completed the behavioural eyetracking tasks (memory-guided saccades and self-paced saccades tasks), and the PAN saccade task in the MRI scanner. Due to technical eyetracking difficulties in the MRI, three healthy control participants’ eyetracking data could not be used. Technical eyetracking difficulties in the behavioural set-up resulted in one healthy control participant’s data being excluded. Therefore the sample analysed consisted of 24 AN participants and 24 control participants for the behavioural eyetracking tasks, and 24 AN participants and 22 control participants for the PAN saccade task in the MRI. Demographic characteristics for the additional control participant who did not complete the entire study but completed the behavioural eyetracking and PAN saccade tasks in the MRI are included in Appendix E.

5.8.2 Tasks

5.8.2.1 Self-paced saccade task

The self-paced saccade task was administered as a behavioural task. Participants were instructed that two dots would appear in the centre of the screen and all they were required to do was to keep looking from one dot to the other as fast as they could for the entire duration of the task (i.e. 30 seconds). Before the presentation of the two 1° dots, a fixation cross appeared in the centre of the screen for 1000 ms so that all participants had the same starting point. The two 1° dots then appeared on the horizontal plane at ±10° from the centre of the monitor. Due to the simplicity of the
task and to reduce practice effects, a practice trial was not undertaken prior to the commencement of the experimental task.

The number of saccades was counted, and the gain, intersaccadic interval (interval between saccade onsets) and peak saccadic velocity of saccades were calculated. Catch-up saccades were deleted and only the primary saccade was analysed. In the case of multiple saccades in the same direction, before a saccade in the opposite direction, the time between primary saccades was not analysed.

5.8.2.2 Memory-guided saccade task

A memory-guided saccade task was administered to participants behaviourally. Participants were asked to fixate on a 1° black cross in the centre of a white screen for a pseudorandom period of time ranging between 1000-3500 ms. The fixation cross remained on the screen while a 1° black dot appeared for 50ms. Participants were instructed to continue fixating on the centre cross and to try to not look at this dot when it appeared. The fixation cross remained on the screen for a further 1000-3500 ms, followed by its disappearance and the presentation of a blank screen for 1000ms. Once the fixation cross had disappeared, participants were required to look at the location they remembered the black dot appearing. A fixation cross then re-appeared in the centre of the screen indicating that a new trial was beginning and that participants needed to fixate on the central target. The task consisted of 52 stimuli, with the peripheral 1° dot presented at 5° and 10° to the left and right of the centre of the screen, with pseudorandom timing and location. There were an equal number of presentations for each location. Furthermore, the dot was never presented in the same location more than twice in a row. The task took approximately 6.5 minutes to complete. Before the presentation of the task, participants also undertook a practice task consisting of five trials.

The task was analysed for percentage of correct responses, percentage of directional errors, and percentage of inhibitory/anticipation errors for 5° and 10° degree stimuli separately and together. Inhibitory errors were saccades that were made from the peripheral stimulus onset to the beginning of the response period, or within the first 80ms of the response period. Gain and latency of correct saccades were also
calculated, as was the peak saccadic velocity for 5° and 10° saccades separately. Correct responses were only analysed if the participant was fixated on the central cross prior to and following the appearance of the peripheral dot. Saccades smaller than 2° were not analysed.

5.8.2.3 Prosaccade/antisaccade/no-go (PAN) saccade task

The PAN saccade task was undertaken in both the MEG and MRI systems, both with affixed eyetrackers. Stimuli were presented on a white screen utilising a step method. A step paradigm was used rather than a gap or overlap paradigm in an attempt to minimise express saccades which have different characteristics to standard saccades. An event-related design was chosen over a block design in an attempt to reduce predictability of upcoming trials. The sequence of events involved a black 1° fixation cross which appeared in the centre of the screen, followed by a 1° coloured dot in the centre of the screen, and finally a 1° black dot in the periphery along the horizontal plane. Participants were asked to fixate on the cross whenever it was on screen. Participants were informed that the coloured dot (cue period) that followed the presentation of the fixation cross indicated what they were required to do when the black dot appeared in their periphery (response period). If the dot was green, it indicated a ‘go’ response, i.e. a prosaccade toward the stimulus. If the dot was red, it indicated a ‘stop’ response, i.e. a no-go response where the participant was required to refrain from making an eye movement and to continue fixating on the centre of the screen where the coloured dot had previously appeared. If the dot was blue, it indicated a ‘mirror image’ response, i.e. an antisaccade where the participant was required to refrain from making an eye movement to the stimulus and to instead make a saccade in the opposite direction but the same distance from the centre of the screen. The reappearance of a fixation cross indicated the beginning of a new trial. The instruction for each coloured dot remained consistent among participants and sessions to reduce confusion. The trials were presented in a pseudorandom order to reduce anticipations and the effects from the previous trial. The peripheral dot appeared at 5° or 10° to the left or right and never appeared in the same location more than twice in a row. The same type of response (prosaccade, antisaccade or no-go saccade) also never appeared in more than two consecutive trials to reduce anticipatory eye movements.
Each stimulus type was analysed for percent errors, percent correct responses, gain, latency, and peak saccadic velocity (5° and 10° targets separately) of both correct and erroneous responses. Antisaccade errors were also separated into corrected and uncorrected errors and analysed separately. Furthermore, the ‘corrected’ saccade following an erroneous response on antisaccade trials was also analysed. The rate of anticipatory saccades was also recorded, but the saccades themselves were not analysed. The criteria for an anticipatory saccade were a saccade of over 2° made during the instruction period which resulted in the participant not being fixated on the centre of the screen when the peripheral dot appeared, or a saccade made within 80ms of the stimulus presentation. Trials containing anticipations and missing data due to eyetracker dropouts were not analysed. Saccades smaller than 2° were not analysed.

5.8.2.3.1 Magnetoencephalography (MEG)

The results of the MEG task are not presented in this thesis. As the PAN saccade task was counterbalanced between MEG and MRI scanners, the MEG task is described in this section to demonstrate the familiarity of the task for half the participants who completed the MEG session prior to the MRI session.

The PAN saccade task in the MEG consisted of 324 trials in total, 108 trials of each stimulus type (prosaccade, antisaccade and no-go saccade). The trials were split into six runs to allow for short breaks. Therefore, there were 18 presentations of each stimulus type per run. The fixation cross, indicating the start of a new trial, was always presented for 1000ms. The time that the coloured dot was presented varied from 1700-2500ms to reduce anticipations (equal number of presentations at each 100ms interval), whereas the peripheral black dot was always presented for 1000ms. Each run ran for approximately four minutes. Prior to the MEG recording, participants also completed a practice trial consisting of two trials per stimulus type.

5.8.2.3.2 Magnetic resonance imaging (MRI)

The PAN saccade task in the MRI was essentially the same as in the MEG scanner, but with fewer trials and different timings. 112 trials in total were presented (54 trials per trial type of stimulus) over three runs. Each run also began with a
15000ms period of fixation prior to the commencement of the task. Each subsequent fixation period was 2000ms. The instruction time varied between 2700ms-3500ms (with an equal number of trials at each 100ms interval), whereas the response time varied between 2000-2800ms (with an equal number of trials at each 100ms interval). Longer trial component times were required for fMRI due to the slow nature of the BOLD response. However, fewer trials in the fMRI paradigm were required as the signal is much noisier in the MEG. The instruction and response times also varied to reduce anticipatory eye movements and to create jitter in the fMRI signal. Each run ran for approximately seven minutes. Prior to entering the scanner, participants completed a practice run consisting of two trials per stimulus type.

5.8.2.4 Analysis

5.8.2.4.1 Eye movements

All of the eyetracking data collected with the EyeLink1000 was analysed with the use of SR Research’s DataViewer program. ‘Saccade reports’ were generated through the program and imported into Microsoft Excel for further analysis, prior to being imported into the study database in SPSS. The eye movement results for each trial in the PAN saccade tasks were used for the fMRI analysis.

5.8.2.4.2 Functional magnetic resonance imaging (fMRI)

MRI data pre-processing and statistical analyses were performed using SPM8, through Matlab R2014a (Mathworks, Natick, MA, USA). Image pre-processing included image realignment, then coregistration of the T1 image to a mean realigned functional image created during realignment. The co-registered T1 image was then normalised to the T1 template supplied with SPM8 (Montreal Neuroimaging Institute, MNI), then the parameters of this transformation were applied to realigned functional images. The normalised functional images were then spatially smoothed with a Gaussian kernel of 8x8x8mm. Due to the fast repetition time achieved with the multiband sequence, it was not necessary to perform slice timing corrections on the data.
5.8.2.4.3 Statistical analysis

5.8.2.4.3.1 Eye movements

Performance on eyetracking components were compared with between groups ANOVAs, following normality checking and the removal of outliers, with alpha set at 0.05 for all analyses.

5.8.2.4.3.2 Functional magnetic resonance imaging (fMRI)

First-level modelling of fMRI data was performed by fitting a convolved hemodynamic response function (HRF) and its temporal derivative separately to the onset times of correct prosaccade, antisaccade and no-go responses. Errors on each trial type were modelled together, as were missing trials and anticipatory responses for each trial type. Due to the small number of errors made for each group, only the correct responses were contrasted. As discussed, cue and response periods can result in different activations and it is therefore more appropriate to model them separately, therefore resulting in six regressors plus their temporal derivative. After parameter estimation, the following six contrast images were produced as in Brown et al. (2006): antisaccade cue > no-go cue, antisaccade cue > prosaccade cue, prosaccade cue > no-go cue, antisaccade response > no-go response, antisaccade response > prosaccade response, and prosaccade response > no-go response.

At the group level, these contrast images were first entered into one-way ANOVA models for AN and control groups separately to investigate within-group effects. Group differences were interrogated with a mixed-effects ANOVA model using the flexible factorial option in SPM8. This model included a between-subjects Group factor (two levels: AN versus controls), a within subjects Condition factor (six levels: antisaccade cue > no-go cue, antisaccade cue > prosaccade cue, etc.) and a Subjects factor (number of levels equals the number of participants) that controlled for within-subject variability (Gläscher & Gitelman, 2008).

Voxel level thresholding applied was corrected for family-wise error rate (FWE multiple comparisons, p < 0.05), and cluster level thresholding for false discovery rate (p-FDR, multiple comparisons, p < 0.05). For the one-way within groups ANOVAs, the main effect of condition and simple effects for each condition
were analysed for each group. The mixed-design analysis involved the investigation of a group by condition interaction, followed by simple effects comparing each condition between groups.

5.8.3 Procedure

Participants completed the saccade tasks over two sessions, the ‘long MEG’ and ‘long MRI’ sessions. Participants were informed that they would be completing a variety of tasks over the two sessions, but were not informed that the same task would be repeated in each scanner. As the PAN saccade task was completed in both sessions, the order of sessions was counterbalanced between participants. Each task began with a nine-point eyetracker calibration sequence, followed by a validation task requiring participants to look at different points on the monitor. The calibration sequence was run between runs as appropriate. The tasks were presented in a fixed order explained in section 2.4.

5.9 Results

The following section describes the results from the saccade tasks. Between groups ANOVAs were carried out on the data and the results are presented separately for each task. Saccadic characteristics of the different response types in the PAN saccade task were analysed separately in the eyetracking analysis as the different trial types are considered independent of one another.

5.9.1 Self-paced saccade task

Groups did not significantly differ on any component of the self-paced saccade task, though there was a trend for AN participants to show a longer average intersaccadic interval (Table 5.1). Further analyses were performed comparing the variability between groups for each measure, though none of the analyses resulted in significant group differences. Exploratory Pearson’s correlation analyses between intersaccadic interval, and scores on the BIS-11 and DASS did not reveal any significant correlations for either group.
Table 5.1

*Self-paced saccade task performance*

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccade rate</td>
<td>67.50</td>
<td>72.50</td>
<td>2.04</td>
<td>0.160</td>
<td>0.41</td>
</tr>
<tr>
<td>Gain</td>
<td>18.06</td>
<td>17.89</td>
<td>0.05</td>
<td>0.831</td>
<td>0.06</td>
</tr>
<tr>
<td>Intersaccadic interval</td>
<td>464.46</td>
<td>401.67</td>
<td>3.50</td>
<td>0.068</td>
<td>0.54</td>
</tr>
<tr>
<td>Peak velocity</td>
<td>446.74</td>
<td>455.16</td>
<td>0.04</td>
<td>0.839</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Note: AN=anorexia nervosa; intersaccadic interval is the interval between saccade onsets and is reported in milliseconds; peak velocity is reported in degrees/second

5.9.2 Memory-guided saccade task

On the memory-guided saccade task, groups significantly differed on rate of correct responses (F(1,45)= 8.82, p= 0.005, Cohen’s d= 0.87). Relatedly, groups significantly differed on inhibitory error rate, specifically for 10° targets, with AN participants making more inhibitory errors at this target amplitude (F(1,42)= 10.44, p= 0.002, Cohen’s d= 0.99). Groups did not significantly differ on any other component of the memory-guided saccade task, though the latency of correct memory-guided saccades fell just short of significance, indicating a trend for AN participants to display longer latencies (Table 5.2).
Table 5.2

Memory-guided saccade task performance

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.78</td>
<td>0.08</td>
<td>0.78</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Latency</td>
<td>296.98</td>
<td>34.56</td>
<td>277.26</td>
<td>32.90</td>
<td>3.84</td>
</tr>
<tr>
<td>Peak velocity, 5°</td>
<td>166.72</td>
<td>30.51</td>
<td>167.95</td>
<td>25.39</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak velocity, 10°</td>
<td>248.07</td>
<td>38.53</td>
<td>265.70</td>
<td>26.64</td>
<td>3.30</td>
</tr>
<tr>
<td>Correct response rate</td>
<td>68.27</td>
<td>16.65</td>
<td>79.85</td>
<td>8.68</td>
<td>8.82</td>
</tr>
<tr>
<td>Directional error rate</td>
<td>0.24</td>
<td>0.86</td>
<td>0.16</td>
<td>0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>Inhibitory error rate</td>
<td>14.81</td>
<td>10.98</td>
<td>8.47</td>
<td>5.32</td>
<td>5.77</td>
</tr>
<tr>
<td>5°</td>
<td>14.55</td>
<td>10.24</td>
<td>11.54</td>
<td>7.50</td>
<td>1.22</td>
</tr>
<tr>
<td>10°</td>
<td>16.22</td>
<td>13.52</td>
<td>6.04</td>
<td>5.24</td>
<td>10.44</td>
</tr>
<tr>
<td>Missing response rate</td>
<td>11.71</td>
<td>6.99</td>
<td>9.36</td>
<td>6.01</td>
<td>1.465</td>
</tr>
</tbody>
</table>

Note: AN=anorexia nervosa; gain, latency and peak velocity are reported for correct responses only; latency is reported in milliseconds; peak velocity is reported in degrees/second; peak velocity and inhibitory error rate are reported separately for 5° and 10° targets.

The distribution of latencies from the onset of the peripheral stimulus for each inhibitory saccade error for all participants at 5° and 10° target distances are displayed in Figures 5.1 A and B, and Figures 5.2 A and B. The distributions suggest that participants made inhibitory errors of shorter latency to 10° targets in the range of reflexive saccade latencies, though the medians did not significantly between groups (U(792)= 71880.50, Z= -0.63, p= 0.529).

Pearson’s correlation analyses were also conducted between inhibitory error rate and latency, and scores on the BIS-11, but did not reveal any significant correlations for either group. Exploratory Pearson’s correlations were also conducted between inhibitory error rate and latency, and scores on the DASS and also did not reveal any significant correlations.
Figure 5.1. Frequency of individual 5° memory-guided saccade inhibitory error latencies, within 200 millisecond bins, for anorexia nervosa (A) and control (B) participants.

Figure 5.2. Frequency of individual 10° memory-guided saccade inhibitory error latencies, within 200 millisecond bins, for anorexia nervosa (A) and control (B) participants.
5.9.3 Prosaccade/antisaccade/no-go saccade (PAN) task

5.9.3.1 Eyetracking

Table 5.3 presents the response rates for each trial type of the PAN saccade task undertaken in the MRI. Groups did not significantly differ in anticipation rate, but AN participants were found to make fewer correct prosaccade, antisaccade and no-go responses. However, groups did not differ in error rate on any trial type. The discrepancy between the correct and incorrect responses is attributable to the increased rate of missing trials for each trial type in AN.
Table 5.3
Prosaccade/antisaccade/no-go saccade task response rates

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th></th>
<th></th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade</td>
<td>72.99 ± 24.83</td>
<td>85.98 ± 10.99</td>
<td>5.10</td>
<td>0.029</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade</td>
<td>56.25 ± 26.97</td>
<td>71.68 ± 14.61</td>
<td>5.67</td>
<td>0.022</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-go</td>
<td>64.89 ± 26.59</td>
<td>81.06 ± 12.75</td>
<td>6.71</td>
<td>0.013</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>64.71 ± 24.55</td>
<td>79.57 ± 10.39</td>
<td>6.92</td>
<td>0.012</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade</td>
<td>1.39 ± 2.58</td>
<td>1.43 ± 1.61</td>
<td>0.01</td>
<td>0.948</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade</td>
<td>18.75 ± 12.72</td>
<td>16.16 ± 11.05</td>
<td>0.54</td>
<td>0.467</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected</td>
<td>18.13 ± 12.34</td>
<td>15.82 ± 10.75</td>
<td>0.45</td>
<td>0.504</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected</td>
<td>0.62 ± 1.61</td>
<td>0.34 ± 0.93</td>
<td>0.51</td>
<td>0.478</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-go</td>
<td>14.51 ± 11.27</td>
<td>12.58 ± 7.98</td>
<td>0.44</td>
<td>0.511</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.55 ± 7.18</td>
<td>10.06 ± 4.97</td>
<td>0.66</td>
<td>0.422</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticipation rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade</td>
<td>1.62 ± 2.21</td>
<td>1.35 ± 3.03</td>
<td>0.12</td>
<td>0.727</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade</td>
<td>1.16 ± 2.30</td>
<td>1.01 ± 1.87</td>
<td>0.06</td>
<td>0.814</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-go</td>
<td>0.31 ± 1.18</td>
<td>0.08 ± 0.39</td>
<td>0.72</td>
<td>0.400</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.03 ± 1.52</td>
<td>0.81 ± 1.56</td>
<td>0.22</td>
<td>0.639</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade</td>
<td>24.00 ± 24.87</td>
<td>11.57 ± 11.55</td>
<td>4.58</td>
<td>0.038</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade</td>
<td>23.84 ± 25.20</td>
<td>11.57 ± 11.56</td>
<td>4.37</td>
<td>0.042</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No-go</td>
<td>20.29 ± 22.96</td>
<td>6.27 ± 7.45</td>
<td>7.47</td>
<td>0.009</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22.71 ± 23.44</td>
<td>9.81 ± 9.15</td>
<td>5.84</td>
<td>0.020</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; response rates reported as percentages
The latency of correct prosaccades made in the PAN saccade task was found to be significantly shorter in AN participants (F(1,43)= 7.01, p= 0.011, Cohen’s d= 0.78). Groups were not found to significantly differ on any other component of prosaccade trials. The distribution of latencies for individual prosaccades for each participants also did not indicate an increased rate of express saccades in AN (i.e. saccades made between 80-120ms) (Figure 5.3 A and B). AN and control participants did not differ in correct antisaccade responses (Table 5.4). Groups also did not differ in corrected error antisaccade responses, but AN participants did show slower peak velocities of no-go errors to 5° targets (F(1,43)= 4.44, p= 0.042, Cohen’s d= 0.67) (Table 5.5). As only few prosaccade errors, antisaccade uncorrected errors and anticipatory responses on each of the trial types were elicited in both groups, these responses were not analysed in terms of their saccadic characteristics.

Pearson’s correlation analyses were also conducted between error rates and latencies of each component of the task, and scores on the BIS-11, but did not reveal any significant correlations for either group. Exploratory Pearson’s correlations between the DASS subscales and error rates and latencies also did not reveal any significant correlations.
Table 5.4

*Saccade characteristics of correct prosaccade and antisaccade responses*

<table>
<thead>
<tr>
<th></th>
<th>AN M</th>
<th>AN SD</th>
<th>Controls M</th>
<th>Controls SD</th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prosaccades</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.91</td>
<td>0.09</td>
<td>0.92</td>
<td>0.04</td>
<td>0.03</td>
<td>0.875</td>
<td>0.14</td>
</tr>
<tr>
<td>Latency</td>
<td>206.87</td>
<td>33.72</td>
<td>250.42</td>
<td>70.97</td>
<td>7.01</td>
<td>0.011</td>
<td>0.78</td>
</tr>
<tr>
<td>Peak Velocity 5°</td>
<td>209.36</td>
<td>37.47</td>
<td>211.06</td>
<td>32.32</td>
<td>0.03</td>
<td>0.870</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak Velocity 10°</td>
<td>288.34</td>
<td>43.76</td>
<td>286.90</td>
<td>35.00</td>
<td>0.02</td>
<td>0.903</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Antisaccades</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.95</td>
<td>0.22</td>
<td>0.86</td>
<td>0.16</td>
<td>2.39</td>
<td>0.129</td>
<td>0.47</td>
</tr>
<tr>
<td>Latency</td>
<td>333.00</td>
<td>82.35</td>
<td>364.78</td>
<td>85.72</td>
<td>1.64</td>
<td>0.207</td>
<td>0.38</td>
</tr>
<tr>
<td>Peak Velocity 5°</td>
<td>225.01</td>
<td>55.12</td>
<td>220.04</td>
<td>49.28</td>
<td>0.10</td>
<td>0.752</td>
<td>0.10</td>
</tr>
<tr>
<td>Peak Velocity 10°</td>
<td>238.47</td>
<td>56.21</td>
<td>247.63</td>
<td>56.18</td>
<td>0.31</td>
<td>0.584</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Note: AN = anorexia nervosa; latency is reported in milliseconds; peak velocity is reported in degrees/second for 5° and 10° targets separately.

*Figure 5.3.* Frequency of individual prosaccade latencies, within 20 millisecond bins, for anorexia nervosa (A) and control (B) participants.
Table 5.5

*Saccade characteristics of corrected antisaccade errors and no-go saccade error responses*

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>Controls</th>
<th>F</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>F</td>
</tr>
<tr>
<td>Antisaccade corrected errors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.85</td>
<td>0.12</td>
<td>0.82</td>
<td>0.12</td>
<td>0.61</td>
</tr>
<tr>
<td>Latency</td>
<td>208.77</td>
<td>52.71</td>
<td>221.58</td>
<td>43.63</td>
<td>0.70</td>
</tr>
<tr>
<td>Peak Velocity 5°</td>
<td>196.40</td>
<td>31.15</td>
<td>193.02</td>
<td>31.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Peak Velocity 10°</td>
<td>263.62</td>
<td>63.07</td>
<td>269.13</td>
<td>43.87</td>
<td>0.10</td>
</tr>
<tr>
<td>Intersaccadic interval</td>
<td>333.88</td>
<td>135.46</td>
<td>317.48</td>
<td>118.37</td>
<td>0.17</td>
</tr>
<tr>
<td>No-go errors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>0.76</td>
<td>0.14</td>
<td>0.82</td>
<td>0.13</td>
<td>2.73</td>
</tr>
<tr>
<td>Latency</td>
<td>348.97</td>
<td>174.88</td>
<td>342.66</td>
<td>124.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak Velocity 5°</td>
<td>172.76</td>
<td>41.99</td>
<td>196.81</td>
<td>29.03</td>
<td>4.44</td>
</tr>
<tr>
<td>Peak Velocity 10°</td>
<td>243.26</td>
<td>53.95</td>
<td>260.02</td>
<td>50.35</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; latency and intersaccadic interval are reported in milliseconds; peak velocity is reported in degrees/second for 5° and 10° targets separately; intersaccadic interval refers to the interval between the onset of antisaccade errors and the onset of the corrected saccade.

5.9.3.2 Functional magnetic resonance imaging (fMRI)

5.9.3.2.1 Within groups analyses

One-way within groups ANOVAs were carried out for AN and healthy control groups separately. For the AN group, a significant main effect of condition was found (F(5,115)= 7.78, p < 0.05 (FWE)). Individual contrasts are presented in Table 5.6. The antisaccade cue > no-go cue contrast resulted in one significant cluster covering the bilateral cuneus, calcarine sulcus, primary visual cortex (V1) and secondary visual cortex (V2). The antisaccade cue > prosaccade cue contrasts revealed two significant clusters: one in the right middle and superior frontal gyri, and one in the left middle and superior frontal gyri. The prosaccade cue > no-go cue contrast resulted in
increased activation in one cluster in the bilateral cuneus, calcarine sulcus, V2, V1, posterior cingulate cortex and associative visual cortex.

The antisaccade response > no-go response contrast resulted in two significant clusters: the first in the left SMA, medial frontal gyrus, superior frontal gyrus, premotor cortex, and the second in the left middle frontal gyrus. The antisaccade response > prosaccade response contrast resulted in a significant cluster covering the same areas as the first cluster of the antisaccade response > no-go response contrast described above. Finally, the prosaccade response > no-go response contrast resulted in increased activity in one cluster in the right inferior and middle occipital gyrus.
Table 5.6

Significant within groups contrasts for the prosaccade/antisaccade/no-go saccade task for anorexia nervosa participants

<table>
<thead>
<tr>
<th>Contrast</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>Peak MNI coordinates</th>
<th>Peak regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cue period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade &gt; no-go</td>
<td>776</td>
<td>6.60</td>
<td>14 -84 8</td>
<td>Cuneus, calcarine sulcus, V1, V2</td>
</tr>
<tr>
<td>Antisaccade &gt; prosaccade</td>
<td>128</td>
<td>5.17</td>
<td>24 -8 54</td>
<td>Middle &amp; superior frontal gyri</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>-24 -10 58</td>
<td>Middle &amp; superior frontal gyri</td>
</tr>
<tr>
<td>Prosaccade &gt; no-go</td>
<td>2592</td>
<td>8.69</td>
<td>-10 -86 12</td>
<td>Cuneus, calcarine sulcus, V2, V1, posterior cingulate cortex, associative visual cortex</td>
</tr>
<tr>
<td><strong>Response period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade &gt; no-go</td>
<td>126</td>
<td>6.95</td>
<td>-8 8 54</td>
<td>SMA, medial &amp; superior frontal gyri, premotor cortex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104</td>
<td>5.17 -25 -2 52</td>
<td>Middle frontal gyrus</td>
</tr>
<tr>
<td>Antisaccade &gt; prosaccade</td>
<td>240</td>
<td>6.46</td>
<td>-8 8 54</td>
<td>SMA, medial &amp; superior frontal gyri, premotor cortex</td>
</tr>
<tr>
<td>Prosaccade &gt; no-go</td>
<td>81</td>
<td>8.45</td>
<td>28 -98 -4</td>
<td>Inferior &amp; middle occipital gyrus</td>
</tr>
</tbody>
</table>

Note: V1= primary visual cortex; V2= secondary visual cortex; SMA= supplementary motor area; MNI=Montreal Neuroimaging Institute; voxel-wise threshold: T(1,115)=4.69, p < 0.05 (family-wise error corrected); cluster threshold: p < 0.05 (false discovery rate corrected)
For control participants, a significant main effect of condition was also found (F(5,105)= 8.159, p < 0.05 (FWE)). Individual contrasts for the control group are presented in Table 5.7. The antisaccade cue > no-go cue contrast resulted in increased activity in two clusters: a cluster in the bilateral cuneus, calcarine sulcus, lingual gyrus, V1 and V2 (similarly to the AN group), and a cluster in the left premotor cortex, and middle and supplementary frontal gyri. The antisaccade cue > prosaccade cue contrast resulted in three significant clusters: a cluster covering the left middle frontal gyrus, premotor cortex, precentral gyrus, and superior and medial frontal gyri; a cluster covering the right superior frontal gyrus, premotor cortex, superior, middle and medial frontal gyri, SMA and precentral gyrus; and a cluster in the right superior parietal lobule. The prosaccade cue > no-go cue contrast resulted in one significant cluster in the bilateral cuneus, calcarine sulcus, lingual gyrus, V1, V2, associative visual cortex, posterior cingulate cortex, precuneus, parahippocampal gyrus and middle occipital gyrus.

The antisaccade response > no-go response contrast revealed a significant cluster in the left premotor cortex, and middle and medial frontal gyri. The antisaccade response > prosaccade response contrasts and the prosaccade response > no-go response contrasts both resulted in significant clusters in the right cingulate cortex.
Table 5.7
Significant within groups contrasts for the prosaccade/antisaccade/no-go saccade task for control participants

<table>
<thead>
<tr>
<th>Contrast</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>MNI coordinates x y z</th>
<th>Peak regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cue period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade &gt; no-go</td>
<td>1797</td>
<td>6.94</td>
<td>16 -76 6</td>
<td>Cuneus, calcarine sulcus, lingual gyrus, V1, V2</td>
</tr>
<tr>
<td></td>
<td>163</td>
<td>6.17</td>
<td>-24 -10 56</td>
<td>Premotor cortex, middle &amp; supplementary frontal gyri</td>
</tr>
<tr>
<td>Antisaccade &gt; prosaccade</td>
<td>805</td>
<td>10.22</td>
<td>-26 -10 56</td>
<td>Middle frontal gyrus, premotor cortex, precentral gyrus, superior &amp; middle frontal gyri</td>
</tr>
<tr>
<td></td>
<td>1198</td>
<td>8.98</td>
<td>24 -6 60</td>
<td>Superior frontal gyrus, premotor cortex, superior, middle &amp; medial frontal gyri, SMA, precentral gyrus</td>
</tr>
<tr>
<td></td>
<td>255</td>
<td>5.99</td>
<td>30 -54 52</td>
<td>Superior parietal lobule</td>
</tr>
<tr>
<td>Prosaccade &gt; no-go</td>
<td>5093</td>
<td>9.66</td>
<td>-8 -80 8</td>
<td>Cuneus, calcarine sulcus, lingual gyrus, V1, V2, associative visual cortex, posterior cingulate cortex,</td>
</tr>
</tbody>
</table>
Table 5.7 cont’d

<table>
<thead>
<tr>
<th>Contrast</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>coordinates</th>
<th>Peak regions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cue period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosaccade &gt; no-go</td>
<td></td>
<td></td>
<td></td>
<td>Precuneus, parahippocampal gyrus, middle occipital gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisaccade &gt; no-go</td>
<td>583</td>
<td>8.95</td>
<td>-10 4 54</td>
<td>Premotor cortex, middle &amp; medial frontal gyri</td>
</tr>
<tr>
<td>Antisaccade &gt; prosaccade</td>
<td>1113</td>
<td>8.19</td>
<td>28 -10 32</td>
<td>Cingulate cortex</td>
</tr>
<tr>
<td>Prosaccade &gt; no-go</td>
<td>269</td>
<td>7.26</td>
<td>30 -10 34</td>
<td>Cingulate cortex</td>
</tr>
</tbody>
</table>

Note: V1= primary visual cortex; V2= secondary visual cortex; SMA= supplementary motor area; MNI=Montreal Neuroimaging Institute; voxel-wise threshold: $T(1,105)=4.82$, $p < 0.05$ (family-wise error corrected); cluster threshold: $p < 0.05$ (false discovery rate corrected)

5.9.3.2.2 Mixed-design analysis

The analysis did not result in a significant group by condition interaction ($F(5,220)= 8.18$, $p > 0.05$ (FWE)). Simple effects between groups for each contrast did not reveal any significant activation differences between AN and control participants.
5.10 Discussion

The aim of this study was to investigate differences in performance between AN and healthy control participants on a set of saccade tasks. The results from the self-paced saccade, memory-guided saccade and PAN saccade tasks are discussed separately below.

5.10.1 Self-paced saccade task

The current study required participants to make constant refixations of 20° between two eccentric horizontal stimuli. Participants were instructed to make constant refixations as fast as they were able to within a 30 second timeframe. Groups were not expected to significantly differ on any component of this task. Though a trend for longer intersaccadic intervals in participants with AN was revealed, no significant differences between groups were found. Although differences between psychiatric groups have been reported for some conditions such as schizophrenia (Gurvich et al., 2008), other conditions such as MDD have not been found to differ in performance from healthy individuals (C. Winograd-Gurvich et al., 2006b). Self-paced saccade tasks are however typically investigated in neurodegenerative disorders such as Parkinson’s disease (C. Winograd-Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White, 2006c), Huntington’s disease (C. T. Winograd-Gurvich et al., 2003) and Niemann Pick disease type C (Abel, 2009), as well as TBI (Heitger et al., 2009), all of which are associated with poorer performance on the task. As these conditions are associated with structural brain changes, the self-paced task was performed as an exploratory task to investigate whether the structural brain changes involved with AN also influence performance. As the self-paced saccade task involves internally generated saccades in the absence of reflexive triggers, it is considered an almost entirely endogenous task. Therefore, the trend for longer intersaccadic intervals in AN may suggest altered functioning in areas related to the triggering of saccades such as the SC. Furthermore, this trend may be related to deficits in BG function as poor performance on this task has been associated with conditions with considerable BG pathology, such as Parkinson’s disease and Huntington’s disease.
5.10.2 Memory-guided saccade task

In relation to the memory-guided saccade task, AN participants were hypothesised to display poorer performance evident by an increased rate of inhibitory errors, and increased latency and reduced gain of correct responses. A trend for longer latencies of correct responses was revealed for AN participants relative to controls, suggesting a potential deficit in the triggering of saccades in the SC, similarly to the self-paced saccade findings. However, contrary to expectations, latency and gain did not significantly differ between groups, which suggests that visuospatial memory of simple stimuli may be unimpaired in AN. Similar findings of intact latency and gain have also been reported in other conditions such as MDD (Sweeney et al., 1998) and TS (A. Straube et al., 1997). Increased latency and differences in gain on the memory-guided saccade task have, however, been reported in other conditions such as schizophrenia (e.g. Brenner et al., 2001; McDowell et al., 2001; Müller et al., 1999), ADHD (Castellanos et al., 2000; Goto et al., 2010; Loe et al., 2009) and ASD (Luna et al., 2007; Luna et al., 2002). AN participants were however found to show an increased rate of inhibitory errors on the memory-guided saccade task. These errors appeared to occur more often with shorter latencies, suggesting participants were generating more reflexive saccades toward the peripheral stimulus rather than an increased rate of inhibitory responses during the response period. Therefore, similarly to the lack of group difference in antisaccade error rate, AN participants did not show a failure to inhibit a planned response in this task. They did, however, demonstrate a failure to inhibit a reflexive response to the peripheral stimulus, which may be indicative of an inhibitory failure during fixation when two competing stimuli are presented. The rate of inhibitory errors specifically to targets presented at 10°, but not to targets presented at 5°, was also found to be increased in AN. The SC is specifically involved in the inhibition and initiation of saccades. Excitatory inputs from the rostral SC project to the omnipause neurons inhibiting excitatory burst neurons, which gives rise to saccades (Munoz & Wurtz, 1993a). Cells that generate saccade-related bursts and when stimulated produce saccades are organised topographically in the SC, with smaller amplitude saccades being initiated by more rostral areas of the SC and larger saccades by more caudal areas (Sparks, 2002). Furthermore, the injection of the gamma-aminobutyric acid (GABA) agonist muscimol into the rostral SC, thereby increasing GABA activity, has been found to
increase the rate of inhibitory errors during a memory-guided saccade task (Munoz & Wurtz, 1993b). Therefore, increased GABA in a specific area of the SC may result in the inhibitory problems to this specific amplitude in AN.

Increased inhibitory errors have also been reported in other psychiatric conditions such as schizophrenia (e.g. Brenner et al., 2001; Camchong et al., 2006; Fukushima, Fukushima, et al., 1990), ASD (Castellanos et al., 2000; Goto et al., 2010; Loe et al., 2009) and ADHD (M. C. Goldberg et al., 2002; Minshew et al., 1999). Individuals with OCD have also been found to make more inhibitory errors on a memory-guided saccade task, but only to targets presented at 9°, and not to larger targets at 18° or 27° (Rosenberg, Averbach, et al., 1997). The current study similarly found an increased rate of inhibitory errors in AN specific to targets presented at 10° from central fixation, suggesting potential involvement of a similar neural mechanism in OCD and AN. Unlike the current study however, the study by Rosenberg, Averbach, et al. (1997) did not present stimuli at smaller amplitudes. Therefore, whether intact performance on 5° saccades is also present in OCD has not been evaluated. Furthermore, the study by Rosenberg, Averbach, et al. (1997) was undertaken in paediatric OCD, and no group differences were found to any target amplitude in another study by the same group in adults with OCD (Rosenberg, Dick, et al., 1997).

It was also hypothesised that the rate of inhibitory memory-guided saccade errors would positively correlated with scores on the BIS-11. The rate of inhibitory errors at both 5° and 10° were however not found to correlate with any measure of the BIS-11. Similarly, self-report measures of impulsivity often suggest that individuals with AN are less impulsive or do not differ in impulsivity from healthy individuals (G. K. L. Butler & Montgomery, 2005; Claes et al., 2002; W. H. Kaye et al., 1995; Rosval et al., 2006). The current study similarly found a lack of group differences on most measures of the BIS-11. However, AN participants were found to report a greater level of attentional impulsivity, and lower motor impulsivity than healthy controls. However, a number of behavioural measures, such as the go/no-go task (not the saccade variant of this task) have suggested greater impulsivity in AN (G. K. L. Butler & Montgomery, 2005; Hatch et al., 2010b). As AN is associated with high levels of perfectionism and particular concerns over making mistakes (Bulik et al.,
2003), the discrepancy between behavioural impulsivity and self-reported impulsivity may be related to the perfectionistic traits possessed by these individuals and their concerns related to performing tasks flawlessly.

5.10.3 Prosaccade/antisaccade/no-go saccade (PAN) task

Participants in the current study also underwent a PAN saccade task while undergoing fMRI. The eyetracking findings and findings from the fMRI analysis are discussed below.

5.10.3.1 Eyetracking

During the PAN saccade task, it was hypothesised that the group of AN participants would demonstrate increased errors on the antisaccade and no-go components of the task, but not the prosaccade task. The results of the study, however, indicated that error rate between groups did not significantly differ on any component of the task. Although the rate of correct responses was significantly lower in AN, the rate of missing responses was also higher in AN. Therefore, the group difference in correct response rate was likely due to AN participants having a greater number of trial losses. These missing trials were typically due to long blinks constituting the entire trial, presumably due to fatigue. Prosaccade error rate is typically found to be intact in psychiatric illnesses, though increased antisaccade error rates are often reported in schizophrenia, BD, MDD and ADHD (see Hutton & Ettinger, 2006 for a review). Increased error rates have also been reported in OCD (Lennertz et al., 2012; Rosenberg, Averbach, et al., 1997; Tien et al., 1992), though others have failed to find a difference in antisaccade error rate (Kloft et al., 2011; Maruff et al., 1999; McDowell & Clementz, 1997; Spengler et al., 2006; van der Wee et al., 2006) and no-go saccade error rate (van der Wee et al., 2006). The finding of intact antisaccade and no-go saccade error rate in the current study suggests intact functioning of the FEF, SEF, ACC and DLPFC, which was further investigated with fMRI and discussed below. Furthermore, the peak velocity of 5° no-go errors was found to be slower in AN, though the significance of this finding is limited as only few no-go errors were made by either group.

AN participants were also hypothesised to show increased latency and reduced gain of correct antisaccade responses. This hypothesis was also not supported by the
findings as latency and gain of antisaccades did not significantly differ between AN and control groups. Similarly to the literature regarding antisaccade errors, clinical populations such as schizophrenia are often reported to make antisaccades of increased latencies and reduced gains (e.g. Ettinger et al., 2004; M. S. H. Harris et al., 2009; Karoumi et al., 1998; Raemaekers et al., 2002), whereas conflicting findings have been reported for other psychiatric conditions such as OCD. Several studies have reported intact latency and gain of antisaccades (Kloft et al., 2011; Rosenberg, Averbach, et al., 1997; Spengler et al., 2006), while others report significantly increased antisaccade latencies in OCD (Maruff et al., 1999; McDowell & Clementz, 1997; van der Wee et al., 2006). The finding of intact latency and gain of antisaccades in the current study suggests an intact representation of simple spatial information in AN.

The hypothesis regarding intact performance on prosaccade trials was also not supported by the findings. Although gain and peak velocity of correct prosaccade responses did not differ between groups, prosaccade latency was shorter in AN compared to healthy controls, but was not related to self-reported impulsivity. The finding of shorter prosaccade latencies differs to that commonly reported in other conditions whose prosaccade performance, including prosaccade latencies, is typically unimpaired. However, one study reported shorter prosaccade latencies in antipsychotic-naïve first-episode schizophrenia patients (Reilly, Harris, Keshavan, & Sweeney, 2005). In this study, participants were tested prior to and following antipsychotic treatment. Though the schizophrenia group displayed shorter prosaccade latencies at baseline, prosaccade latencies were not found to differ from healthy individuals following treatment with the atypical antipsychotic risperidone. The typical antipsychotic haloperidol, however, did not result in improved latencies at follow-up. The authors suggested that the shorter prosaccade latencies pre-treatment may be explained by reduced neocortical (DLPFC, FEF, SEF and parietal eye fields) regulation of brainstem systems in schizophrenia, which are improved with atypical antipsychotic treatment. This study however differs from the majority of the literature which has suggested preserved prosaccade latencies in schizophrenia (e.g. Landgraf et al., 2008; Raemaekers et al., 2002). As individuals with schizophrenia are found to make an increased rate of express saccades (saccades occurring within 120ms) (Clementz, 1996; C. Winograd-Gurvich et al., 2008), the findings by Reilly et al.
(2005) may be attributable to this. However, express saccades are typically found at an increased rate during a gap paradigm which was not used in the study by Reilly et al. (2005). A gap paradigm was also not utilised in the current study and the shorter prosaccade latencies in AN did not appear to be influenced by an increased rate of express saccades, but shorter latencies on average of prosaccades. The SC is involved in triggering saccades and lesions of the SC result in increased prosaccade latency (Schiller et al., 1987). However, the injection of GABA into the rostral SC has been found to result in shorter latencies to visual targets (Munoz & Wurtz, 1993b). Therefore, increased GABA activity in the rostral SC may be involved in the faster prosaccade latencies observed in AN. Furthermore, the shorter latency of prosaccades, but intact latency of antisaccades, may suggest a faster neural response in AN than healthy individuals to more reflexive responses requiring fewer resources from higher cognitive areas. More specifically, reduced prosaccade latencies may reflect a speeded neural response in the sensorimotor pathway between visual input and the visuomotor system. Therefore, further investigations utilising MEG to investigate the temporal characteristics of these responses would be beneficial.

5.10.3.2 Functional magnetic resonance (fMRI)

AN participants were hypothesised to show decreased FEF, SEF, ACC and DLPFC activity during response periods of correctly executed antisaccades relative to prosaccades and no-go trials, in comparison to healthy controls. Furthermore, activation differences were not expected between groups during preparatory (cue) periods. The findings of the study partially supported the hypotheses. Groups were not found to significantly differ in cue periods in contrasts between any of the PAN saccade components. Groups were, however, also not found to differ during the response periods of any components. These results are perhaps not unforeseen following the results of the eyetracking analyses, which produced largely non-significant findings. Other psychiatric illnesses such as schizophrenia are associated with differences in BOLD activity during antisaccade trials relative to healthy individuals, but these studies also reported poorer behavioural performance (Camchong et al., 2008; McDowell et al., 2002; Tu et al., 2006). As prosaccade performance is typically intact in psychiatric conditions, BOLD activity is consequently also not found to differ between groups (Keedy et al., 2006; McDowell
et al., 2002). The finding of shorter prosaccade latencies in AN was perhaps too subtle to be observed in BOLD activity differences due to the slow nature of the BOLD signal. Furthermore, as the SC is difficult to image due its small size, deep location and close proximity to vascular structures, its potential involvement in reducing prosaccade latencies in AN may not have been achievable with the current fMRI acquisition which was not optimised to image the SC as it was not an area of expected deficit.

5.10.4 Summary and conclusions

Overall, the results of the study suggest intact performance on the majority of saccade components in self-paced, memory-guided and PAN saccade tasks in AN. The findings from the eyetracking and fMRI analyses suggest largely intact functioning of the brain regions involved in these tasks, including the FEF, SEF, ACC and DLPFC. Two specific differences were however observed in AN participants: an increased rate of inhibitory errors to 10° targets during the memory-guided saccade task and faster prosaccade latencies during the PAN saccade task. Together these results potentially implicate altered functioning of the SC in AN, and may be related to GABA function in this area. However, whether medications that AN participants were taking influenced these results, particularly benzodiazepines which enhance GABA transmission, is unclear. Though, to the best of our knowledge, no medications have been found to result in increased inhibitory errors in the memory-guided saccade task or reduced prosaccade latencies.

AN participants were also found to have an increased number of missing responses during the PAN saccade task which may have influenced the power of the fMRI analysis. Missing responses were typically due to eyetracker drop-outs as a result of partial lid closures or increased blink durations. Although this may have resulted in reduced engagement in the task, the fMRI results did not indicate a disengagement of the task in AN participants. The increased fatigue observed in patients may reflect their malnourished state. The AN participants in this study were medically stable and the majority were not inpatients at the time of testing. However, studies more often investigate inpatients with AN who are physically very unwell and who would presumably fatigue more easily. As this study examined eyetracking with fMRI, we were able to determine potential fatigue in our participants and missing
trials were excluded from the analysis. Whether other studies monitored participants for fatigue during fMRI tasks is rarely commented on in the literature, and may be partly responsible for the inconsistency among fMRI findings in AN, particularly for event-related tasks with short trial durations in which an entire trial may be missed due to fatigue. A further limitation of the current study is that although the findings suggest a potential role of GABA and the SC in AN, their roles remain speculative as they were not specifically investigated. Future research utilising magnetic resonance spectroscopy to investigate GABA concentrations in the SC would increase the value of these findings and may assist in the explanation of the results. It would also be beneficial to utilise neuroimaging techniques with superior temporal resolution to fMRI, such as MEG, to investigate whether temporal characteristics differ between groups on these tasks; particularly the prosaccade task where reduced latencies were found in the AN group.

Overall, this study suggests that individuals with AN have intact performance on a number of saccade tasks frequently found to show deficits in other psychiatric conditions, and suggests unimpaired functioning of brain areas involved in these task components in AN. The findings however suggest similarities to some reported findings in OCD, particularly an increased rate of inhibitory memory-guided saccade errors of similar amplitude. This increased rate of inhibitory errors, together with the finding of shorter prosaccade latencies in the AN group, suggest reduced fixation engagement and a potential role of GABA and the SC in the psychopathology of AN.
6.1 Emotion processing in anorexia nervosa

AN has long been associated with deficits in the perception of emotion. In one of the earliest reports, Bruch (1962) observed a marked deficiency in the description of feelings and emotional responses in patients with AN. Later research has linked these observations to the construct of alexithymia, which is defined as a difficulty in identifying and describing subjective feelings, a difficulty in distinguishing between feelings and the bodily sensations of emotional arousal, an externally oriented cognitive style, and a lack of imaginal capacity and fantasy (Nemiah, Freyberger, & Sifneos, 1976; G. J. Taylor, 2000). In the early 1990’s, Bagby et al. (1994) developed the TAS-20, which has become the most widely used instrument of the alexithymia construct. Utilising this measure, various researchers have investigated the rate of alexithymia in eating disorders and AN. In a study by Bourke, Taylor, Parker, and Bagby (1992), 77.1% of individuals with AN were found to have alexithymia compared to a prevalence of 6.7% in healthy matched controls, which was unrelated to duration of illness, severity of weight loss or level of depression. In a more recent study however, individuals with AN were found to show higher levels of alexithymia than healthy controls, though this difference was no longer apparent after controlling for depression and anxiety (Parling, Mortazavi, & Ghaderi, 2010). As individuals with anxiety and depression have been consistently found to show emotion processing difficulties (for reviews see Etkin & Wager, 2007; Leppänen, 2006), and AN is often associated with high levels of these traits (W. H. Kaye et al., 2004; Pollice et al., 1997; Wade et al., 2000), it is important to control for them to ensure that any emotion processing deficits are not due to these factors. For example, a study by Castro, Davies, Hale, Surguladze, and Tchanturia (2010) observed that obsessive-compulsive symptoms were a stronger predictor of impaired emotion discrimination of sad faces than was a diagnosis of AN per se. Combined groups of individuals with AN-R, AN-BP and BN have also been found to score higher on the alexithymia construct than healthy individuals (Cochrane, Brewerton, Wilson, & Hodges, 1993; Corcos et al., 2000; Eizaguirre, de Cabezon, de Alda, Olariaga, & Juaniz, 2004; Kessler, Schwarze, Filipic, Traue, & von Wietersheim, 2006; Schmidt, Jiwany, & Treasure, 1993; Troop, Schmidt, & Treasure, 2006). Additionally, individuals with AN have been shown to
display higher alexithymia scores than individuals with BN (Corcos et al., 2000; Schmidt et al., 1993). However, when controlling for rate of depression, alexithymia scores have been found to not differ between the different eating disorder groups (Corcos et al., 2000); and similarly to the study by Parling et al. (2010) comparing AN to healthy controls, when controlling for both depression and anxiety, differences in alexithymia between eating disorder groups and healthy controls have been found to disappear (Eizaguirre et al., 2004). However, a study by Bydlowski et al. (2005) reported higher levels of alexithymia among eating disorder patients compared to controls that persisted after controlling for anxiety but not after controlling for depression. This study also reported no difference between AN subtypes in alexithymia scores or emotional awareness as measured by the Level of Emotional Awareness Scale (LEAS). The LEAS assesses an individual’s capacity to describe their own emotions as well as the emotional states of others (Lane, Quinlan, Schwartz, Walker, & Zeitlin, 1990).

Furthermore, Bydlowski et al. (2005) reported lower emotional awareness of both the self and others in comparison to both individuals with BN and healthy controls. Scores on the LEAS have however been reported to not differ between AN and healthy individuals in one study (Parling et al., 2010), and only differ in imagining emotions in oneself in another study (Oldershaw et al., 2010). The later study also reported that individuals recovered from AN did not differ from either current AN or healthy control groups on level of emotional awareness. This study also investigated emotional theory of mind in ill and recovered AN, and healthy individuals. Although differences in the reading the mind in the eyes task were not found overall, as was the case in a study by A. Harrison et al. (2009), individuals ill with AN showed poorer performance for negative emotions in comparison to recovered AN and healthy controls, who did not differ. Furthermore, in the reading the mind in the voice task, individuals currently ill with AN demonstrated poorer performance than recovered individuals and controls. More specifically, individuals ill with AN were poorer at inferring negative emotions from voices. Additionally, the recovered AN group demonstrated superior performance than ill AN on the voice stimuli portraying positive valence.
Individuals with AN have also been found to show difficulties in recognising emotions expressed by human faces. The most widely used set of human face images displaying different emotions was developed by Ekman, Friesen, and Press (1975). It consists of individuals displaying the six universal emotions, i.e. happiness, sadness, anger, fear, disgust and surprise, in addition to faces displaying a neutral condition. This standard set of images has been utilised to assess perception of emotional faces in both clinical and nonclinical populations. In AN, a study using these stimuli to investigate emotion recognition difficulties revealed that patients made significantly more errors in emotion identification and had significantly longer response times than healthy individuals (Jänsch, Harmer, & Cooper, 2009). Furthermore, the study revealed that no particular emotion was identified more poorly or slowly in AN, suggesting an overall emotion recognition deficit which was not emotion-specific. Research utilising different stimulus sets have however reported different results. A study by Kessler et al. (2006) who compared a group of AN and BN participants to healthy controls found an emotion recognition deficit specific to surprised faces in the eating disorder group. Legenbauer, Vocks, and Rüddel (2008) also reported normal emotion recognition to the six basic emotions in BN, but poorer recognition of surprise. However, in a study by Ashworth et al. (2011) in which angry and disgusted faces were presented to participants during fMRI, BN participants were poorer at correctly matching emotions. This study also reported no difference in neural activation when comparing angry and disgusted face presentations in BN compared to controls. However, when utilising a region of interest analysis, BN participants were found to show greater right amygdala activity to angry faces, but this study did not employ a neutral condition, or neutral face stimuli, making the interpretation of the results difficult.

A study in AN using photographs depicting the six universal emotions described above as well as the emotions of interest, contempt and shame, found that the patient group were poorer at recognising negative emotions, particularly faces depicting sadness and fear (Kucharska-Pietura, Nikolaou, Masiak, & Treasure, 2004). The same study also investigated emotion recognition of spoken sentences. A set of five semantically neutral sentences were spoken aloud by an actor expressing one of the six basic emotions. AN patients were reported to less accurately perceive emotions in this task, in comparison to controls, particularly for the trials depicting happiness.
and sadness. In a study where the set of emotional face stimuli consisted of the six universal emotions, in addition to contempt, Zonnevijlle-Bendek, Van Goozen, Cohen-Kettenis, Van Elburg, and Van Engeland (2002) examined forced-choice emotion recognition and free labelling of emotions in a group of eating disordered individuals (AN, BN and EDNOS). The study revealed that the eating disordered group were significantly poorer at accurately recognising emotions than healthy controls in both conditions of the task. However, in another study utilising a set of emotional face stimuli developed by Hess and Blairy (1995) portraying the emotions of happiness, sadness, anger, disgust and fear performed by two actors in still images, no significant differences in emotional face recognition were observed between AN patients and controls (Mendlewicz, Linkowski, Bazelmans, & Philippot, 2005). Instead of asking participants to label the emotion of facial stimuli, a novel study undertaken by Joos, Cabrillac, Hartmann, Wirsching, and Zeeck (2009) asked participants to rate how they personally experienced these stimuli. The stimuli consisted of the facial expressions of happiness, sadness, anger and fear, and participants were required to express their own feelings when presented with these stimuli out of the emotions of happiness, sadness, anger, fear and disgust, and on a severity scale of 1-7. Individuals with AN were found to show increased fear to stimuli depicting anger, though they were not found to differ on perception of any of the other emotions.

Recent neuroimaging studies have also revealed emotional face processing deficits in AN. In a visual-evoked potential study of emotional human faces by Pollatos, Herbert, Schandry, and Gramann (2008), the authors used stimuli consisting of the emotions of happiness, sadness, anger, fear and disgust, and neutral affect faces. In addition to individuals with AN showing difficulties in emotion recognition, especially for sad, neutral and disgusted images, the investigators also reported increased N200 amplitudes to all of the emotions, and decreased P300 amplitudes to aversive emotions in AN patients compared to controls. Similarly, Hatch et al. (2010a) reported reduced early and late ERP components when AN patients were underweight and weight-restored, particularly in temporo-occipital regions to face stimuli depicting the same emotions as the study by Pollatos et al. (2008). The study by Hatch et al. (2010a), however, reported no significant difference in emotion identification accuracy or reaction time in the ill AN group, and no difference in
accuracy but significantly faster reaction times for the correctly identified happy faces following weight gain. In an fMRI study where AN participants were presented with mildly happy, prototypically happy and neutral faces during an implicit gender discrimination task, increased right fusiform gyrus activity was reported to all emotions, relative to controls (Fonville, Giampietro, Surguladze, Williams, & Tchanturia, 2014). In an earlier study where recovered AN participants and healthy controls were presented with fearful and happy human faces, whole brain and region of interest analysis revealed no difference between conditions or groups (Cowdrey, Harmer, et al., 2012). The findings of this study are however limited as only happy and fearful emotional stimuli were utilised rather than a more comprehensive range including other emotions, particularly neutral stimuli which could provide a basis for appropriate comparisons. In a study presenting negative words related to interpersonal relationships however, individuals with AN were found to show increased activity in the DLPFC, orbitofrontal and medial prefrontal cortex compared to processing neutral words, suggesting more cognitive processing of emotional stimuli (Miyake et al., 2012). Furthermore, activity of the amygdala, and anterior and posterior cingulate cortices were found to be negatively correlated with level of alexithymia in the AN group.

6.2 Emotion processing in the brain

The processing of emotion has long been associated with involvement of the limbic system of the brain (LeDoux, 2000). Included among the structures of the limbic system are the hippocampus, amygdala, cingulate gyrus and anterior thalamic nuclei (Kandel, Schwartz, & Jessell, 2000). The medial prefrontal cortex is also highly associated with emotional processing, particularly with the cognitive processes associated with emotion processing, with neuroimaging studies reporting activity not specific to any particular emotion (see Phan, Wager, Taylor, & Liberzon, 2002 for a meta-analysis). In a meta-analysis undertaken by Phan et al. (2002), the authors describe that specific emotions have also been associated with activity of specific regions of the brain. Activation of the amygdala is regularly reported in studies examining fear, the cingulate is often associated with sadness, and the BG are often activated in response to happiness and disgust. Furthermore, activity in these areas,
among others, has also been associated with emotional processing specifically in response to images of human faces.

6.2.1 Face processing and perception

The perception of faces is a unique process which allows us to seemingly effortlessly gather information about an individual, including information about their identity, age, gender and emotional state. A number of models exist which aim to outline how face processing is achieved, including developmental, cognitive, computational, social and ecological approaches (for reviews see A. Calder, Rhodes, Johnson, & Haxby, 2011; Hole & Bourne, 2010). Of particular interest are the neural systems involved in the perception of faces. Three bilateral regions (though more reliably and consistently found in the right hemisphere) of the occipital-temporal extrastriate cortex respond maximally to faces: the posterior superior temporal sulcus (pSTS), the occipital face area (OFA), and the lateral fusiform gyrus, also known as the fusiform face area (FFA) (Haxby et al., 2001; Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997; Kanwisher & Yovel, 2006). The pSTS appears to play a role in the perception of facial movement, including eye gaze and facial expression (Engell & Haxby, 2007; Hoffman & Haxby, 2000), the FFA is thought to have greater involvement in recognising identity (Hoffman & Haxby, 2000), whereas the OFA is thought to provide input to both of these areas (Haxby et al., 2000). The FFA has been of specific interest as activity in this area in response to faces has been well documented in the literature, and has been found to be active in comparison to a wide variety of non-face stimuli including a basic fixation cross (S. A. Surguladze et al., 2003), images of houses (Haxby et al., 2000; Kanwisher et al., 1997), insects (Rhodes, Byatt, Michie, & Puce, 2004), letter-strings and textures (Puce, Allison, Asgari, Gore, & McCarthy, 1996). Not only has the FFA consistently been found to respond to images of faces, but it has also been reported to respond to line drawings depicting faces and two-tone face images known as Mooney faces (Kanwisher, Tong, & Nakayama, 1998; Spiridon & Kanwisher, 2002). The FFA is also activated when individuals are presented with the face-vase illusion, but only when the individual reports perceiving faces rather than a vase (Andrews, Schluppeck, Homfray, Matthews, & Blakemore, 2002). The FFA, as well as the OFA and pSTS, have also been found to result in stronger activations when faces depict emotion rather
than neutral expressions (Engell & Haxby, 2007). Moreover, emotional facial expressions also result in activity of areas of the brain responsible for the perception of that specific emotion.

6.2.1.1 Emotional face processing and perception

The perception of facial emotion appears to be an innate human ability that is universal across different cultures. The ability to correctly classify the six basic, or universal, emotions has been found in both literate cultures including the United States, Brazil and Japan, and in illiterate cultures such as the Fore people of Papua New Guinea and the Sadong people of Borneo, though with poorer accuracy than those of Western cultures (Ekman & Friesen, 1971; Ekman, Sorenson, & Friesen, 1969). These studies however presented individuals with images of different emotions posed by American models. A recent study by Wickline, Bailey, and Nowicki (2009) reported that individuals are better able to accurately judge an emotion when the emotion is expressed by someone of their own cultural group. Individuals are also better able to and faster at recognising positive emotions, such as happiness, over negative emotions (Calvo & Lundqvist, 2008). However, there is only one clearly positive emotion (happiness), whereas several negative emotions exist (sadness, anger, fear and disgust). Therefore, it has been suggested that happiness may not be easier to differentiate, but negative emotions are more easily confused for other emotions (Hole & Bourne, 2010).

Although healthy individuals are able to perceive different emotions with ease, whether specific neural substrates exist for processing different categories of emotion is unclear. Functional imaging studies of emotional face perception are typically performed as implicit tasks, such as gender decision tasks, rather than explicit tasks as they are less cognitively demanding and do not interfere with emotional processing. As explicit tasks have a higher cognitive demand, more frontal areas are involved and it is more difficult to observe the areas involved in emotion processing (Critchley et al., 2000; Gorno-Tempini et al., 2001). Some evidence exists which links the emotions of anger, sadness, happiness and surprise to specific neural substrates. In comparison to the presentation of neutral faces, the presentation of angry faces has been found to result in increased activity of the right posterior cingulate cortex, right
amygdala and the left inferior frontal and posterior temporal cortices (H. Fischer et al., 2005; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). Sad faces have been reported to activate the left FFA, right inferior frontal gyrus, thalamus, amygdala, bilateral posterior cingulate cortex, and the postcentral and dorsomedial frontal gyri, in comparison to neutral faces (S. A. Surguladze et al., 2003). S. A. Surguladze et al. (2003) also found increased activity of the bilateral posterior cingulate, left FFA and right superior frontal gyrus in response to happy versus neutral faces, whereas M. L. Phillips, Bullmore, et al. (1998) reported increased activity of the ACC, posterior cingulate, supramarginal gyrus and medial frontal cortex in an explicit task. In a passive viewing task however, Breiter et al. (1996) reported increased amygdala activity to happy faces in comparison to faces of neutral affect. In implicit viewing tasks comparing happy to fearful faces, increased activity of the left superior parietal cortex and striate, and right middle temporal gyrus and putamen has been found (J. S. Morris et al., 1998; J. S. Morris et al., 1996). Implicit viewing of surprised facial images relative to neutral images has been reported to lead to increased activity of parahippocampal regions (Schroeder et al., 2004). A study where participants were presented with surprised and neutral faces while undergoing fMRI and asked to rate the faces on perceived positive or negative valence revealed that surprised faces with more negative interpretations resulted in increased right ventral amygdala activity compared to neutral faces, and more positive interpretations were associated with increased activity of the medial prefrontal cortex (H. Kim, Somerville, Johnstone, Alexander, & Whalen, 2003). In a follow-up study, H. Kim et al. (2004) presented positively or negatively valenced sentences before images of surprised faces rather than relying on subjective experience of participants. Similar results were reported. Increased ventral amygdala activity was found to positively cued surprised faces, and greater ventromedial prefrontal cortex activity was found to negatively cued surprised images.

Although limited evidence exists linking specific neural substrates to the emotions of happiness, sadness and anger, strong evidence exists for the role of the amygdala in the processing and recognition of fear, and the insula in the processing of disgust. Implicit tasks investigating neural responses associated with the processing of disgusted facial expressions have reported increased activity predominantly of the anterior insula but also of the FFA, posterior cingulate, BG and inferior frontal cortex,
in comparison to neutral faces (M. L. Phillips, Young, et al., 1998; M. L. Phillips et al., 1997; Schroeder et al., 2004; Sprengelmeyer et al., 1998; S. A. Surguladze et al., 2003).

Faces depicting a fearful facial expression have been consistently found to activate the amygdala, but have also been found to activate the FFA, and extrastriate, cingulate and frontal cortices, in comparison to faces of neutral expression (Breiter et al., 1996; M. L. Phillips, Young, et al., 1998; M. L. Phillips et al., 1997; Sprengelmeyer et al., 1998; S. A. Surguladze et al., 2003; Vuilleumier, Armony, Driver, & Dolan, 2001). Increased activity of the amygdala has also been reported in a series of PET studies contrasting stimuli of fearful faces to happy faces (J. S. Morris et al., 1998; J. S. Morris et al., 1996). However, a small number of studies have found increased amygdala activation which was not selective to the emotion of fear, but was also activated in response to happy, sad, angry, disgusted and neutral facial expressions (D. A. Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Habel et al., 2007; T. T. Yang et al., 2002). Although functional neuroimaging studies have provided strong support for the roles of the amygdala and insula in fear and disgust processing, respectively, lesion studies have also provided evidence for the roles of these regions in emotional face processing and perception. Several studies have reported an association between amygdala lesions and deficits in the recognition of fear from facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs et al., 1999; A. J. Calder, 1996), and insula lesions and the inability to recognise disgust (A. J. Calder, Keane, Manes, Antoun, & Young, 2000). Furthermore, one study reported difficulty in recognising sad faces in bilateral amygdala lesions but not unilateral amygdala lesions (A. J. Calder, Keane, Lawrence, & Manes, 2004), whereas another study reported difficulty in recognising angry faces in ventral striatal lesions (A. J. Calder et al., 2004). Additionally, evidence for the role of different brain areas in emotional face recognition has come from studies in neurodegenerative disorders in which specific areas of the brain are affected. Frontotemporal dementia is associated with difficulty in recognising a range of negative emotions (Keane, Calder, Hodges, & Young, 2002; Rosen et al., 2002). Huntington’s disease, which is associated with neuropathology of the striatum (Halliday et al., 1998), has been associated with impaired emotional face discrimination, particularly for the emotion of disgust (Sprengelmeyer et al., 1996). In contrast, Parkinson’s disease, which targets the BG
(Blandini, Nappi, Tassorelli, & Martignoni, 2000), is not associated with emotion recognition deficits (Adolphs, Schul, & Tranel, 1998). The processing of emotional faces has also been investigated with the use of eyetracking studies, or more specifically, with the use of visual scanpath analyses.

6.2.2 Visual scanpaths

Saccadic eye movements do not occur in isolation but are preceded and followed by a period of fixation, resulting in a continuous sequence of saccade, fixation, saccade, fixation, and so on. This sequence is referred to as a visual scanpath and describes the pattern of eye movements that we use to view visual scenes. In one of the earliest scanpath studies, Buswell (1935) took a photographic record of participants’ eye movements as they observed works of art. The author demonstrated that fixations were not made to random locations of the scene, but were made to regions rich in information, suggesting a relationship between eye movements and visual attention. Visual attention appears to be driven by two processes, ‘bottom-up’ and ‘top-down’ processes. Bottom-up processing describes attention that is driven by sensory stimuli and directed toward salient stimuli (Itti & Koch, 2001; Sarter, Givens, & Bruno, 2001). For example, bottom-up processing would occur when attention is drawn to a blue flower among a field of yellow flowers. Whereas top-down processing is driven by higher cortical processes regardless of visual salience (Sarter et al., 2001), for instance, when looking for a small blue flower in a field of large blue flowers. Visual attention tends to be better predicted by top-down processing, where saccades are made toward locations that provide important information for the task at hand (Liversedge et al., 2011). Moreover, scanpaths differ depending on the task or the instruction given. In a pioneering study by Yarbus (1967), participants were presented with a picture, Repin’s ‘An Unexpected Visitor’. The investigator reported that scanpaths differed and attention was focused on different areas of the scene depending on the instruction provided, whether to freely view or to evaluate different aspects of the scene. A number of factors have the potential to influence gaze direction and duration on a scene including saliency factors such as the quality, contrast and luminance of stimuli in the scene (Einhauser & Konig, 2003; Vu & Chandler, 2008), and semantic influences demonstrated by more and longer fixations on relevant and informative stimuli (see De Graef, 2005 for a review).
Essentially, a visual scanpath is a gaze map tracing the direction and extent of gaze on a visual scene (Noton & Stark, 1971). Measurements relating to fixation are typically the main parameters studied in visual scanpath research, where fixation typically refers to gaze that is restricted to less than 1° of the visual field for a minimum of 200ms (Noton & Stark, 1971). Temporal scanpath parameters typically analysed include average number of fixations and average fixation duration. Spatial parameters, such as saccadic amplitudes or raw distance between fixations, are also sometimes analysed, though less frequently. To investigate visuospatial attention, scanpath studies also assess spatio-temporal parameters such as the number of and duration of fixations to regions of interest in the scene (M. L. Phillips & David, 1997, 1998; L. M. Williams, Loughland, Gordon, & Davidson, 1999). Visual scanpath tasks can be assessed in both healthy and clinical populations, providing valuable information on visual processing and visuospatial cognition in an unlimited range of scenes or images. Research has investigated gaze patterns to a variety of stimuli, particularly human faces.

6.2.2.1 Visual scanpaths to human faces

During the processing of neutral facial stimuli, healthy individuals typically focus on salient features such as the eyes, but also the nose and mouth. These fixations tend to create an inverted triangular gaze pattern between the two eyes, nose and mouth (Walker-Smith, Gale, & Findlay, 1977). Furthermore, we typically display more scanning of the left side of the visual field, or the right side of a face, compared to the opposite side. This phenomenon appears to be unique to the scanning of faces and is not reported when viewing other types of stimuli (Kolb & Whishaw, 2009). As stimuli presented to the left visual field are processed by the right hemisphere of the brain, it has been suggested that facial processing is a predominantly right hemisphere function, a theory which is supported by visual field studies which have reported a right hemisphere dominance for both positive and negative facial stimuli (Ashwin, Wheelwright, & Baron-Cohen, 2005; Christman & Hackworth, 1993).

Recent research has redirected its focus away from general face processing toward the processing of faces of different emotions and their corresponding visual scanpaths. Typically, the most time is spent focusing on the eyes irrespective of the
emotion portrayed in the face (Eisenbarth & Alpers, 2011; Hernandez et al., 2009). However, for the emotions of fear and happiness, Eisenbarth and Alpers (2011) reported that the mouth is fixated on as frequently as the eyes, and the mouth is fixated on for longer durations for happy expressions. The same authors also reported that there are more fixations to the eyes than the mouth for both sad and angry faces. Furthermore, M. Green, L. Williams, and D. Davidson (2003) reported an increased number of and duration of fixations to areas of interest which included the eyes, nose and mouth, for the emotions of anger and fear compared to a neutral face. Similarly, Bate, Haslam, and Hodgson (2009) reported an increased number of fixations to both angry and happy faces compared to neutral faces when the stimuli were familiar to participants, i.e. famous faces. However, when the faces were unfamiliar to the observer, fewer fixations to angry faces than happy or neutral faces were observed.

Although research investigating visual scanpaths is rather limited in AN, reduced visual attention to faces has been found when presented with whole body stimuli of others (Watson et al., 2010) and oneself (R. Freeman et al., 1991). Specifically to the processing of face stimuli, Watson et al. (2010) reported that AN participants spent less time fixating on the eyes of stimuli than controls. The findings of this study are however limited as the set of stimuli utilised were not a standardised set of images but were downloaded from a dating website, and consequently resulted in a number of emotions and poses expressed in the images.

6.2.3 Emotional face processing in clinical populations

Facial emotion processing deficits have been observed in a variety of conditions including a range of neurological and neurodegenerative conditions such as TBI (Croker & McDonald, 2005), multiple sclerosis (Henry et al., 2009), Huntington’s disease (Sprengelmeyer et al., 1996), Alzheimer’s disease (Hargrave, Maddock, & Stone, 2002), Parkinson’s disease (Sprengelmeyer et al., 2003) and frontotemporal dementia (Keane et al., 2002). This review will however focus on facial emotion processing deficits in psychiatric populations, namely, schizophrenia, childhood-onset disorders, mood disorders and anxiety disorders. As limited research in AN has been undertaken in this area, the current review will allow for the comparison of patterns between AN and other psychiatric illnesses.
6.2.3.1 Schizophrenia

It is well documented in the literature that individuals with schizophrenia demonstrate emotion processing difficulties. Individuals with schizophrenia not only exhibit difficulties in expressing emotions, but are also found to show deficits in the perception and recognition of emotion. Research has typically shown a general emotion recognition deficit in schizophrenia that is not restricted to specific emotions (e.g. Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000; Kohler et al., 2003; Salem, Kring, & Kerr, 1996). Recent neuroimaging research has also revealed BOLD activation differences between individuals with schizophrenia and healthy controls to different types of emotion, but also to faces of emotional affect in general. When presented with emotive faces, individuals with schizophrenia have been found to show decreased activity in the FFA, occipital cortex (Johnston, Stojanov, Devir, & Schall, 2005; Seiferth et al., 2008), amygdala and hippocampus (R. E. Gur et al., 2002).

Specifically, the presentation of faces displaying a neutral expression has been found to elicit increased activity of the parahippocampal gyrus (S. Surguladze et al., 2006) and amygdala (Hall et al., 2008) during implicit gender-identification tasks; and increased activity of the DLPFC, inferior and superior parietal lobules, putamen, precuneus, and the middle orbital gyrus (Habel et al., 2010), and reduced activity of the orbitofrontal cortex (Reske et al., 2009), fusiform gyrus, cuneus and superior temporal gyrus (Habel et al., 2010), during explicit emotion-discrimination tasks. When presented with happy faces relative to neutral faces, reduced activity of the ACC, medial, dorsomedial and ventrolateral prefrontal cortices, superior and middle temporal gyri, parahippocampal gyrus, fusiform gyrus, insula, hippocampus, thalamus, and areas of the occipital cortex, has been found compared to healthy controls (Habel et al., 2010). The same study also reported increased cuneus activity to happy faces in schizophrenia participants. Seiferth et al. (2008) also reported increased cuneus activity, in addition to reduced activity of the inferior occipital gyrus, fusiform gyrus and thalamus using an emotion-discrimination paradigm. However, other studies have reported no difference in activation to happy faces between schizophrenia and control groups (R. E. Gur et al., 2007; Reske et al., 2009).
Reske et al. (2009) reported increased parietal activity in schizophrenia participants when they were presented with sad faces. The presentation of sad faces has also been found to result in decreased activity of the inferior, middle and superior occipital gyri, superior temporal gyrus, posterior cingulate gyrus, inferior parietal areas, hippocampus, thalamus, insula and cerebellum of schizophrenia participants (Seiferth et al., 2008). Habel et al. (2010) found reduced activity of the ACC, and dorsomedial and ventrolateral prefrontal cortex, but increased activity of the DLPFC, cuneus, precuneus and putamen. In contrast, R. E. Gur et al. (2007) reported no activation difference compared to healthy controls when participants were asked to respond to whether a stimulus displayed a predetermined emotion or not. Although R. E. Gur et al. (2007) found no group differences for sad and happy faces, the authors did report reduced activity of the inferior frontal cortex and orbitofrontal regions to angry faces in schizophrenia patients. Reduced activity to angry faces has also been reported in the inferior occipital and fusiform gyri, thalamus (Seiferth et al., 2008), superior and middle temporal gyri and ACC (Habel et al., 2010), whereas hyperactivity has been found in the cuneus, precuneus, inferior frontal gyrus (Seiferth et al., 2008), precentral gyrus, superior parietal lobule, cuneus and medial prefrontal cortex regions (Habel et al., 2010).

In response to faces depicting fear, individuals with schizophrenia have been shown to display reduced activity of the amygdala (R. E. Gur et al., 2007; Hall et al., 2008; Michalopoulou et al., 2008), inferior frontal cortex (R. E. Gur et al., 2007; Michalopoulou et al., 2008), medial prefrontal cortex (L. L. M. Williams et al., 2007), fusiform and superior temporal gyri (Michalopoulou et al., 2008; Seiferth et al., 2008), dorsomedial prefrontal cortex, ACC, cuneus (Habel et al., 2010), and parahippocampal gyrus (Michalopoulou et al., 2008). In a study examining increasing intensity of fear stimuli, S. Surguladze et al. (2006) reported increasing parahippocampal gyrus activity for healthy individuals as the intensity increased, but reduced parahippocampal gyrus activity for schizophrenia participants. Additionally, some areas of the brain have been found to show greater activation to fearful face stimuli in schizophrenia including the cuneus (Habel et al., 2010; Seiferth et al., 2008), putamen and middle occipital gyrus (Habel et al., 2010). The BOLD response to implicit viewing of disgust has also been examined in schizophrenia with reduced medial prefrontal cortex activity being reported (L. L. M. Williams et al., 2007).
Individuals with schizophrenia also show disturbed visual scanpaths to human faces of different emotions. Generally, these individuals show restricted scanpaths to a variety of stimuli but also specifically to human faces of different emotions, evident by fewer fixations of longer duration and reduced scanpath lengths (Bestelmeyer et al., 2006; E. Gordon, Coyle, Anderson, & Healey, 1992; M. J. Green, L. M. Williams, & D. Davidson, 2003; Loughland, Williams, & Gordon, 2002b; Loughland, Williams, & Harris, 2004; Manor et al., 1999; M. L. Phillips & David, 1997, 1998; Streit, Wölwer, & Gaebel, 1997; L. M. Williams et al., 1999). Individuals with schizophrenia have also been found to make saccades during a scanpath sequence of smaller amplitude and consequently lower peak velocity than healthy controls (Bestelmeyer et al., 2006). Additionally, irrespective of the emotion displayed, individuals with schizophrenia make fewer and shorter fixations to salient facial features such as the eyes, nose and mouth (E. Gordon et al., 1992; M. J. Green et al., 2003; Loughland et al., 2002b; L. M. Williams et al., 1999). Furthermore, differing results have been observed for patients with schizophrenia depending on whether they experience delusions. Patients with delusions have been shown to have reduced fixation durations irrespective of the emotion displayed, and reduced fixation durations specifically to salient features of sad faces, relative to healthy controls (M. J. Green et al., 2003). In comparison to schizophrenia patients who do not experience delusions, the group with delusions showed fewer fixations to faces depicting fear and more fixations to salient features of happy faces (M. J. Green et al., 2003). In a series of earlier studies utilising non-standardised stimuli of human facial expressions, M. L. Phillips and David (1997, 1998) found that patients with delusions made fewer fixations overall, and made longer fixations to non-feature areas than those without delusions and healthy controls. When the delusion group was re-tested as delusions were subsiding, the increased fixation durations to non-salient features was no longer present. Additionally, schizophrenia patients with affective flattening have been found to look less at the eyes of emotional face stimuli than healthy controls and patients without affective flattening (Streit et al., 1997).

Together the findings from emotional face perception and visual scanpath studies suggest dysfunction in a range of emotional face processes in schizophrenia. Coupled with functional neuroimaging findings, a number of brain areas appear to be disturbed in schizophrenia which may be responsible for these results. A better
understanding of the emotional processes disturbed in schizophrenia has been obtained through these studies, as has a better understanding of the brain areas involved in the condition. Although a large proportion of the psychiatric literature has focused on schizophrenia, the same paradigms have been used in other conditions, particularly ASD.

6.2.3.2 Childhood-onset disorders

ASD is a condition characterised by difficulties in social interaction and marked impairments in the use of multiple nonverbal behaviours including facial expressions (American Psychiatric Association, 2013). Individuals with ASD are typically found to show difficulties in recognising the six basic emotions of facial stimuli (Bolte & Poustka, 2003; Deruelle, Rondan, Gepner, & Tardif, 2004; Wallace, Coleman, & Bailey, 2008), particularly fear (Humphreys, Minshew, Leonard, & Behrmann, 2007). Additionally, Wallace et al. (2008) found that when presenting stimuli using a piecemeal technique in which either the eyes or mouth were presented first, individuals with ASD had difficulty recognising fear from the eyes and disgust from the mouth. Furthermore, the ASD group also confused the eyes of fear stimuli as depicting anger. However, studies by Castelli (2005) and Spezio, Adolphs, Hurley, and Piven (2007) found that individuals with ASD did not differ from healthy controls in recognition of the six basic emotions of differing intensity. Teunisse and de Gelder (2001) indicated that ASD individuals low in social intelligence were more impaired on emotional face recognition than those of higher social intelligence, which may assist in explaining the contradicting results.

Brain activity during the processing of face images in ASD has been of considerable interest in the last decade. A reduction of fusiform gyrus activity is often observed in ASD when viewing faces displaying emotion (Corbett et al., 2009; Dalton, Nacewicz, Alexander, & Davidson, 2007; Dalton et al., 2005; Deeley et al., 2007; Hubl et al., 2003; Kleinhans et al., 2011; Pelphrey, Morris, McCarthy, & LaBar, 2007; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001). Reduced activation has also been observed in the amygdala (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Corbett et al., 2009; Kleinhans et al., 2011; Pelphrey et al., 2007; Pierce et al., 2001), inferior occipital gyrus, superior temporal sulcus (Pierce et al.,
2001), pulvinar, superior colliculi (Kleinhans et al., 2011) and the extrastriate cortex (Deeley et al., 2007). Specific to emotion type, individuals with ASD have shown reduced left amygdala and orbitofrontal cortex activity, and greater activity of the ACC and superior temporal cortex to faces depicting different intensities of fear (Ashwin et al., 2007). In a series of studies undertaken by Dalton et al (2005, 2007), the authors combined functional neuroimaging with eyetracking to investigate deviant processing of faces in ASD. When individuals were presented with happy, fearful, angry and neutral faces and required to respond to whether the face was emotional or neutral, control participants showed greater activation in the bilateral fusiform and occipital gyri, whereas the ASD group showed greater left orbitofrontal gyrus and left amygdala activity. ASD participants also spent less time fixating on the eyes than the healthy control group, but did not differ in fixation time in general, or fixation time specifically to the mouth.

Individuals with ASD have also been found to attend less to salient features such as the eyes, nose and mouth of emotional and neutral affect faces irrespective of the type of viewing, whether passive or active (de Wit, Falck-Ytter, & von Hofsten, 2008; Hernandez et al., 2009; Pelphrey et al., 2002). However, other studies have failed to find this difference (Spezio et al., 2007). It is a common belief that individuals with ASD look at the eyes less than healthy individuals. Although individuals with ASD have been found to spend more time fixating on the eye region than any other region of a face, they spend less time looking at the eyes than healthy individuals (Hernandez et al., 2009). It has also been proposed that individuals with ASD spend more time fixating on the mouth than any other area of the face. Neumann, Spezio, Piven, and Adolphs (2006) reported that when presented with happy and fearful faces, high-functioning ASD participants spent longer fixating on the mouth of happy and fearful stimuli than healthy controls. However, other studies have failed to find a difference between ASD and healthy groups in the time spent looking at the mouth (Hernandez et al., 2009; Rutherford & Towns, 2008) or the eyes (de Wit et al., 2008; Rutherford & Towns, 2008).
6.2.3.3 Mood disorders

Individuals suffering from mood disorders have also been found to show emotion processing difficulties. MDD in particular has been associated with poorer facial affect recognition of the six basic emotions and neutral affect faces (R. C. Gur et al., 1992; Langenecker et al., 2005; Mendlewicz et al., 2005; Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996; Rubinow & Post, 1992). In particular, R. C. Gur et al. (1992) found that a combined group of individuals with MDD and individuals in the depressed phase of BD were more likely than healthy controls to misinterpret neutral faces as sad and happy faces as neutral. Furthermore, in a study by Joormann and Gotlib (2006) the investigators found that individuals with MDD required a greater intensity of emotion to identify happy facial expressions, and less intensity to identify facial expressions of sadness and anger, than healthy controls or a group of individuals with social phobia.

Individuals with MDD have also demonstrated atypical neural responses to faces of different emotions. B. T. Lee et al. (2008) found reduced activity bilaterally in the inferior and medial orbitofrontal cortices to angry faces and decreased bilateral activation of the DLPFC, inferior and medial orbitofrontal cortex, hippocampus and caudate to faces of sad affect in MDD. A more recent study undertaken by Demenescu et al. (2011) showed increased DLPFC activation in MDD to faces depicting a happy expression. Reduced activity in the pulvinar nucleus of the left thalamus and the left parahippocampal gyrus, including the hippocampus, has also been found in response to differing intensities of happiness and fear (N. S. Lawrence et al., 2004). In a study where participants were presented with neutral faces of increasing happiness or sadness during a gender-decision task, a sample of MDD patients was found to show a linear increase in activity in the left putamen and parahippocampal gyrus and right FFA to expression of increasing sadness, whereas the healthy comparison group demonstrated a linear increase in the right putamen and bilateral fusiform gyrus to increasing happiness (S. Surguladze et al., 2005).

Responses to emotionally expressive faces have also been examined in relation to MDD treatment. In a study by Sheline (2001), MDD and control participants were presented with masked fearful, happy and neural faces at two time
points, before and after MDD participants received antidepressant treatment. MDD patients demonstrated increased left amygdala activity to all faces, particularly for faces portraying fear. Following treatment, the MDD group showed reduced bilateral amygdala activation to all faces, whereas control participants showed no difference between scanning sessions. In contrast, Canli et al. (2005) reported that increased amygdala activity in MDD patients to facial expressions of happiness, sadness, anger and fear was predictive of reduced depressive symptoms in the long-term, suggesting that neural markers may help identify those at risk of poor outcome. In a series of studies by Fu et al. (2004, 2007, 2008), the researchers investigated responses specifically to happy and sad faces before and after treatment for MDD. In the first of these studies, MDD and healthy control participants were presented with sad faces of differing intensity prior to and following antidepressant treatment (Fu et al., 2004). At baseline, patients demonstrated increased activity of the hippocampus extending to the parahippocampal gyrus, the hypothalamus, thalamus, caudate nucleus, ventral striatum, insula, dorsal cingulate gyrus and the inferior parietal cortex of the left hemisphere, and the cerebellum and ACC extending to the rostral prefrontal cortex bilaterally, relative to controls. Following treatment, reduced activations were seen in a number of these areas, in addition to a reduction in other areas, including the left amygdala, striatum and frontoparietal cortex, whereas the prefrontal cortex showed an increase in activation. Improvement of MDD symptoms was associated with decreased activity in the cerebellum, pregenual cingulate cortex and ventral striatum. In a more recent study, the investigators used the same study design to investigate responses to faces of varying intensity of happiness (Fu et al., 2007). Reduced activity of extrastriate areas was observed in MDD prior to antidepressant treatment, which was found to reverse following treatment. In the most recent study of this series, Fu et al. (2008) used a similar study design to investigate the effects of CBT in MDD in response to sad faces. Greater amygdala activity was initially observed in MDD participants, which normalised following treatment. Furthermore, MDD participants showed increased dorsal ACC and parietal cortex activity following treatment, whereas healthy control participants showed decreased activity at follow-up.

A small number of studies have also aimed to investigate whether individuals with depressive symptoms utilise different eye movement strategies when viewing faces. In a study by L. Wu, Pu, Allen, and Pauli (2012), the investigators presented
images portraying the six basic emotions and a neutral expression to a non-clinical sample of high- and low-depression scorers who were required to report the emotion displayed in the image. Participants scoring high on the depression scale spent less time fixating on feature areas which the authors indicated as the eyes, nose, mouth and eyebrows. The high-depression scorers were also found to show a bias to the left side of the image which the authors suggested may be an indicator of right hemisphere hyperactivation during recognition of emotional faces. Loughland, Williams, and Gordon (2002a) utilised clinical samples of individuals with an affective disorder (either MDD or BD), schizophrenia and a healthy control group to investigate scanpath differences to faces. Participants in this study were presented with degraded and undegraded happy, sad and neutral faces. During both a face matching task and a facial affect recognition task, the affective disorder group did not differ to control participants in any spatial or temporal variable, but showed a reduced median fixation duration and increased scanpath lengths compared to schizophrenia participants. The affective disorder group also demonstrated an avoidance of salient facial features (i.e. eyes, nose and mouth), particularly for degraded images, relative to controls and schizophrenia participants.

Recent studies have also aimed to investigate whether individuals with BD also show facial affect processing difficulties. Although some studies have failed to show any facial expression recognition deficits in BD (Malhi et al., 2007; Venn et al., 2004), other studies have reported a difference. Lembke and Ketter (2002) examined emotion recognition in manic participants with BD I, euthymic participants with BD I or II and a healthy comparison group. Overall, the manic group were poorer at emotion recognition to the six basic emotions than the other groups, and showed a particular deficit in the recognition of fear and disgust compared to the control group. The euthymic BD II participants were better able to recognise faces depicting fear than the euthymic BD I and manic participants, but did not differ to controls. McClure, Pope, Hoberman, Pine, and Leibenluft (2003) also found poorer emotion recognition in paediatric BD when presented with faces of children, but no difference to healthy controls when presented with stimuli of adult faces. Recent studies have also provided evidence for neural processing differences to facial affect in both paediatric and adult BD.
In a study by Pavuluri, Passarotti, Harral, and Sweeney (2009), the authors presented paediatric BD participants and a group of healthy individuals with happy and angry faces during two tasks, an implicit age discrimination task and an explicit emotion discrimination task. Compared to the explicit condition, during the implicit condition, BD participants showed greater left middle frontal gyrus and posterior cingulate cortex, and right amygdala and insula activity relative to controls who showed greater right superior frontal gyrus activity. In both conditions, BD participants demonstrated weaker ACC and prefrontal cortex activity, and increased fusiform gyrus and precuneus activity in comparison to controls. Dickstein et al. (2007) presented paediatric BD and healthy control groups with images of happy, angry, fearful and neutral facial expressions during fMRI. The task was split into four different blocks in which participants were asked to respond to the stimuli in one of four ways: passive viewing, to rate the threat level, to rate how afraid the image makes them feel, and a non-emotional condition in which they had to estimate the width of the model’s nose. Following the scan, participants were given a surprise recognition memory test as a measure of successful encoding of stimuli. After controlling for the poorer memory for emotional faces by the BD group, increased striatum and ACC activity was found when successfully encoding happy faces, and increased orbitofrontal cortex activity when successfully encoding angry faces. However, no group differences were observed when encoding fearful faces. Utilising the same viewing paradigm of four different viewing conditions, Rich et al. (2008) reported reduced functional connectivity between the left amygdala and the right posterior cingulate/precuneus, and the right fusiform gyrus/parahippocampal gyrus in BD. Although several studies have found differences in neural response to facial affect in paediatric BD, the majority of research has tended to focus on adult BD.

Keener et al. (2012) found that adults with euthymic BD I showed greater amygdala activity than healthy controls overall to happy, sad, angry and fearful faces during an implicit colour recognition task. Specific to the processing of happy faces, BD I participants demonstrated increased amygdala and medial prefrontal cortex activity in comparison to controls. Hassel et al. (2009) presented remitted BD participants with happy, fearful and neutral faces in an implicit gender-decision task. The BD group were found to show decreased DLPFC activity to all faces, and increased subcortical-striatal activity to happy and neutral faces compared to controls.
In contrast, Malhi et al. (2007) presented euthymic BD and healthy control participants with faces depicting fear, disgust and a neutral expression in an explicit emotion recognition task. Relative to faces of disgust, BD participants showed increased bilateral lingual gyri and left middle occipital gyrus activity, and reduced activity of the bilateral cuneus, left middle and inferior frontal and fusiform gyri, and cerebellum, and the right precuneus, insula, and pre- and postcentral and supramarginal gyri, in comparison to controls. In response to faces depicting fear, the BD group showed greater activations in the left hippocampus, claustrum, superior temporal gyri and inferior parietal lobule, and reduced activity of the precentral gyrus. J. Liu et al. (2012) utilised a BD group which included those with elevated, depressed or euthymic mood states. In this study, BD and control participants were presented with an implicit gender-decision task while viewing happy, fearful and neutral facial expressions. Happy and neutral faces were associated with decreased ventral ACC and orbitofrontal cortex activations in the BD group, and were not associated with mood state. Depressed mood was, however, associated with greater orbitofrontal cortex activation to fearful faces, and elevated mood was associated with decreased rostral prefrontal cortex activation to both fearful and neutral faces. The results of this study suggest that state factors may play a more important role in facial affect processing in BD than trait factors.

Furthermore, faces depicting fear have also been associated with decreased DLPFC and increased amygdala activity in BD (Yurgelun-Todd et al., 2000). During a backward masking task, BD participants were found to demonstrate greater DLPFC, ACC and amygdala activity to fearful faces, and greater right DLPFC, amygdala and subgenual ACC activity compared to healthy individuals who showed increased midcingulate and left DLPFC activity (Sagar, Dahlgren, Gönenç, & Gruber, 2013). Relative to the intensity of facial expressions, BD participants have been found to show increased activity of the ventral striatum, hippocampus, thalamus and prefrontal cortex in response to faces of mild and intense fear, and both mild happiness and sadness (N. S. Lawrence et al., 2004), as well increased activity in the amygdala to mild sadness (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010). In a study by Killgore, Gruber, and Yurgelun-Todd (2008), participants passively viewed blocks of resting fixation and fearful faces. In comparison to the early stages of the task, during the later stages, healthy individuals but not the BD group, demonstrated greater ACC,
striatum and orbitofrontal cortex activity. Relative to the early stages of the task, the BD group was instead associated with increased activity in the hippocampus, parahippocampal gyrus, cerebellum, insula, and prefrontal, parietal and occipital cortices. These findings suggest that the BD participants utilised areas involved in visual perception and memory encoding and retrieval, rather than cortico-striatal areas which are involved in emotion-based learning and motivation.

A limited number of studies have also investigated visual scanpaths to facial affect in BD. In a study by Bestelmeyer et al. (2006), the investigators presented schizophrenia, BD and healthy control participants with faces depicting the six basic emotions and a neutral facial expression, and other images, including landscapes, in a passive viewing task. The BD group was found to not significantly differ from either healthy control or schizophrenia participants in the number of or duration of fixations, or saccade durations. BD participants were found to make saccades of lower peak velocity and smaller amplitude than the healthy control group. Although these findings were evident for the face stimuli, they were not restricted to the face images and were also observed when viewing stimuli of other scenes. Loughland et al. (2002a) reported that a group of mixed affective disorders (either MDD or BD) showed decreased median fixation durations and increased scanpath lengths when looking at emotional faces compared to schizophrenia participants, but did not differ from healthy control participants on any spatial or temporal variables. The affective disorders group did, however, demonstrate greater attention to non-salient rather than salient facial features, compared to schizophrenia and control groups.

6.2.3.4 Anxiety disorders

The study of emotion processing in social anxiety disorder (SAD) has also been of great interest in recent times. SAD, or social phobia, is an anxiety disorder characterised by persistent fear of social situations in which the individual is exposed to unfamiliar people or to possible scrutiny by others (American Psychiatric Association, 2013). How individuals with SAD process social information has been of increasing interest. Specifically, how these individuals respond to human faces, particularly faces of different emotions. Individuals with SAD have been found to show general facial emotion recognition deficits (Simonian, Beidel, Turner, Berkes, &
Long, 2001). More specifically, these individuals show emotion recognition deficits to faces of negative emotion, particularly anger and disgust, but also to fear and sadness, but not to happiness and surprise (Montagne et al., 2006).

Individuals with SAD have also been reported to show differences in neural activity compared to healthy individuals when viewing faces. When processing neutral facial expressions, individuals with SAD have been found to show increased bilateral amygdala activity in one study (Birbaumer et al., 1998), and increased right amygdala but decreased left amygdala activity compared to controls in another study (Cooney, Atlas, Joormann, Eugène, & Gotlib, 2006). In a study by Gentili et al. (2008), the investigators presented SAD and control participants with happy, angry, disgusted, fearful and neutral facial expressions. The SAD group were found to show increased left amygdala and insula activity, and increased bilateral superior temporal gyrus activation to all faces. Furthermore, the SAD group demonstrated reduced left FFA, DLPFC and bilateral intraparietal sulcus activity when compared to healthy controls. In contrast, T. Straube, Mentzel, and Miltner (2005) presented SAD and control participants with angry, happy and neutral facial expressions in a passive viewing task and found increased extrastriate cortex activity regardless of facial affect. Additionally, the SAD group were found to show increased insula activity to angry faces, and greater amygdala activity to angry and happy faces as compared to healthy controls, relative to a fixation condition. In an earlier study, T. Straube, Kolassa, Glauer, Mentzel, and Miltner (2004) presented participants with both photographs and schematic pictures of angry and neutral facial expressions during an explicit emotion discrimination task and an implicit task where participants decided whether the image was photographic or schematic. Regardless of task, the SAD group demonstrated greater insula activity to angry than neutral photographic faces, but increased activity of the amygdala, parahippocampal gyrus and extrastriate cortex during the implicit task only. For schematic faces however, increased extrastriate cortex and insula activity was found in SAD in response to angry faces during both tasks. Schematic angry faces have also been found to result in increased amygdala activity compared to neutral faces in SAD (Evans et al., 2008). Stein, Goldin, Sareen, Zorrilla, and Brown (2002) reported greater amygdala, uncus and parahippocampal gyrus activity to photographic angry faces, but no difference for fear or neutral faces, relative to happy faces in SAD compared to controls. In comparison to happy faces
however, Phan, Fitzgerald, Nathan, and Tancer (2006) found greater amygdala activity to angry, fearful and disgusted facial expressions in SAD, which correlated with the severity of social anxiety symptoms. Specifically to faces depicting disgust, increased ACC activity has been reported in SAD in comparison to controls, relative to faces of neutral expression (Amir et al., 2005). In response to faces of fearful expression relative to neutral expressions, individuals with SAD have shown increased rostral ACC, frontal gyrus, lateral frontal cortex, inferior and superior temporal cortex, culmen and amygdala activity, when compared to healthy individuals (Blair et al., 2008). Furthermore, Yoon, Fitzgerald, Angstadt, McCarron, and Phan (2007) investigated amygdala activity to faces of varying emotional intensity. The authors reported greater bilateral amygdala activity to high intensity expressions relative to low intensity expressions in SAD relative to controls, suggesting that more arousing stimuli may contribute to hyperactivity of brain areas related to emotion processing in SAD.

Research in SAD has also been particularly interested in how these individuals look at human faces. During passive viewing of faces depicting the six basic emotional expressions and a neutral expression, SAD patients were found to make fewer and shorter fixations to the eye area for all emotions (Moukheiber et al., 2010). Staugaard and Rosenberg (2011) reported reduced total fixation durations to the eyes of neutral, sad and disgusted facial affects in SAD, whereas Horley, Williams, Gonsalvez, and Gordon (2003) presented participants with images of happy, sad and neutral facial expressions and also reported avoidance of the eyes in SAD, but also of other feature areas including the nose and mouth. Overall, the SAD participants demonstrated hyperscanning behaviours evident by reduced fixation durations and an increased scanpath length. In a more recent study, Horley, Williams, Gonsalvez, and Gordon (2004) also included faces depicting anger. The SAD group were found to make fewer fixations of shorter duration to angry faces and more fixations of longer duration to happy faces; a pattern which was reversed in healthy individuals, suggesting that individuals with SAD may be avoidant of negative or threatening stimuli.

Another anxiety disorder which has been of interest in relation to emotional face processing is OCD. Individuals with OCD have been found to be particularly
disturbed in their recognition of disgust from human faces (Corcoran, Woody, & Tolin, 2008; Sprengelmeyer et al., 1997). H. A. Parker, McNally, Nakayama, and Wilhelm (2004) reported that only one of their OCD participants was impaired in their classification of disgusted facial expressions. This participant was found to suffer from especially severe OCD. In their study, Corcoran et al. (2008) found that deficits in disgust recognition in OCD was related to severity of OCD symptoms, a finding which may explain the inconsistency reported. A number of recent studies have also investigated whether individuals with OCD respond differently to emotional faces than healthy individuals. During both implicit and passive viewing of fearful, happy, disgusted and neutral facial expressions, individuals with OCD have been found to show reduced bilateral amygdala (Britton et al., 2010; Cannistraro et al., 2004) and hippocampus activity (Britton et al., 2010) to all faces relative to a fixation condition, in comparison to healthy controls. During a masked task where participants were presented with fearful or disgusted faces immediately followed by a neutral mask or a neutral face however, individuals with OCD have been found to show increased ventrolateral activity and reduced thalamus activity to facial expressions of disgust, but no difference in response to fearful faces (N. S. Lawrence et al., 2007). However, further analysis revealed that the increased ventrolateral prefrontal cortex activity was primarily driven by individuals with high washing symptoms, who were also found to report more sensitivity to disgust. Unlike the other psychiatric illnesses discussed thus far, no research has been undertaken investigating visual scanpaths to faces in OCD. Studies examining visual scanpaths to other types of stimuli in OCD are also rare, though a study by T. Kojima et al. (1992) indicated that scanpaths in OCD did not differ from healthy individuals when observing geometric figures.

Recently, the study of body dysmorphic disorder (BDD) has gained increasing attention. BDD is an anxiety disorder characterised by a preoccupation with an imagined defect in personal appearance (American Psychiatric Association, 2013). The condition is also associated with a number of cognitive deficits (see Toh, Rossell, & Castle, 2009 for a review), including facial expression recognition. Individuals with BDD have been found to be less accurate in identifying the six basic emotions from facial expressions (Buhllmann, McNally, Etcoff, Tuschen-Caffier, & Wilhelm, 2004; Feusner, Bystritsky, Hellemann, & Bookheimer, 2010). Studies investigating differences in neural activity in response to human faces have also been reported in
BDD, but have not specifically investigated facial affect. In a study by Feusner, Townsend, Bystritsky, and Bookheimer (2007), the researchers presented BDD and control participants with faces of neutral expression which were unaltered or altered to include high or low spatial frequency information. The BDD participants demonstrated increased activity in the lateral prefrontal cortex and lateral temporal lobe to all faces, and the dorsal ACC to faces of low spatial frequency (low spatial resolution) relative to controls, whereas the control group showed increased prefrontal cortex and dorsal ACC activity to faces of high spatial frequency (fine spatial resolution). In a more recent study, Feusner, Moody, et al. (2010) presented BDD and control groups with neutral own-face and familiar-face stimuli while undergoing fMRI. BDD participants showed increased left orbitofrontal cortex and bilateral caudate activation to own faces relative to familiar faces, which positively correlated with BDD symptoms.

Visual scanpaths to faces have also been investigated recently in BDD. In a study by Grocholewski, Kliem, and Heinrichs (2012), participants viewed photographs of themselves and unfamiliar faces portraying happy, sad and neutral facial expressions. Irrespective of emotional expression, the BDD group were found to not significantly differ from controls in duration of fixations, but were found to make more fixations to areas of imagined defect in their own face and in corresponding regions in unfamiliar faces. These findings suggest different viewing strategies employed by individuals with BDD, who repeatedly return focus for a short duration to areas of imagined defect of their own faces but also of unfamiliar faces.

6.2.3.5 Emotional face processing in clinical populations: conclusions

The study of facial affect processing in clinical psychiatric populations has provided a great deal of information on emotion processing deficits experienced by these groups. Not only has research provided information about deviant emotion perception in these illnesses, but also information on the areas of neural deficit in these disorders. A range of conditions are associated with poorer emotion identification and have also been found to show differences in brain activity, particularly in emotion-processing areas such as the limbic system. Research has also indicated an avoidance of salient facial features in a range of conditions, and
distinctive scanpath strategies with schizophrenia patients tending to hyposcan stimuli and individuals with SAD demonstrating hyperscanning behaviours. These studies have also stressed the importance of viewing conditions, whether passive, implicit or explicit, as the type of instruction participants receive dramatically influences results. By gaining an understanding of how individuals with AN differ or show similarities with reports in other psychiatric illnesses will enable a better understanding of the illness and how AN may relate to other conditions. Although research has indicated emotion identification problems and BOLD activity differences to emotional faces in AN, the investigation of visual scanpaths has rarely been undertaken. During a free-viewing task where weight-recovered AN participants were presented with whole body stimuli and face stimuli, Watson et al. (2010) reported reduced attention to the eye region of face stimuli, and less time visually attending face regions when whole bodies were presented. However, the implications of this study are limited as no attempt was made to standardise the stimuli acquired from a dating website. R. Freeman et al. (1991) presented participants images of their own bodies photographed in a black leotard and reported that while healthy control participants spent relatively the same amount of time focusing on the four interest areas (face, chest, abdomen and legs), individuals with AN spent more time looking at the their legs and abdomen and less time looking at their face, suggesting an avoidance of fixating one’s own face in AN or a preoccupation with areas of the body related to weight.

6.3 Own face processing in clinical populations

A number of recent studies have also been interested in how different clinical populations process stimuli of individuals’ own faces. Frontoparietal areas of the right hemisphere in particular are often implicated in the processing of one’s own face. In a study by Uddin, Kaplan, Molnar-Szakacs, Zaidel, and Iacoboni (2005), the investigators reported increased activity in the inferior parietal lobule, inferior frontal gyrus, superior parietal lobule and the inferior occipital gyrus when observing one’s own face. A study by Kircher et al. (2001) reported increased activity in right limbic areas including the insula, hippocampal formation and ACC, as well as the superior temporal, left parietal and left prefrontal cortices; whereas Sugiura et al. (2005) found increased right occipito-temporo-parietal junction and frontal operculum, left fusiform gyrus, and bilateral posterior cingulate cortex and parahippocampal gyrus activity to

194
one’s own face. To investigate whether differences in activation to one’s own face are influenced by increased familiarity to images of the self, Platek et al. (2006) presented participants with self-images, and images of both familiar and unfamiliar individuals. The authors reported increased activity in the right postcentral, supramarginal and superior temporal gyri, left cerebellum and bilateral lentiform nucleus to self-face images compared to unfamiliar face images, and elevated activity to participants’ own faces relative to familiar faces in the right superior and medial frontal gyri, right inferior parietal lobule and left middle temporal gyrus, indicating a different neural response to self-images relative to familiar and unfamiliar faces.

As described above in section 6.2.3.4, individuals with BDD have been found to show increased left orbitofrontal cortex and bilateral caudate activity to images of their own face relative to familiar faces (Feusner, Moody, et al., 2010), and have shown increased fixations to areas of imagined defect to both their own and unfamiliar faces (Grocholewski et al., 2012). Self-face processing has also been recently investigated in ASD. In a recent study by Morita et al. (2012), decreased posterior cingulate cortex activity to participants’ own faces relative to controls was found in ASD. Uddin et al. (2008) found no group differences in BOLD activity between ASD and typically developing children to self-face images. Though the processing of self-face images has not been investigated in AN, the processing of self-body images has indicated decreased activity in the middle frontal gyri, precuneus and occipital regions (Sachdev et al., 2008), and reduced activity of the inferior parietal lobule (Vocks, Busch, Grönnemeyer, et al., 2010), indicating differential responses to the processing of oneself in AN.

Although the processing of emotional faces has been examined through the investigation of visual scanpaths and functional neuroimaging, the literature search did not reveal any studies investigating emotion perception of one’s own face. Furthermore, the study of visual scanpaths to self-face images was limited to BDD (Feusner, Moody, et al., 2010; Grocholewski et al., 2012).

6.4 Current study aims and hypotheses

The aim of the current study was to investigate facial affect processing in AN. Participants were presented with faces expressing different emotions and images of
their own face with a neutral expression during an implicit emotion processing task that required gender identification of stimuli while undergoing fMRI, and an explicit emotion identification task behaviourally, both while undergoing eyetracking. Given the overlap with anxiety disorders in AN, the patient group were expected to exhibit similar scanning behaviours, namely, hyperscanning (i.e. increased fixations of shorter duration) of face stimuli during both tasks. AN participants were also expected to show an avoidance of salient features (i.e. eyes, nose and mouth) of the emotional face stimuli during the implicit task. As typical attention to salient features has been found when explicit task instructions are given in clinical populations that demonstrate poor attention to salient features during implicit tasks (e.g. schizophrenia) (Delerue, Laprévote, Verfaillie, & Boucart, 2010), groups were not expected to differ in areas of attentional focus during the explicit task. In relation to participants’ own face stimuli, the AN group were hypothesised to show less attention to salient features during both tasks. Individuals with AN were also expected to show emotion identification deficits to the emotional face stimuli expressing negative emotion, but not to their own face. Related to this hypothesis, the AN group were expected to show reduced activity in limbic areas of the brain to negative affect stimuli, relative to neutral control faces; and to show reduced activity to stimuli of their own face in frontoparietal brain areas which are involved in the processing of ones’ own face (Uddin et al., 2005). Exploratory analyses were also undertaken to identify whether the rate of emotion recognition errors and the level of salient feature avoidance positively correlated with the inability to recognise emotions within the self as measured by the TAS-20.

6.5 Method

6.5.1 Participants

Twenty-four individuals with AN and 25 healthy control individuals completed the faces task in the MRI and the faces tasks behaviourally. One participant in the AN group declined to have her own face included among the stimuli and her data was not included in the analysis. A programming error resulted in one control participant being presented with too few own face stimuli and her data was excluded. Technical difficulties encountered with use of the eyetracking equipment in the MRI
resulted in the data of three AN participants and three control participants being excluded, allowing eyetracking analyses to be conducted on 20 AN and 21 control participants. All 23 AN and 24 control participants’ data were included in the fMRI and emotion identification analyses. Demographic characteristics for the additional control participant who did not complete the entire study but completed the faces task behaviourally and in the MRI are included in Appendix E.

6.5.2 Emotional faces task

Participants completed an emotional faces task in the MRI and behaviourally outside the scanner. An implicit (gender discrimination) task was completed in the MRI, whereas an explicit (emotion discrimination) task was completed behaviourally. An implicit task was completed in the MRI to reduce the cognitive demand, allowing more implicit emotional processing. An implicit task was chosen over passive viewing of stimuli in an attempt to reduce fatigue and to ensure concentration on the task as participants were required to make a gender response.

6.5.2.1 Functional magnetic resonance imaging (fMRI) task

Participants were presented stimuli from the Pictures of Facial Affect, a standardised set of 110 black and white photographs of male and female actors trained to display different facial expressions (Ekman et al., 1975). For the purpose of this task, 48 stimuli of four males and four females, each displaying the emotions happy, sad, angry, disgust, fear and neutral were presented. The stimuli chosen were those having the highest inter-rater agreement for all seven emotions. Each photograph was 336x640 pixels, equalling 17x27.5cm or subtending 18x13° at the viewing distance from the eye. This stimulus size was chosen to reflect normal face viewing size. Each stimulus was presented twice in a pseudorandom fashion. Therefore, each emotion had 16 presentations. The presentation was divided into two runs allowing for one presentation of each stimulus per run. Faces were displayed for 8000ms on a white background, followed by the presentation of a black 1° fixation cross on the same white background for 3000-4300ms to introduce jitter and to reduce anticipations related to the next stimulus (with an equal number of presentations of each 100ms interval). Participants were instructed to simply look at the face while it was on screen.
and to make a gender response only when the fixation cross appeared following the face presentation. Participants held a button box in their dominant right hand and were asked to press the left button if the face was male and the right button if it was female. They were instructed to only press the button once to make their response and then to wait for the presentation of the next face. Participants’ own neutral face photographs were also included among the stimuli which required participants to respond in the same way, making a gender response. The photograph of participants was taken during the first session and was edited to match the properties of the Ekman face stimuli in terms of size and resolution. The images were also converted to black and white. The instructions for participants when being photographed was to look straight ahead with a relaxed expression, similarly to taking a passport photograph. Participants’ own face images were pseudorandomly presented a total of 16 times, eight presentations per run, similarly to the total number of presentations for each emotion.

Each run began with a long period of fixation for 15000ms. Long periods of fixation, between 10200 and 11400ms were also presented pseudorandomly throughout the task to increase BOLD signal variance by allowing the signal to return to baseline. Due to the extended length of the task in the MRI, participants were not presented with surprised faces in the implicit task as it is the most ambiguous emotion, displaying neither a positive nor negative emotion. Each run ran for approximately 12.5 minutes and participants were given a short break between runs. Prior to entering the scanner, participants completed a practice task consisting of six stimuli from the Pictures of Facial Affect which were not of the actors included in the experimental task.

6.5.2.2 Behavioural task

In the behavioural emotional faces task, participants were pseudorandomly presented with the same stimuli as in the fMRI task, but with only one presentation per stimulus (i.e. eight presentations per emotion). Similarly, eight pseudorandom presentations of participants’ own face were also included among the stimuli. In addition, the stimulus for the emotion of surprise for each actor was also included. The stimuli in the behavioural set-up were 374x612 pixels, equalling to 12.6x20.8cm,
again subtending 8x13° at the viewing distance from the eye as in the fMRI task. Prior to the presentation of each stimulus in this task, a fixation cross appeared in the centre of the screen for 500ms. Similarly to the fMRI task, the face stimuli were presented for 8000ms. Following the presentation of each face stimulus, a forced-response screen appeared on the monitor asking participants to identify the emotion displayed in the previous face from a list containing all of the emotions. The participants were given as much time as they required to make a response. The task duration varied among participants due to the amount of time taken in making emotion identification decisions, but generally took approximately 10 minutes to complete. Prior to the commencement of the task, participants completed a practice task comprised of six stimuli from the Pictures of Facial Affect which were not of the actors included in the experimental task.

6.5.2.3 Analysis

6.5.2.3.1 Behavioural data and eye movements

Eyetracking and behavioural data was analysed with SR Research’s analysis program, DataViewer. Areas of interest (AOIs) were created in the program and included the eyes, nose and mouth as separate AOIs. ‘Trial reports’ and ‘interest area reports’ were generated in DataViewer and imported into Microsoft Excel for further analysis, prior to being imported into the study database in SPSS. The data was intentionally not cleaned, to allow the analysis of raw scanpaths. Average fixation count, fixation duration and saccade amplitude were calculated for each emotion and participants’ own faces. To investigate the proportion of fixations and fixation durations to salient features (eyes, nose and mouth; see Figure 6.1) and non-salient features, two spatial-temporal parameters were calculated: the feature fixation index (FFI) and the feature duration index (FDI) (L. M. Williams et al., 1999). The FFI is derived by dividing the number of fixations to salient features minus the number of fixations to non-salient features by the total number of fixations (i.e. (number of fixations to salient stimuli – number of fixations to non-salient stimuli) / total number of fixations). The FDI is derived in the same manner. Indices range from -1 to +1, with positive values indicating more fixations or longer durations to salient features, and negative values indicating more visual attention to non-salient features.
6.5.2.3.2 Functional magnetic resonance imaging (fMRI)

MRI data pre-processing and statistical analyses were performed using SPM8, through Matlab R2014a (Mathworks, Natick, MA, USA). Image pre-processing included image realignment, then co-registration of the T1 image to a mean realigned functional image created during realignment. The co-registered T1 image was then normalised to the T1 template supplied with SPM8 (MNI), then the parameters of this transformation were applied to realigned functional images. The normalised functional images were then spatially smoothed with a Gaussian kernel of 8x8x8mm. Due to the fast repetition time achieved with the multiband sequence, it was not necessary to perform slice timing corrections on the data.

6.5.2.4 Statistical analysis

6.5.2.4.1 Behavioural data and eye movements

Performance on eyetracking components was compared between groups with between groups and mixed design ANOVAs, following normality checking and the removal of outliers. Emotion identification performance (rate of emotion identification errors) was also compared between groups with a mixed design ANOVA. For conditions in which groups significantly differed in error rate, between groups ANOVAs were carried out to identify which emotions were incorrectly reported. Alpha was set at 0.05 for all analyses. Pearson’s correlation analyses were
also performed between behavioural and eyetracking data, and scores on the TAS-20, with alpha set at 0.01 to account for multiple comparisons.

6.5.2.4.2 Functional magnetic resonance imaging (fMRI)

First-level modelling was performed by fitting a convolved HRF and its temporal derivative separately to the onset times of angry, disgust, fear, happy, sad, neutral and own faces (seven regressors plus their temporal derivative). After parameter estimation, each emotion parameter and the participants’ own face parameter was contrasted with the neutral face parameter producing six contrast images (angry > neutral, disgust > neutral, etc.).

At the group level, these contrast images were first entered into one-way ANOVA models for AN and control groups separately to investigate within-group effects. Group differences were interrogated with a mixed-effects ANOVA model using the flexible factorial option in SPM8. This model included a between-subjects Group factor (two levels: AN versus controls), a within subjects Condition factor (six levels: angry > neutral, disgust > neutral, etc.) and a Subjects factor (number of levels equals the number of participants) that controlled for within-subject variability (Gläscher & Gitelman, 2008).

Voxel level thresholding applied was corrected for FWE multiple comparisons (p < 0.05), and cluster level thresholding was corrected for FDR multiple comparisons (p < 0.05). For the one-way within groups ANOVAs, the main effect of condition and simple effects for each condition were analysed for each group. The mixed-design analysis involved the investigation of a group by condition interaction, followed by simple effects comparing each condition between groups.

Following the mixed-design analysis, clusters which resulted in significant differences between groups were defined as different regions of interest (ROIs) with the MarsBar toolbox (Brett, Anton, Valabregue, & Poline, 2002) run under Matlab R2014a. Contrast estimates for each ROI were correlated with eyetracking and behavioural data, and scores on the EDE-Q and TAS-20.
6.5.3 Procedure

The two tasks were both completed during the ‘long MRI’ session. Participants were informed that they would complete a faces task in the MRI and some additional tasks following the scan, but were not informed that they would be presented with an additional faces task behaviourally until just prior to the task commencement. The implicit task in the MRI was undertaken first so that participants were not aware of the true nature of the task (emotion processing), which might have interfered with neural processing in emotion-related areas. Following the fMRI task, participants underwent the explicit emotion discrimination task in an adjacent interview room. The tasks in the MRI and behavioural environments both began with a nine-point eyetracker calibration sequence, followed by a validation task requiring participants to look at different points on the monitor. The calibration sequence was run between runs as appropriate. The tasks were presented in a fixed order explained in section 2.4. Practice tasks were completed before the commencement of the task in the MRI and behaviourally.

6.6 Results

The following section describes the results from the emotional faces tasks. Mixed design ANOVAs were carried out on the data. As the primary aim of the study was to investigate group differences, for brevity, only significant interactions with group are presented in detail in this chapter (see Appendix F for additional analyses).

6.6.1 Behavioural

During the fMRI task, participants were required to make a gender response following the presentation of a face. Between groups ANOVAs revealed that the rate of gender errors and missing responses did not significantly differ between groups (F(1,47)= 0.12, p= 0.740; F(1,47)= 0.01, p= 0.965). The behavioural task involved the identification of emotional expressions of the faces presented. For rate of emotion identification errors, a 2 (group) x 8 (condition) mixed design ANOVA was undertaken (see Table 6.1). The analysis revealed a significant main effect of condition (F(3.69,169.74)= 8.30, p < 0.001). A significant main effect of group
(F(1,46)= 5.28, p= 0.026) and a significant interaction between group and condition (F(3.69,169.74)= 4.07, p= 0.005) were also found. Within subjects contrasts revealed that groups did not significantly differ in emotion identification errors to any individual emotion, but AN participants made significantly more emotion identification errors to their own faces (F(1,46)= 5.10, p= 0.029). As this result may have influenced the findings for the main effect of group and the interaction between group and condition, two separate analyses were conducted for the emotional faces and own faces.

Table 6.1

<table>
<thead>
<tr>
<th>Emotion</th>
<th>AN</th>
<th>Controls</th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Anger</td>
<td>16.30</td>
<td>11.58</td>
<td>22.00</td>
<td>20.18</td>
</tr>
<tr>
<td>Disgust</td>
<td>9.78</td>
<td>14.58</td>
<td>12.50</td>
<td>16.14</td>
</tr>
<tr>
<td>Fear</td>
<td>22.28</td>
<td>19.20</td>
<td>17.00</td>
<td>16.09</td>
</tr>
<tr>
<td>Happy</td>
<td>2.17</td>
<td>6.14</td>
<td>1.50</td>
<td>4.15</td>
</tr>
<tr>
<td>Sad</td>
<td>21.74</td>
<td>16.52</td>
<td>13.50</td>
<td>15.28</td>
</tr>
<tr>
<td>Surprise</td>
<td>8.70</td>
<td>9.56</td>
<td>4.50</td>
<td>7.97</td>
</tr>
<tr>
<td>Neutral</td>
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<td>23.52</td>
<td>2.50</td>
<td>5.10</td>
</tr>
<tr>
<td>Own</td>
<td>32.61</td>
<td>44.07</td>
<td>5.50</td>
<td>20.44</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>7.68</td>
</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; error rates are reported as percentages

For rate of emotion identification errors, a 2 (group) x 7 (emotion) mixed design ANOVA revealed a significant main effect of emotion (F(4.59,215.52)= 12.57, p < 0.001), with more errors to faces depicting anger, fear and sadness. A main effect of group, and a significant interaction between group and emotion were not found.

Emotion responses to participants’ own faces were analysed with Mann-Whitney U tests. When errors were made to own face emotion, analyses revealed that
AN participants were more likely than controls to report their own face as sad (U(46)= 200.00, Z= -2.94, p= 0.003), whereas control participants were more likely to correctly report their own neutral face as portraying a neutral expression (U(46)= 209.00, Z= -2.29, p= 0.022) (Table 6.2).

Pearson’s correlation analyses were also conducted between scores on the TAS-20 subscales, and emotion responses to the Ekman faces and participants’ own faces. No significant correlations were revealed for either group.

Table 6.2

<table>
<thead>
<tr>
<th>Own face emotion responses, behavioural task</th>
<th>AN</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
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<tr>
<td>Anger</td>
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<td>0.00</td>
</tr>
<tr>
<td>Disgust</td>
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<td>100.00</td>
</tr>
<tr>
<td>Fear</td>
<td>0.00</td>
<td>12.50</td>
</tr>
<tr>
<td>Happy</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Sad</td>
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<td>100.00</td>
</tr>
<tr>
<td>Surprise</td>
<td>0.00</td>
<td>12.50</td>
</tr>
<tr>
<td>Neutral</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; rates are reported as percentages

6.6.2 Eyetracking

6.6.2.1.1 Scanpath characteristics

Average fixation count, fixation duration and saccade amplitude were analysed in separate 2 (group) x 7 (condition) x 2 (task) mixed design ANOVAs. As the first run of the fMRI task consisted of the same number of trials as the behavioural task, these two tasks were included in the analysis. Furthermore, as the behavioural task also consisted of surprised faces which were not included in the fMRI task, these
trials were excluded from the analysis. Means and standard deviations for fixation count, fixation duration and saccade amplitude are presented in Table 6.3.

For fixation count, a significant main effect of condition was found (F(4.08,159.20)= 2.96, p= 0.021) with a greater number of fixations made to participants’ own faces and faces depicting anger and fear. A significant main effect was also found for group (F(1,39)= 5.25, p= 0.027), with AN participants making more fixations than controls. A significant interaction between condition and task was also found (F(3.38,131.91)= 7.61, p < 0.001) with a decreased number of fixations between implicit and explicit tasks for participants’ own faces and faces depicting fear. There was however no significant main effect of task, and no significant interaction between condition and group, or task and group. There was also no interaction between condition, group and task. Analyses conducted on fixation duration revealed a significant main effect of group (F(1,38)= 8.45, p= 0.006) with AN participants making fixations of shorter duration than healthy individuals. No other significant main effects or interactions were found. Analyses conducted on saccade amplitude resulted in no significant main effects or interactions.

Pearson’s correlation analyses conducted between scores on the TAS-20 subscales, and scanpath parameters to the Ekman faces and participants’ own faces revealed no significant correlations for either group.
Table 6.3
Scanpath characteristics to own faces and faces of different emotion during the fMRI and behavioural tasks

<table>
<thead>
<tr>
<th></th>
<th>Fixation count</th>
<th></th>
<th>Fixation duration</th>
<th></th>
<th>Saccade amplitude</th>
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<tr>
<td>fMRI task, part 1</td>
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<td></td>
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<tr>
<td>Anger</td>
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<td>3.87</td>
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<td>109.63</td>
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<td>Disgust</td>
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<td>19.77</td>
<td>4.55</td>
<td>287.10</td>
<td>114.91</td>
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<tr>
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<td>20.37</td>
<td>4.15</td>
<td>268.07</td>
<td>88.64</td>
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<tr>
<td>Happy</td>
<td>24.74</td>
<td>9.25</td>
<td>20.27</td>
<td>3.57</td>
<td>274.46</td>
<td>92.20</td>
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<tr>
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<td>20.09</td>
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<td>Neutral</td>
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<td>19.30</td>
<td>3.78</td>
<td>291.72</td>
<td>126.37</td>
</tr>
<tr>
<td>Own</td>
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<td>11.03</td>
<td>21.58</td>
<td>4.57</td>
<td>281.94</td>
<td>102.45</td>
</tr>
<tr>
<td>Behavioural task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>23.75</td>
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<td>21.53</td>
<td>3.80</td>
<td>291.97</td>
<td>144.74</td>
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<tr>
<td>Disgust</td>
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<td>4.61</td>
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<td>6.71</td>
<td>21.07</td>
<td>3.84</td>
<td>268.48</td>
<td>79.34</td>
</tr>
<tr>
<td>Neutral</td>
<td>23.53</td>
<td>7.05</td>
<td>20.19</td>
<td>4.09</td>
<td>253.98</td>
<td>73.94</td>
</tr>
<tr>
<td>Own</td>
<td>21.82</td>
<td>8.12</td>
<td>19.17</td>
<td>2.97</td>
<td>288.34</td>
<td>77.60</td>
</tr>
</tbody>
</table>

Note: AN = anorexia nervosa; fMRI = functional magnetic resonance imaging; fixation duration is reported in milliseconds and saccade amplitude in degrees.
6.6.2.1.2 Areas of interest (AOIs)

Means and standard deviations of the FFI and FDI data for each emotion and task are presented in Table 6.4. A 2 (group) x 7 (condition) x 2 (task) mixed design ANOVA conducted on the FDI revealed a significant main effect of condition (F(2.28,81.95)= 16.37, p < 0.001), and a significant interaction between condition and task (F(4.03,144.93)= 3.01, p= 0.020), with greater attention to salient features of one’s own face during the implicit compared to explicit task. Analyses conducted on the FFI revealed significant main effects of condition (F(2.20,72.47)=19.69, p < 0.001) and task (F(1,33)= 10.06, p= 0.003), with greater attention to salient facial features during the explicit task compared to the implicit task. Significant interactions were also found between condition and task (F(3.82,125.94)= 3.13, p= 0.014) and condition and group (F(2.20,72.47)= 3.24, p= 0.041). Within-subjects contrasts did not reveal any significant differences between groups for any emotions, but a significant difference for own faces between AN and control participants (F(1,33)= 5.85, p= 0.021). As this result may have influenced the findings for the main effect of group and the interaction between group and condition, two separate analyses were conducted for the emotional faces and own faces.

A 2 (group) x 6 (emotion) x 2 (task) mixed design ANOVA conducted on the FFI revealed a significant main effect of emotion (F(5,185)= 15.56, p < 0.001) with less attention to salient facial features of neutral faces. A significant interaction between task and emotion was also found (F(5,185)=2.95, p= 0.014). No other significant main effects and no significant interactions were found. Analyses conducted on the FDI also revealed significant main effect of emotion (F(5,165)= 12.93, p < 0.001) with less attention to salient facial features of neutral faces, and task (F(1,33)=9.40, p= 0.004) with greater attention of salient features during the explicit task.

Separate 2 (group) x 2 (task) mixed design ANOVAs were also conducted on the FFI and FDI to participants’ own face. A significant main effect of task, and an interaction between task and group were not found for either the FFI or FDI. A significant main effect of group was, however, found for both the FFI (F(1,36)= 7.58, p= 0.009) and FDI (F(1,36)= 6.78, p= 0.013). Control participants showed more
visual attention to salient features of their own faces, whereas the attention shown to salient and non-salient features of their own faces in AN was roughly equal.

Pearson’s correlation analyses conducted between scores on the TAS-20 subscales, and the FFI and FDI to the Ekman faces and participants’ own faces revealed no significant correlations for either group.
Table 6.4
Feature fixation index (FFI) and feature duration index (FDI) scores for own faces and faces of different emotion during the fMRI and behavioural tasks

<table>
<thead>
<tr>
<th>Feature fixation index</th>
<th>Feature duration index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AN (M, SD)</td>
</tr>
<tr>
<td>fMRI task, part 1</td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>0.16 0.33</td>
</tr>
<tr>
<td>Disgust</td>
<td>0.23 0.36</td>
</tr>
<tr>
<td>Fear</td>
<td>0.24 0.32</td>
</tr>
<tr>
<td>Happy</td>
<td>0.26 0.33</td>
</tr>
<tr>
<td>Sad</td>
<td>0.17 0.36</td>
</tr>
<tr>
<td>Neutral</td>
<td>0.14 0.36</td>
</tr>
<tr>
<td>Own</td>
<td>-0.06 0.40</td>
</tr>
<tr>
<td>Behavioural task</td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>0.40 0.30</td>
</tr>
<tr>
<td>Disgust</td>
<td>0.39 0.29</td>
</tr>
<tr>
<td>Fear</td>
<td>0.50 0.24</td>
</tr>
<tr>
<td>Happy</td>
<td>0.40 0.29</td>
</tr>
<tr>
<td>Sad</td>
<td>0.45 0.28</td>
</tr>
<tr>
<td>Neutral</td>
<td>0.36 0.26</td>
</tr>
<tr>
<td>Own</td>
<td>0.08 0.33</td>
</tr>
</tbody>
</table>

Note: AN=anorexia nervosa; fMRI=functional magnetic resonance imaging; positive values indicate more fixations or longer durations to salient features, and negative values indicate more visual attention to non-salient features.

6.6.3 Functional magnetic resonance imaging (fMRI)

6.6.3.1 Within-groups analyses

For the AN group, a significant main effect of condition was found (F(5,110)= 7.89, p < 0.05 (FWE)). Simple effects are presented in Table 6.5. The own > neutral contrast was the only contrast to result in significant activations at this threshold,
revealing widespread activation in bilateral areas including clusters within the inferior frontal, temporal and occipital cortices. Significant activations were also revealed within the right supplementary motor area, and anterior and mid cingulate cortices. Significant activations within the left hemisphere included clusters within the precentral sulcus, superior and inferior parietal cortices, and superior and medial frontal areas (Figure 6.2 A).

Table 6.5

*Significant within groups contrasts for the emotional faces task for anorexia nervosa participants, own > neutral*

<table>
<thead>
<tr>
<th>Peak regions</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>Peak MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>4880</td>
<td>12.27</td>
<td>46</td>
</tr>
<tr>
<td>Brainstem, thalamus</td>
<td>1012</td>
<td>10.22</td>
<td>4</td>
</tr>
<tr>
<td>Inferior occipital, inferior temporal</td>
<td>4267</td>
<td>9.92</td>
<td>42</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>2667</td>
<td>8.77</td>
<td>-16</td>
</tr>
<tr>
<td>Inferior frontal, insula</td>
<td>1920</td>
<td>8.73</td>
<td>-34</td>
</tr>
<tr>
<td>Precentral sulcus</td>
<td>717</td>
<td>7.55</td>
<td>-46</td>
</tr>
<tr>
<td>Inferior occipital, inferior temporal</td>
<td>445</td>
<td>7.84</td>
<td>-44</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>119</td>
<td>7.34</td>
<td>-8</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>1163</td>
<td>7.09</td>
<td>8</td>
</tr>
<tr>
<td>Anterior and mid cingulate</td>
<td>621</td>
<td>6.19</td>
<td>2</td>
</tr>
<tr>
<td>Medial frontal</td>
<td>217</td>
<td>5.68</td>
<td>-6</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>171</td>
<td>5.66</td>
<td>-62</td>
</tr>
</tbody>
</table>

Note: Voxel-wise threshold: \( T(1,110)= 4.72, \ p < 0.05 \) (FWE); MNI= Montreal Neuroimaging Institute

210
A significant main effect of condition was also found for the control group (F(5,115)= 7.96, p < 0.05 (FWE)). Individual contrasts for each emotion compared to neutral did not result in any significant activations at this threshold. Significant activations were found in the own face > neutral face comparison. Similarly to the finding in the AN group, widespread activation was found to control participants’ own face in comparison to the neutral affect faces (Table 6.6 and Figure 6.2 B), but unlike the bilateral pattern observed with AN participants, the activations observed in the control group were predominantly located in the right hemisphere. Activations in the right hemisphere included clusters within the superior parietal and occipital cortices, inferior and mid frontal cortices, inferior parietal, temporal and occipital cortices, mid cingulate cortex, precuneus, supplementary motor area, precentral sulcus, and the insula. Significant activations within the left hemisphere included clusters in inferior and superior frontal areas, the insula and precuneus.
Figure 6.2. Increased activity in anorexia nervosa participants (A) and healthy control participants (B) to own face stimuli compared to neutral face stimuli
Table 6.6

**Significant within groups contrasts for the emotional faces task for control participants, own > neutral**

<table>
<thead>
<tr>
<th>Peak regions</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>Peak MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Inferior and mid frontal, precentral sulcus, insula</td>
<td>3318</td>
<td>11.85</td>
<td>48</td>
</tr>
<tr>
<td>Superior parietal, superior occipital, precuneus</td>
<td>1686</td>
<td>9.58</td>
<td>22</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>517</td>
<td>7.87</td>
<td>8</td>
</tr>
<tr>
<td>Inferior frontal, insula</td>
<td>991</td>
<td>7.78</td>
<td>-36</td>
</tr>
<tr>
<td>Inferior temporal, inferior occipital</td>
<td>228</td>
<td>7.54</td>
<td>46</td>
</tr>
<tr>
<td>Superior frontal</td>
<td>303</td>
<td>6.49</td>
<td>-8</td>
</tr>
<tr>
<td>Mid cingulate</td>
<td>146</td>
<td>6.45</td>
<td>8</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>133</td>
<td>6.34</td>
<td>56</td>
</tr>
<tr>
<td>Mid cingulate</td>
<td>189</td>
<td>6.29</td>
<td>6</td>
</tr>
<tr>
<td>Precuneus</td>
<td>108</td>
<td>6.08</td>
<td>-10</td>
</tr>
</tbody>
</table>

Note: Voxel-wise threshold: $T(1,115)=4.76$, $p<0.05$ (FWE); MNI= Montreal Neuroimaging Institute

6.6.3.2 Mixed-design analysis

The analysis did not result in a significant group by condition interaction ($F(5,225)=7.29$, $p>0.05$ (FWE)). Simple effects between groups for each condition revealed a significant difference between groups only for the own > neutral face contrast. Increased activation was found in AN compared to controls in the own > neutral contrast in two clusters: one in the right inferior temporal and middle temporal gyri, and one in the right lingual gyrus (Table 6.7 & Figure 6.3). These two clusters
were defined as two separate ROIs and correlational analyses were conducted. BOLD activity in the own > neutral face contrast in either ROI did not significantly correlate with any eyetracking parameter, rate of emotion identification errors, or the results of the EDE-Q and TAS-20 for either group.

Table 6.7.

**Significant activations for participants’ own faces compared to neutral faces between anorexia nervosa and control participants (own > neutral, anorexia nervosa > healthy controls)**

<table>
<thead>
<tr>
<th>Peak regions</th>
<th>No. of voxels</th>
<th>Peak t</th>
<th>Peak MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior temporal gyrus, middle</td>
<td>104</td>
<td>6.45</td>
<td>50 -54 -4</td>
</tr>
<tr>
<td>temporal gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>118</td>
<td>5.37</td>
<td>28 -88 -8</td>
</tr>
</tbody>
</table>

Note: Voxel-wise threshold: T(1,225)= 4.597, p < 0.05 (FWE); MNI= Montreal Neuroimaging Institute
Figure 6.3. Increased activity in the anorexia nervosa group compared to the control group in the right inferior and middle temporal gyri (A), and the right lingual gyrus (B) for participants’ own faces compared to neutral faces
6.7 Discussion

The aim of this study was to investigate facial affect processing and the processing of own face stimuli in AN. Participants were presented with an implicit processing task in the MRI and an explicit, emotion identification task behaviourally, both while undergoing eyetracking. The behavioural, eyetracking and fMRI findings are discussed separately below.

6.7.1 Behavioural

During the explicit task, AN participants were expected to show poorer emotion discrimination of negative affect. This hypothesis was not supported by the findings. Individuals with AN were not found to differ from healthy individuals in the perception of face stimuli depicting the basic human emotions. This finding is consistent with the finding by Mendlewicz et al. (2005) who reported intact emotion perception of human faces in AN. Other studies have however reported emotion identification deficits in AN specific to faces depicting sad (Kucharska-Pietura et al., 2004; Pollatos et al., 2008), disgusted (Pollatos et al., 2008), fearful (Kucharska-Pietura et al., 2004) and surprised (Kessler et al., 2006) affects, whereas Jänsch et al. (2009) reported an emotion discrimination deficit in AN which was not specific to any individual emotion. These findings suggest that different methodologies may account for the inconsistent results reported between studies. The findings of the current study also differ to those reported in other psychiatric illnesses such as schizophrenia (Kohler et al., 2000; Kohler et al., 2003; Salem et al., 1996), BD (Lembke & Ketter, 2002), MDD (R. C. Gur et al., 1992; Langenecker et al., 2005; Mendlewicz et al., 2005; Mikhailova et al., 1996; Rubinow & Post, 1992) and SAD (Montagne et al., 2006; Simonian et al., 2001), all of which are reported to show emotion identification deficits. Furthermore, a search of the literature did not reveal any studies in psychiatric illnesses that investigated emotion identification of own neutral faces.

Though the AN group were not expected to show emotion identification problems to their own face, the findings of the current study indicated an increased rate of emotion identification errors to own face images in the patient group. More specifically, although the majority of AN participants reported their own face as portraying a neutral expression, when making an emotion identification error, they were more
likely than healthy individuals to report their own face as depicting a sad expression. Similarly to the findings of the current study, which suggest higher alexithymia in AN, this result may suggest an emotion identification deficit specific to oneself in AN. However, this result may more likely reflect how individuals with AN feel they look as the identification errors reported were specific to identifying themselves as looking sad and not any other emotions.

6.7.2 Eyetracking

AN participants were hypothesised to show hyperscanning behaviours in both tasks and an avoidance of salient features during only the implicit task, to the standard set of emotional faces. AN participants were also expected to show hyperscanning and an avoidance of salient features of their own face images during both tasks. The results of the study partially supported the hypotheses. An increased average rate of fixations and shorter fixation durations were found in AN to the stimuli overall, irrespective of the task undertaken. Therefore, AN participants displayed hyperscanning behaviours to the stimuli regardless of the emotion portrayed or if the image was of their own face, and regardless of the instructions provided for the task. Research in other psychiatric populations has suggested that conditions such as MDD and BD are not associated with different scanpath characteristics (Bestelmeyer et al., 2006; Loughland et al., 2002a), but conditions such as schizophrenia are associated with hyposcanning of face stimuli (Bestelmeyer et al., 2006; E. Gordon et al., 1992; M. J. Green et al., 2003; Loughland et al., 2002b; Loughland et al., 2004; Manor et al., 1999; M. L. Phillips & David, 1997, 1998; Streit et al., 1997; L. M. Williams et al., 1999). SAD is associated with hyperscanning of face stimuli of different emotions (Horley et al., 2003), evident by shorter fixation durations and longer raw scanpath lengths. Other anxiety disorders, such as generalised anxiety disorder, have however been observed to not differ from healthy control participants in scanpath behaviour (D. Freeman, Garety, & Phillips, 2000). Horley et al. (2003) suggested the increased scanning behaviour in SAD may reflect a fear of social evaluation. This explanation may also be relevant to the current findings. Due to a preoccupation with physical appearance, individuals with AN are particularly sensitive to social evaluations made by others (Striegel-Moore, Silberstein, & Rodin, 1993) and may show increased scanning behaviours to related stimuli.
Additionally, and contrary to expectations, AN participants were not found to differ from the control group in areas of attentional focus to the Ekman face stimuli, demonstrated by the lack of group differences in the FFI and FDI for either task. These findings largely differ to those reported in other psychiatric illnesses. An avoidance of salient features is often reported in individuals with ASD (de Wit et al., 2008; Hernandez et al., 2009; Pelphrey et al., 2002), SAD (Horley et al., 2003; Moukheiber et al., 2010) and schizophrenia (E. Gordon et al., 1992; M. J. Green et al., 2003; Loughland et al., 2002b; L. M. Williams et al., 1999). Individuals with psychiatric conditions such as schizophrenia and ASD are also often reported to demonstrate emotion identification problems (e.g. Kohler et al., 2000; Wallace et al., 2008). Together these results suggest that problems in emotion identification may be related to focusing on irrelevant areas when making a facial affect judgment. Furthermore, reduced attention to salient facial features in schizophrenia has been found during passive viewing tasks, but not during active tasks where explicit instructions are given (Delerue et al., 2010). An interaction between task instructions and group was not found in the current study. Together these findings suggest that individuals with AN devote the same level of visual attention to salient features of faces of different emotions as healthy individuals, and do not differ from healthy individuals in the areas of visual attention in tasks of different instruction.

Areas of visual attention, as well as scanpath characteristics, were found to differ between groups when observing one’s own face. Similarly to the findings related to the Ekman face stimuli and as hypothesised, the group of AN participants demonstrated hyperscanning to images of their own face, evident by increased fixations of shorter duration. Although healthy control participants were found to show more attention to salient rather than non-salient features of their own face, as hypothesised, AN participants showed roughly equal visual attention to salient and non-salient features of their own face images during both tasks. This finding suggests that unlike healthy individuals who tend to focus on the eyes, nose and mouth of their own face, the AN group allocated more attention to non-salient features of own face images. As the AN group did not differ in attention to salient features of the standard set of face stimuli, this suggests that the deficit in AN is specific to observing one’s own face. In a visual scanpath study undertaken by R. Freeman et al. (1991), the investigators reported that when AN participants were presented with whole body
images of themselves, less visual attention was allocated to their faces compared to controls, though the level of visual attention to different body areas did not differ. Furthermore, Giel et al. (2011) reported a similar pattern of visual attention as in the current study in which AN and control participants were presented with food and non-food images simultaneously. The authors reported that although healthy individuals showed more visual attention to food stimuli, the AN group displayed roughly equal attention to food and non-food stimuli. These results may therefore be related to the finding that decreased visual attention is associated with the presentation of anxiety-inducing and phobic stimuli. Similarly, a study by Horley et al. (2003) reported that individuals with SAD made fixations of shorter duration to salient features of emotional face images, stimuli considered anxiety-provoking in SAD. In a study by Pflugshaupt et al. (2007), individuals with spider phobia were found to display fewer fixations to spider stimuli and instead diverted their attention to neutral areas of the stimulus. The authors described this behaviour as a strategy to cope with threatening and confrontational stimuli, and to consequently reduce anxiety. Therefore, individuals with AN may utilise similar strategies when viewing their own face as they may find these stimuli induce anxiety. Furthermore, when participants were questioned following the task about their overall experience, healthy controls often reported that they found it ‘funny’ looking at their own face, whereas AN patients tended to report feeling disgusted. A measure of how participants experienced the task was however not undertaken and should be quantified in future research.

In the only other study to investigate visual scanpaths to participants’ own face in psychiatric conditions, Grocholewski et al. (2012) reported an increased fixation count to facial areas of perceived flaw in BDD relative to healthy individuals and individuals with social phobia, who did not differ in areas of visual attention. An increased rate of fixations was also found in BDD to these areas of perceived flaws when observing a standard set of happy, sad and neutral expressions. This study did not however examine visual attention to one’s own face to the standard areas of visual attention, i.e. the eyes, nose and mouth (Walker-Smith et al., 1977). Therefore, whether individuals with BDD and other psychiatric illnesses display visual processing deficits to standard salient areas of their own face is unclear as it is yet to be investigated. Other psychiatric illnesses such as schizophrenia and ASD are however found to show reduced visual attention to salient features of standard face
stimuli, a result not found in the current study of AN patients. The deficit in visual attention observed in the current study was specific to one’s own face and suggests visual processing deficits specific to own face stimuli in AN.

6.7.3 Functional magnetic resonance imaging (fMRI)

During the implicit emotional faces task undertaken in the MRI, AN participants were hypothesised to show decreased activity in limbic areas of the brain to the Ekman face stimuli portraying negative emotions, and decreased frontoparietal activity to images of their own face. Contrary to expectations, the results of the study did not support the hypotheses. BOLD activity was not found to differ to any of the emotions relative to a control affect (neutral expression) between AN and control groups. In the only other studies to investigate facial affect processing in AN with fMRI, Fonville et al. (2014) found increased right fusiform activity to mildly happy, prototypically happy and neutral expressions in AN compared to controls, whereas Cowdrey, Harmer, et al. (2012) did not find any group differences to fearful and happy faces in a group of recovered AN participants. The findings of these two studies are however limited as neither contrasted the affect images to neutral affect images to act as a control; Fonville et al. (2014) contrasted the emotions to a baseline (fixation cross) and Cowdrey, Harmer, et al. (2012) contrasted fearful and happy conditions to one another. The current study contrasted each emotion to the neutral affect condition in an attempt to reduce activations related to face processing, therefore allowing activations related to the processing of emotions to emerge. However, activation differences were not found for each emotion compared to neutral stimuli in the within groups analyses for each group. Though these results may suggest that the task did not activate different brain areas for different emotions, a strict threshold was applied in attempt to control for multiple comparisons which may have prevented weaker activations becoming evident. However, the contrasts between participants’ own face and the neutral face condition survived this strict threshold.

The AN group were found to show deficits specific to the processing of one’s own face. As a group, AN participants displayed a greater level of bilateral activity when observing their own face compared to the neutral control face images, whereas healthy individuals displayed a greater level of right hemisphere activity which is consistent with the literature suggesting that self-face processing is predominantly a
right hemisphere function (Uddin et al., 2005). This finding suggests that although the processing of one’s own face comprises greater right hemisphere involvement in healthy individuals, individuals with AN employ more bilateral regions when observing one’s own face. In analyses directly comparing AN to healthy individuals, AN participants showed increased activity to their own face in the right inferior and middle temporal gyri, and lingual gyrus, areas related to higher-order visual perception. Controls were not found to show increased activity in any areas relative to AN participants. The inferior temporal gyrus is specifically involved in the processing of faces, with neurons in this area selectively responding to face stimuli in primate studies (Desimone, 1991; Hasselmo, Rolls, & Baylis, 1989). Furthermore, the inferior temporal gyrus contains cells particularly responsive to identity of faces (Hasselmo et al., 1989). The middle temporal gyrus has been found to play a role in the emotion identification of faces, as electrical stimulation of this area in humans results in emotion labelling difficulties (Fried, Mateer, Ojemann, Wohns, & Fedio, 1982). During fMRI studies of own face processing, increased activity in the right inferior temporal gyrus (Sugiura et al., 2008) and right middle temporal gyrus (Kircher et al., 2001; Platek et al., 2006) have been reported in samples of healthy individuals when presented with their own face compared to familiar faces. Therefore, the findings of the current study suggest increased processing of own face stimuli in AN in areas related to visual perception of oneself. Furthermore, increased activity of the bilateral lingual gyri has been reported during the presentation of neutral face stimuli, relative to scrambled stimuli (Kesler/West et al., 2001). The lingual gyrus is also related to other types of processing, particularly the processing of local and global stimuli. In a series of studies by Fink and colleagues (Fink, Halligan, et al., 1997; Fink, Marshall, et al., 1997), the investigators reported increased activity in the left lingual gyrus during global processing and increased right lingual gyrus activity during local processing. As AN participants tended to hyperscan stimuli and avoid salient features of their own face, therefore scanning more features of the image than controls, increased right lingual gyri activity may suggest increased local processing of own face stimuli in AN. This hypothesis is supported by findings that individuals with AN show a preoccupation with details and utilise local processing at the expense of global processing during certain tasks, such as the Embedded Figures Test (Tokley & Kemps, 2007). However, as neither increased lingual gyrus activity nor a deficit in the
areas of attentional focus were present to the Ekman face stimuli, it suggests that this increased local processing of faces may be specific to the processing of oneself in AN.

Differences in lingual gyrus and temporal gyrus activity have also been reported when individuals with AN are presented with images of their own body compared to other individuals’ bodies. However, increased activity in these areas was found for controls relative to AN participants (Sachdev et al., 2008; Vocks, Busch, Grönemeyer, et al., 2010), rather than increased activity in AN as found in the current study. However, both of these studies masked the faces of the stimuli presented to participants. Therefore, the differences in activation between the current findings and the findings of these two studies may be related to the specific processing of self-face and self-body images which result in increased and decreased activity in these areas in AN, respectively. However, further research investigating activation differences between both own face and own body stimuli in AN is required to further investigate the discrepancy between studies in the processing of self-images.

6.8 Summary and conclusions

In summary, the study suggests that although individuals with AN have more difficulty identifying and describing emotions within oneself (alexithymia), they are able to accurately identify emotions of others when viewing images of facial affect. Individuals with AN were also found to show distinctive scanpath strategies when viewing face stimuli, tending to hyperscan faces, which did not differ depending on the affect displayed in the image or if the stimulus was of their own face. Hyperscanning to face stimuli may suggest increased anxiety in AN when presented with images related to oneself and images related to social evaluation from others. Furthermore, AN participants were not found to differ in areas of visual attention to the Ekman face stimuli. As individuals with psychiatric conditions such as schizophrenia and ASD are often reported to demonstrate both emotion identification deficits and an avoidance of salient facial features, these results may suggest that problems in emotion identification may be related to not looking at the correct areas of a face when making an affect judgment. This hypothesis is supported by the finding that explicit instructions result in corrected attention to salient features in schizophrenia (Delerue et al., 2010).
The patient group in the current study were, however, found to show less attention to salient features and a greater level of attention to non-salient features of their own face than healthy individuals. This finding further supports the notion of increased anxiety to self-related stimuli in AN as they specifically avoided salient features of only their own face. Furthermore, the AN group were found to show increased activity in higher order visual perception areas when viewing their own face relative to neutral affect control faces, in comparison to healthy controls. This finding suggests increased processing of own face stimuli in AN in areas related to face processing and local processing of stimuli. Increased local processing in AN was further supported by the finding that individuals with AN tended to scan a greater area of their own face stimuli, showing the same level of attention to salient and non-salient features, therefore focusing on more details irrelevant to the task. However, differences in BOLD activity have been found depending on the areas of a face that are visually attended to (J. P. Morris, Pelphrey, & McCarthy, 2007). Therefore, the finding of increased activity in right inferior middle and temporal gyri, and the right lingual gyrus, may be related to the finding that individuals with AN spent a greater amount of time focusing on non-salient features of their own face than controls.

Though groups were found to differ in the processing of one’s own face, differences in BOLD activity observed in response to different emotions were not found for either group. As strict thresholding was utilised in an attempt to correct for multiple comparisons, the task may not have had sufficient power to result in significant differences in activation of each emotion relative to the neutral face condition. However, as the contrasts between participants’ own face and the neutral face condition survived this threshold, the results indicate that BOLD activity elicited in response to the different emotions was not as strong. As the current study was interested in assessing visual scanpaths to face stimuli, the extended presentation time was required for this purpose and the number of trials was therefore limited to remain within a reasonable duration for an MRI task. In future research where visual scanpaths are not of interest, an increased number of trials should be utilised to increase power. It would also be of interest in future research to investigate differences in visual scanpaths and BOLD activity to both own-face and own-body stimuli in AN, and an evaluation of how these images make participants feel.
The findings of this study have important potential clinical implications for AN. Participants with AN did not differ from healthy control participants in the areas of attentional focus when viewing the Ekman face stimuli, nor did they differ in emotion identification of these stimuli. AN participants did however display an avoidance of salient features of one’s own face which may have consequently led to the mislabelling of their own emotions. In other words, the emotion identification deficit to one’s own face in AN may be related to patients not looking at the correct areas of their own face when making an affect judgment. Consequently, this may also be related to the emotional disturbances and alexithymia reported in AN. Therefore, remediation techniques which train participants to focus on the correct areas of the face may be beneficial in AN. These techniques have proven useful in other psychiatric conditions such as schizophrenia, with trained individuals demonstrating an improvement in attention to salient facial features and emotion recognition (Marsh, Luckett, Russell, Coltheart, & Green, 2012; T. A. Russell, Green, Simpson, & Coltheart, 2008). Furthermore, the majority of deficits reported in the current study were specific to the processing of self-images in AN. This emphasises the importance of therapies such as cognitive behavioural therapy to address distorted perceptions of oneself in AN and correctly analysing events and the patient’s own internal dialogue.

In summary, the study suggests intact emotion identification of facial affect stimuli and distinct hyperscanning behaviours when viewing faces in AN. Significant differences were also found in the processing of one’s own face in AN, with AN participants showing a greater level of visual attention to non-salient features and increased activity in inferior and middle temporal, and lingual gyri, relative to healthy individuals. These findings suggest overlap with anxiety disorders, as demonstrated by the hyperscanning behaviours displayed, and by an apparent avoidance of salient features of one’s own face. Together, the results of the study suggest that the processing of self-face images differs in individuals with AN, and may contribute to the distorted perception of oneself experienced by individuals with this illness.
Chapter 7: Resting State

During typical fMRI studies, brain activity is compared between an experimental condition and a control or baseline condition. Therefore, only task-specific activations can be explored. Recently however, researchers have begun to investigate brain activity at baseline, or at rest, when no active task is presented. In an fMRI setting, this is achieved through analysing the functional connectivity, or the synchronous activations, of different brain areas when at rest. The term ‘functional connectivity’ is used to signify the correlation of activity time courses between brain regions. The benefit of examining functional connectivity at rest is that it provides information about neuronal communication in the brain, and how integration of information may relate to behaviour (M. P. Van Den Heuvel & Hulshoff Pol, 2010). A number of resting state networks, describing anatomically distinct but functionally connected brain regions, have been identified with the use of fMRI. These include, but are not limited to, the primary sensorimotor network, primary visual and extrastriate network, a network comprised of bilateral temporal/insular and anterior cingulate cortex regions, two lateralised networks consisting of superior parietal and superior frontal regions, and the ‘default mode network’ comprised of the precuneus, medial frontal, inferior parietal and medial temporal regions (for a review, see M. P. Van Den Heuvel & Hulshoff Pol, 2010). The default mode network has been of particular interest in functional connectivity studies as increased activity has been reported during rest, relative to when cognitive tasks are undertaken (Raichle et al., 2001). In psychiatric conditions, altered functional connectivity within the default mode network, and other resting state networks, may contribute to the clinical phenomenology and/or cognitive symptoms experienced in these conditions.

7.1 Resting state functional connectivity in eating disorders

As described in Chapter 1, a number of recent studies have found resting state differences in both weight-recovered and underweight AN. In a study by Cowdrey, Filippini, et al. (2012), the investigators identified different resting state networks of interest, namely the medial visual, lateral visual, auditory, sensory-motor, cognitive control, left and right fronto-parietal and default mode networks, during an eyes-open resting state task. Comparisons between weight-recovered AN and healthy
controls revealed differences in the default mode network between groups, but not for the other resting state networks. The weight-recovered AN group showed an increased temporal correlation between the default mode network functional connectivity map, and in a region of the right precuneus near the border of the posterior cingulate gyrus and the DLPFC/inferior frontal gyrus. Similarly, in a study by Boehm et al. (2014) the authors identified the default mode, salience, visual, sensory-motor and the fronto-parietal networks in acute AN and healthy controls during an eyes-closed resting state task. Within the default mode network, increased functional connectivity was found for the anterior insula, whereas increased functional connectivity was found between the angular gyrus and other regions of the front-parietal network, in AN compared to controls. The other resting state networks were, however, not found to differ between groups. During an eyes-closed resting state scan, Favaro et al. (2012) identified the medial, lateral and ventral visual networks, as well as the somatosensory network. In relation to the ventral visual network, underweight individuals with AN showed hypoconnectivity in the left occipital junction, whereas the recovered AN group showed decreased connectivity in the right middle frontal gyrus. Therefore, both AN groups showed areas of decreased connectivity in the network involved in the ‘what?’ pathway of visual perception (i.e. regions involved in spatial memory and representation). Significant differences in the other visual networks were not apparent, though the degree of coactivation in the left superior parietal cortex, including the somatosensory and premotor cortices, of the somatosensory network was found to be increased in ill but not recovered AN. This study also reported poorer visuospatial performance in AN, demonstrated by poorer visual memory and lower central coherence on the Rey-Osterrieth complex figure test, which correlated with the functional connectivity differences. The authors argued that a failure to integrate visual and somatosensory perceptual information may underlie body image disturbance in AN, but they did not directly examine this hypothesis.

In another study, the same group utilised a seed-voxel correlation approach to investigate functional connectivity in the prefrontal cortex, with seeds placed in the DLPFC, ventrolateral prefrontal cortex and ventromedial prefrontal cortex (Favaro et al., 2013). No significant group differences between AN and control participants were reported; however, differences in the AN group between different genotypes were reported. AN participants who were Met-Met allele carriers of the COMT gene
showed greater co-activation in the DLPFC and ventromedial prefrontal cortex compared to Val carriers of the gene, a relationship that was not found in the control group. A more recent study by the same group investigated functional connectivity of three regions of interest: the dorsal caudate, dorsal rostral putamen and nucleus accumbens (Favaro, Tenconi, Degortes, Manara, & Santonastaso, 2014). Group differences in functional connectivity were not found for the either dorsal caudate or nucleus accumbens seed regions for either acute or recovered AN compared to healthy controls. However, reduced co-activation was found between the left and right dorsal putamen, which was more evident for patients who reported lifetime binge-eating and purging behaviours.

Also utilising a seed-based approach, Kullmann et al. (2014) compared functional connectivity between the inferior frontal gyrus and other areas of the brain in individuals with AN and healthy control participants. Relative to healthy individuals, participants with AN demonstrated decreased effective connectivity between the right inferior frontal gyrus and the midcingulum. Increased effective connectivity in AN was found between the right inferior frontal gyrus and the bilateral orbitofrontal cortex, and between the left inferior frontal gyrus and bilateral insula, compared to healthy individuals. The authors suggest that these findings may be related to increased functional connectivity in AN in areas related to salience processing, but decreased functional connectivity in areas related to cognitive control. In a study by S. Lee et al. (2014), the investigators utilised a seed-based approach to investigate functional connectivity of the dorsal ACC in AN and BN participants. The investigators reported increased functional connectivity between the dorsal ACC and the retrosplenial cortex in AN compared to both BN and healthy individuals, and increased functional connectivity between the dorsal ACC and the precuneus in AN compared to healthy controls. Increased functional connectivity between the dorsal ACC and the medial orbitofrontal cortex was found for BN participants relative to healthy individuals.

Amianto et al. (2013) explored intrinsic connectivity networks in the cerebellum with the use of independent components analysis (ICA) and a supplementary seed-voxel correlation method. The authors reported intrinsic connectivity networks in the cerebellum which were more restricted to vermian areas,
and showed greater medial and less lateral connectivity in the cerebellum for AN patients relative to healthy controls. The AN group were also reported to show more cerebellar connectivity with the posterior cingulate cortex, left insula and bilateral temporal pole, but less connectivity with the parietal lobe. The anterior portion of the left insula was also found to show hyperconnectivity in AN, whereas the posterior portion of the insula showed hyperconnectivity in BN, relative to controls. Similarly to the contrast between AN participants and control participants, the BN group were also found to show greater connectivity with vermis and paravermis areas in the cerebellum, the left insula and temporal pole, and less connectivity with the parietal lobe, in comparison to healthy control participants. The BN group were however also found to have greater connectivity with lateral areas of the cerebellum, ACC and precuneus. In a more recent study in BN, Lavagnino et al. (2014) investigated the default mode, salience, executive and somatosensory networks utilising a seed-based approach. Though no group differences were reported for the default mode, salience or executive networks, participants with BN were found to display reduced functional connectivity within the somatosensory network. Further analyses revealed decreased functional connectivity in BN between the paracentral lobule of the somatosensory network, and the left posterior cingulate cortex, right middle occipital gyrus and right cuneus. These findings suggest reduced functional connectivity between somatosensory and visual region in BN. This pattern may contribute to the disturbance in body image reported in these individuals.

Although resting state studies of functional connectivity in eating disorders are limited to the studies described above, a larger number of resting state studies have been undertaken in other psychiatric disorders, with a particular focus on the default mode network. These are described below.

7.2 Clinical populations

7.2.1 Schizophrenia

Resting state studies in schizophrenia have revealed differences in functional connectivity in various areas of the brain, potentially contributing to the difficulties experienced by these individuals. Some findings have suggested abnormalities in
brain activity are widely distributed throughout the brain in schizophrenia rather than being restricted to specific areas or networks of the brain (Liang et al., 2006; Liu et al., 2006). However, a number of studies have reported functional connectivity differences in specific areas and networks of the brain. In relation to the default mode network, individuals with schizophrenia have shown reduced connectivity in the posterior cingulate cortex and hippocampus (Rotarska-Jagiela et al., 2010), medial prefrontal cortex (Öngür et al., 2010), and medial frontal and anterior cingulate gyri (Camchong, MacDonald, Bell, Mueller, & Lim, 2011). Decreased functional connectivity has also been found between the medial prefrontal cortex relative to every other voxel in the brain in schizophrenia patients and their first-degree relatives, but greater connectivity between the posterior cingulate cortex in schizophrenia patients alone compared to controls (Whitfield-Gabrieli et al., 2009). Functional connectivity differences have also been reported in the frontoparietal network, specifically, increased connectivity in the left parietal cortex and decreased connectivity in the right middle frontal gyrus (Rotarska-Jagiela et al., 2010). The task-positive and task-negative (default mode) networks have also been investigated in schizophrenia. H. Liu et al. (2012) used seeds in the posterior cingulate cortex/precuneus and the right DLPFC to identify the task-negative and task-positive networks. In the task-negative network, individuals with schizophrenia were found to show increased connectivity between the posterior cingulate cortex/precuneus and left inferior temporal gyrus, and between the ventral medial prefrontal cortex and the right lateral parietal cortex. The schizophrenia patients, as well as their unaffected siblings, were also found to have increased connectivity between the bilateral inferior temporal gyri. Differences in connectivity between the schizophrenia and control groups were not found in the task-positive network. In an earlier study by the same group however, increased functional connectivity was reported in the task-positive network in the DLPFC, SMA and orbitofrontal gyrus, and increased functional connectivity in the task-negative network in the dorsal medial prefrontal cortex, inferior temporal gyrus, lateral parietal region and the posterior cingulate cortex/precuneus (Zhou, Liang, Tian, et al., 2007).

Seed-based approaches have also been used to investigate specific regions of interest at rest. Zhou, Liang, Jiang, et al. (2007) assigned a seed to Brodmann’s area 46 of the DLPFC and reported decreased connectivity with the parietal lobe, posterior
cingulate cortex, striatum and thalamus in schizophrenia patients, but increased connectivity to the left mid-posterior temporal lobe and paralimbic regions. Using the hippocampus as a region of interest, Zhou et al. (2008) reported reduced connectivity with the medial prefrontal cortex, occipital gyrus/cuneus, extrastriate cortex, parahippocampal gyri, superior temporal gyrus and the medial temporal pole in schizophrenia participants relative to controls. Furthermore, differences in the functional connectivity between different networks have been reported. A study by Meda et al. (2012), found reduced connectivity between meso/paralimbic and sensory-motor pathways in schizophrenia, and the fronto/occipital and anterior default mode/prefrontal networks in both schizophrenia and BD patients relative to controls. Unlike the schizophrenia group, the BD group were also found to have increased connectivity between the meso/paralimbic and fronto-temporal/paralimbic networks compared with controls.

7.2.2 Mood disorders

Similarly to patients with schizophrenia, individuals with BD have also been found to have reduced default mode network connectivity in the medial prefrontal cortex, specifically, the ventral medial prefrontal cortex (Öngür et al., 2010). The same study also reported increased recruitment of the parietal cortex in BD patients which correlated with mania severity, and increased recruitment of the BG/frontopolar cortex in schizophrenia. A recent study by Chai et al. (2011) also compared resting state findings in the medial prefrontal cortex in BD, schizophrenia and control participants. BD patients were reported to show positive correlations between the medial prefrontal cortex and the ventrolateral prefrontal cortex, and insula. The control group were however found to show anticorrelations (negative correlations) between these areas, whereas the schizophrenia patients did not exhibit either correlations or anticorrelations in these regions. Furthermore, the control group exhibited anticorrelations between the DLPFC and medial prefrontal cortex which were not found in either patient group, suggesting a decoupling in these areas which may contribute to the executive functioning difficulties experienced by these individuals.
Resting state differences in the DLPFC have also been reported in paediatric BD, specifically, reduced connectivity between the left DLPFC and right superior temporal gyrus (Dickstein et al., 2010). The same study also reported no resting state connectivity differences between BD and healthy controls in seeds placed in the nucleus accumbens or amygdala. Negative correlations have however been reported between the amygdala and the ventrolateral prefrontal cortex, though to a lesser extent in BD patients than controls (Chepenik et al., 2010). Chepenik et al. (2010) also reported increased connectivity between the left and right ventrolateral prefrontal cortices, and the ventral striatum in BD participants during whole-brain analyses. With the use of region of interest analysis, Anand, Li, Wang, Lowe, and Dzemidzic (2009) reported decreased connectivity between the pregenual ACC and the amygdala, and pallidostriatum in BD patients, and decreased connectivity between the pregenual ACC and dorsomedial thalamus in both BD and unipolar depression patients relative to controls. Differences between the BD and unipolar depression patients were not found. However, a number of resting state connectivity differences have been reported by other studies in unipolar depression, or MDD, relative to healthy individuals.

Several recent studies have investigated the default mode network in MDD. Zhu et al. (2012) reported increased connectivity in the dorsal medial prefrontal cortex/ventral ACC, ventral medial prefrontal cortex and medial orbital prefrontal cortex, and decreased connectivity in the angular gyrus and posterior cingulate cortex/precuneus. Utilising a precuneus/posterior cingulate cortex seed to identify the default mode network, Bluhm et al. (2009) found reduced connectivity between the seed and the bilateral caudate in the MDD group relative to the control group, and no regions of increased connectivity in the MDD patients. Veer et al. (2010) utilised ICA and identified thirteen functionally relevant networks. Three of these networks were found to show abnormal connectivity in the MDD group. Specifically, decreased frontal pole connectivity in a network associated with working memory and attention, reduced lingual gyral connectivity within ventromedial visual regions, and decreased anterior insula and amygdala connectivity in an affective network. A recent study by Sheline, Price, Yan, and Mintun (2010) also investigated the affective network, as well as the cognitive control network and default mode network. In relation to controls, the MDD participants were found to have increased connectivity of these
networks to the same dorsal medial prefrontal cortex region, which the authors termed the dorsal nexus. The investigators suggested that the symptoms of MDD that are thought to arise in distinct networks may be linked together through the dorsal nexus and may occur concurrently.

Treatment-responsive and treatment-resistant MDD have also been compared to one another and functional connectivity differences between the two have been observed. In comparison to healthy controls, both MDD groups have shown reduced functional connectivity in bilateral prefrontal-limbic-thalamic areas. The treatment-responsive group, however, showed decreased connectivity within the left amygdala-ACC-right insula-precuneus region in comparison to the treatment-resistant group (Lui et al., 2011). The ACC, specifically the subgenual ACC, has also been shown to have reduced functional connectivity with a network of cortical areas including the medial, superior and inferior frontal cortex, superior temporal cortex, insular cortex and supragenual ACC in adolescents with MDD (Cullen et al., 2009). Furthermore, a relationship between functional connectivity and medication status, duration of illness or the presence of an anxiety disorder was not found. However, this study is limited in its findings as participants listened to music of their choice during the resting state scan resulting in potential state-related changes in functional connectivity.

7.2.3 Anxiety disorders

High state and trait anxiety in healthy individuals has been found to result in decreased functional connectivity between the amygdala and the ventromedial prefrontal cortex and dorsal medial prefrontal cortex (M. J. Kim, Gee, Loucks, Davis, & Whalen, 2011). Altered connectivity between the amygdala and other regions of the brain has also been reported in generalised anxiety disorder. Etkin, Prater, Schatzberg, Menon, and Greicius (2009) reported decreased amygdala connectivity with the ventrolateral prefrontal cortex, superior temporal gyrus, SMA, thalamus, caudate, putamen, dorsal/mid cingulate and insula. The study also found increased amygdala connectivity with the posterior parietal cortex, occipitotemporal cortex, and dorsolateral, ventrolateral, dorsomedial and ventromedial prefrontal cortices. Together, the findings from this study suggest decreased connectivity of areas related to salience processing and increased connectivity in regions related to cognitive
control of emotional stimuli. Due to the amygdala’s role in emotion processing, it has been of particular interest in the study of anxiety disorders, particularly SAD.

Liao, Qiu, et al. (2010) reported decreased functional connectivity between the amygdala and inferior temporal gyrus, among other regions including the middle temporal, postcentral and superior frontal gyri, hippocampus, and areas of the parietal cortex. Increased amygdala connectivity in SAD was found in the limbic/paralimbic cortex, and areas of the occipital and temporal cortices. Furthermore, increased functional connectivity was reported between the left amygdala and cerebellum, but decreased connectivity between the right amygdala and cerebellum. The authors also reported increased amygdala connectivity with areas of the default mode network including the precuneus and middle cingulate gyrus. The same group found increased connectivity between the parahippocampal/hippocampal gyrus and middle temporal gyrus, and the posterior inferior temporal gyrus and inferior occipital gyrus in SAD (Liao et al., 2011). An earlier study, by the same group, found decreased connectivity in the somato-motor and visual networks, and increased connectivity in the self-referential network which includes the medial prefrontal cortex (Liao, Chen, et al., 2010). Increased functional connectivity was also found in areas of the dorsal attention network, central executive network, and areas of the default mode network. Though, areas of these networks were also found to show decreased connectivity in SAD patients. A recent study by Pannekoek et al. (2013), reported no difference in default mode network connectivity between SAD and healthy comparison participants. The study did, however, find decreased amygdala connectivity with the middle temporal and supramarginal gyri, and lateral occipital cortex. Furthermore, greater dorsal ACC connectivity in the salience network was demonstrated with the precuneus and lateral occipital cortex in SAD patients.

Resting state functional connectivity has also been increasingly studied in recent times in OCD. Decreased default mode network connectivity in the ACC, middle frontal gyrus and putamen has been found in OCD (Jang et al., 2010), as well as increased connectivity with the fronto-parietal network, and greater connectivity between the insula and thalamus (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). Decreased functional connectivity between the medial dorsal thalamus and dorsal striatum to the dorsal and rostral ACC, respectively, has also been reported in children.
with OCD, and this was also found to correlate with illness severity (K. D. Fitzgerald et al., 2011). The same study reported greater dorsal striatum connectivity to the ventral medial frontal cortex in children, adolescents and adults with OCD. Together, these findings suggest hypoconnectivity of cognitive control areas at the early stages of the illness and hyperconnectivity of emotion processing areas throughout the condition. In an earlier study, the same group of investigators observed reduced anterior operculum and ventral medial frontal-posterior cingulate cortex connectivity in OCD (K. D. Fitzgerald et al., 2010). Functional connectivity of the BG in OCD has also been of recent interest. Seed-based analyses in the BG have revealed increased connectivity between the ventral striatum and orbitofrontal cortex, and ventral medial prefrontal cortex and DLPFC (Sakai et al., 2011). Placing seeds at the dorsal and ventral caudate, and dorsal caudal and ventral rostral putamen, B. J. Harrison et al. (2009) reported a number of functional connectivity differences in OCD. Included among these connectivity differences were decreased connectivity of the ventral caudate/accumbens to the VTA and right medial temporal lobe; dorsal putamen to the ventrolateral thalamus and inferior parietal cortex; and ventral putamen to the VTA and inferior frontal cortex. Greater connectivity was also found in OCD in ventral putamen to the subgenual ACC and posterior medial prefrontal cortex; and increased ventral caudate/accumbens connectivity to the medial orbitofrontal cortex and anterior prefrontal and perigenual ACC. The strength of the ventral caudate and medial orbitofrontal cortex connectivity was also found to positively correlate with symptom severity.

7.2.4 Resting state functional connectivity in clinical populations: conclusions

Resting state studies have allowed us to gain a better understanding of how the brain functions when no active task is undertaken and have been investigated in two main ways: investigating the functional connectivity within and/or between networks, and the functional connectivity between a region of interest and other areas of the brain. The second method is often utilised when a specific region of the brain is of interest. In contrast, the first method investigates connectivity within predefined networks and has the benefit of utilising networks of brain areas that are consistently found to be functionally connected. Investigating functional connectivity within
specific networks is also advantageous in that resting state network connectivity differences between different psychiatric illnesses can be explored.

The summary of functional connectivity differences in psychiatric illnesses was therefore presented to permit comparisons with other potentially related mental illnesses and to illustrate the benefit of investigating specific networks rather than regions of interest whose functional connectivity with other brain areas is less well defined. The default mode network has been of particular interest in psychiatric conditions and poorer connectivity within this network has been reported in schizophrenia, BD, MDD and OCD. A recent study investigating default mode network connectivity in a group of weight-recovered AN participants reported increased functional connectivity within the default mode network (Cowdrey, Filippini, et al., 2012), as has a recent study of acute AN (Boehm et al., 2014). Favaro et al. (2012) investigated the medial, lateral and ventral visual networks, and the somatosensory network in groups of recovered and currently ill AN, and healthy individuals. The authors investigated these resting state networks as separate networks and reported functional connectivity differences between groups. This study also reported poorer visuospatial performance in AN, demonstrated by poorer visual memory and lower central coherence on the Rey-Osterrieth complex figure test. As individuals with AN are often reported to show poor performance on visuospatial processing tasks (Fonville et al., 2013; Gillberg et al., 2007; Jones et al., 1991; Kemps et al., 2006; Kingston et al., 1996), it would be beneficial to investigate the visual and sensorimotor networks as a single network rather than separate networks. In a study by M. Van Den Heuvel, Mandl, and Pol (2008), the authors identified a combined sensorimotor and visual network and suggested that the separate visual and sensorimotor networks reported in other studies may be reflective of sub-networks within this network. An additional advantage of examining the sensorimotor and visual network is to examine whether functional connectivity within these areas may be related to the body image distortion that individuals with AN experience.

7.3 Current study aims and hypotheses

The aim of this study was to investigate resting state functional connectivity within the sensorimotor and visual network, and the default mode network in
individuals with AN. As the study aimed to investigate differences in functional connectivity between different areas within a network, a seed-driven approach with region-to-region functional connectivity analysis was performed in which the correlation of time courses is analysed between different pre-defined brain regions. In relation to the default mode network, AN participants were expected to display increased functional connectivity as has been reported in the only previous studies examining this network in AN. Related to the findings of poor visuospatial task performance and the body image distortion experienced by individuals with AN, they were hypothesised to show reduced connectivity between somatosensory and visual areas, relative to healthy individuals. An additional aim of the study was to investigate whether functional connectivity within this network was correlated with performance on two visuospatial tasks of the MATRICS, the WMS III®: Spatial Span and BVMT-R™. Performance on these measures was hypothesised to positively correlate with functional connectivity of the sensorimotor and visual network.

7.4 Method

7.4.1 Participants

Twenty-six individuals with AN and 27 healthy control individuals completed the resting state task in the MRI. Clinical and demographic information for the additional two AN and three healthy control participants who completed the resting state task but did not complete all three sessions is provided in Appendix E.

7.4.2 Task

Participants were presented with a white one degree fixation cross against a black background and were asked to fixate on this cross for the entire duration of the task. The task was presented for 6 minutes and 40 seconds. Eyetracking was not recorded, but the ‘host’ computer and cameras for the eyetracker were enabled to monitor whether participants were awake and attempting to fixate on the cross.
7.4.3 Analysis

Data processing was undertaken through the CONN fMRI functional connectivity toolbox version 14.i (Whitfield-Gabrieli & Nieto-Castanon, 2012), run under Matlab R2014a. Pre-processing of data was undertaken in SPM8. Images were realigned, normalised to MNI space, spatially smoothed with a 5mm kernel, and temporally band-pass filtered (0.008 - 0.200Hz). Anatomical images were segmented into grey and white matter as well as CSF. Physiological noise and motion parameters were regressed from the functional images using the CompCor strategy (Behzadi, Restom, Liau, & Liu, 2007). Temporal confounds regressed from the time series included three translational and three rotational head motion parameters and their first order temporal derivatives, and average white matter and CSF signals. Slice timing corrections were not performed on the data due to the fast acquisition time of multiband data. Detrending was performed to remove linear trend within each functional session; and despiking was performed to reduce the influence of potential outlier scans.

ROIs of the default mode network, and sensorimotor and visual network were specified as defined by Van Den Heuvel et al. (2008; 2010). The default mode network consisted of the ventral posterior cingulate cortex (Brodmann area (BA) 23), dorsal posterior cingulate cortex (BA 31), angular gyrus (BA 39), middle temporal gyrus (BA 21), supramarginal gyrus (BA 40), dorsal frontal cortex (BA 8) and the orbitofrontal cortex (BA 11). The sensorimotor and visual network consisted of primary somatosensory cortex (BA 1, 2, 3), primary motor cortex (BA 4), ventral ACC (BA 24), primary visual cortex (BA 17), secondary visual cortex (BA 18) and associative visual cortex (BA 19).

7.4.3.1 Statistical analysis

Functional connectivity analysis was performed using a seed-driven approach for each network separately. The BOLD time series used for each ROI was the average time series of all voxels within the ROI. ROI-to-ROI analyses were performed by computing Pearson’s correlation coefficients between the time course of each ROI and the time course of all other ROIs within the network. Correlation coefficients were converted to normally distributed z-scores using the Fisher
transformation to allow for second-level general linear model analyses. A false discovery rate corrected p value of p < 0.05 was applied over the set of target ROIs.

Pearson’s correlation analyses were also performed between the correlation outputs of the fMRI data for each ROI to ROI pair that resulted in significant group differences, and the results of the two visuospatial tasks of the MATRICS (WMS III®: Spatial Span and BVMT-R™) and the subscales of the FRS and EDE-Q, with alpha set to p= 0.01 to account for multiple comparisons.

7.4.4 Procedure

Participants were instructed to simply look at the fixation cross in the centre of the screen for the entire duration of the task. They were not given any further instructions. The resting state fixation task was the first task presented in the MRI to reduce the effects of fatigue and the effects of other tasks.

7.5 Results

The following section describes the results of the resting state task. Functional connectivity within nodes of the default mode network were not found to differ between groups. A number of group differences were however found within nodes of the sensorimotor and visual network (Table 7.1). Reduced functional connectivity was found between primary somatosensory, and both secondary and associative visual cortex ROIs, and between primary motor and both secondary and associative visual cortex ROIs in AN (Figure 7.1 A-D). However, there were no group differences in functional connectivity between the different visual regions, nor were there significant differences between the different primary somatosensory and primary motor areas. Furthermore, functional connectivity differences between AN and control groups were not found in the ventral ACC or the primary visual cortex. Increased functional connectivity in AN compared to healthy individuals was also not found between any nodes.
Table 7.1
Significant nodes of connectivity, sensorimotor and visual network, anorexia nervosa > healthy controls

<table>
<thead>
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<th>Seed</th>
<th>Target</th>
<th>beta</th>
<th>T(51)</th>
<th>p-unc</th>
<th>p-FDR</th>
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Note: L= left; R= right; BA 18= secondary visual cortex; BA 19= associative visual cortex; BA 1/2/3= primary somatosensory cortex; BA 4= primary motor cortex; p-unc= uncorrected p value; p-FDR= false discovery rate corrected p value
Figure 7.1. Reduced functional connectivity in anorexia nervosa compared to healthy controls within the sensorimotor and visual network for seeds at the left secondary visual cortex (BA 18) (A), right secondary visual cortex (BA 18) (B), left associative visual cortex (BA 19) (C), and right associative visual cortex (BA 19) (D) (black dots represent seeds and blue dots represent areas of reduced connectivity, with the size of the dots representing the effect size)

Pearson’s correlation analyses between each ROI-to-ROI pair that resulted in significant group differences, and the FRS and EDE-Q subscales did not result in any significant correlations for either group. Analyses with the Spatial Span and BVMT-R tasks also did not result in any significant correlations, but a trend was found between the total recall score of the BVMT-R, and functional connectivity between the left secondary visual cortex (BA 18) and the right motor cortex (BA 4) for the AN group (r = -0.51, p = 0.010). A trend was also revealed between the total recall score of the BVMT-R, and functional connectivity between the right secondary visual cortex (BA 18) and the right motor cortex (BA 4) for the AN group (r = -0.49, p = 0.016). No correlations were revealed for the control group.
7.6 Discussion

The aim of this study was to investigate functional connectivity within two resting state networks, namely the default mode network, and the sensorimotor and visual network, in individuals with AN and healthy controls. The AN group were hypothesised to display increased functional connectivity within the default mode network, and decreased functional connectivity within the sensorimotor and visual network, particularly between somatosensory and visual areas, relative to healthy individuals.

7.6.1 Default mode network

Contrary to expectations, default mode network connectivity did not differ between AN and healthy control participants. Two recent studies however reported increased functional connectivity in the default mode network in recovered (Cowdrey, Filippini, et al., 2012) and acute AN (Boehm et al., 2014). However, a number of key differences between these studies and the current study exist. The AN participants in the study of Cowdrey, Filippini, et al. (2012) had recovered whereas in our study the AN patients were currently ill (i.e. were underweight and met all the criteria for AN as assessed by the MINI). Therefore, the discrepancy between the studies may be related to the long-term effects of malnourishment or the effects of weight restoration. In the current study, we also examined specific correlations between areas within a network, whereas the other groups utilised ICA to investigate the strength of the default mode network. Furthermore, although the study by Boehm et al. (2014) recruited a large sample, the study by Cowdrey, Filippini, et al. (2012) used a much smaller sample size than the current study and therefore may not have been statistically powerful enough to reveal accurate findings. Additionally, the power in the current study was further increased by employing a multiband sequence for the acquisition of fMRI data, with an unprecedented sampling rate.

Differences in default mode network connectivity, particularly reduced connectivity within the network, have however been reported in other psychiatric illnesses such as schizophrenia (Rotarska-Jagiela et al., 2010), BD (Öngür et al., 2010), MDD (Bluhm et al., 2009), OCD (Jang et al., 2010) and ASD (Monk et al., 2009). As regions of the default mode network are active during rest and are
 deactivated when active tasks are undertaken (Damoiseaux et al., 2006), altered functional connectivity within the network may contribute to the dysfunctions experienced in these conditions. The lack of significant group differences in the current study suggests that this network of functional connectivity, including the ventral and dorsal posterior cingulate cortices, dorsal frontal and orbitofrontal cortices, and angular, middle temporal, and supramarginal gyri, may not be involved in the psychopathology of AN.

7.6.2 Sensorimotor and visual network

The hypothesis that individuals with AN would exhibit reduced functional connectivity within the sensorimotor and visual network was supported by the findings of this study. Reduced functional connectivity was found between primary somatosensory, and secondary visual and associative visual cortices; and between primary motor, and secondary visual and associative visual cortices in AN participants. Together these results suggest a dysfunction in the functional connectivity of sensorimotor and visual areas of the brain in AN. The reduced functional connectivity observed in AN between the primary motor cortex, and secondary and associative visual areas suggests a visuomotor disturbance in AN. Contrary to expectations, a trend for a negative correlation between BVMT-R\textsuperscript{TM} performance, and functional connectivity of the left and right secondary visual cortices with the right primary motor cortex was revealed for AN participants. Though groups did not significantly differ in BVMT-R\textsuperscript{TM} performance, as described in Chapter 4, performance on this task may be modulated by functional connectivity of these brain areas in AN. As increased functional connectivity within these regions was related to poorer performance on the BVMT-R\textsuperscript{TM}, this may suggest that individuals with AN differ from healthy individuals in their recruitment of specialised visuomotor neural mechanisms. Furthermore, although a significant correlation was not found between functional connectivity of areas of the sensorimotor and visual network and the Spatial Span task, a trend toward poorer performance in AN was observed during the backward component of this task, a task requiring motor replication of visuospatial information. Poorer performance in AN has also been observed in other tasks requiring motor replication of visuospatial information of greater complexity, such as the Rey Complex Figure Test (Kingston et al., 1996; Stedal et al., 2012).
Furthermore, the specific connectivity disturbance between the primary somatosensory cortex and visual areas reported in this study may be involved in the visuospatial processing deficits and body image distortions that individuals with AN experience.

AN is characterised by a disturbance in the way that body weight or shape is experienced. As indicated by the FRS in this study, individuals with AN did not differ to healthy individuals in their perceived body size (think condition), despite having significantly lower BMIs. Furthermore, AN participants reported feeling heavier than control participants, again despite their low weight. A discrepancy between how AN participants thought and felt they looked was also apparent, with AN participants reporting feeling larger than they thought they appeared; a discrepancy which was not evident for healthy individuals. Therefore, the perception of body size and the discrepancy between how individuals with AN feel and think they look may be attributed to the dysfunctional connectivity between somatosensory and visual processing areas. Significant correlations between the FRS or EDE-Q subscales and functional connectivity were however not found. The EDE-Q is not a specific measure of body image distortion, but indicates level of body dissatisfaction. The FRS, evaluates body image disturbance, but its utility was limited with the use of correlational analyses due to the low variability in responses. Therefore, the use of a more sensitive measure of body image distortion would be beneficial in future research.

A recent study by Favaro et al. (2012) investigated the visual and somatosensory networks as separate networks in AN and reported decreased connectivity within the ventral visual network, but increased connectivity within the somatosensory network. This study was limited as the visual and somatosensory networks were not analysed as a single network, nor was the functional connectivity between the separate networks compared to one another. The study by Favaro et al. (2012) did however report poorer visuospatial performance, demonstrated by poorer visual memory and lower central coherence on the Rey-Osterrieth complex figure test. Though the current study revealed a trend for poorer performance on the backward component of the Spatial Span task in our group of AN participants, the results of this task and that of the other visuospatial processing task (i.e. the BVMT-R) were not
found to correlate with somatosensory and visual cortices connectivity. However, the functional connectivity disturbance between somatosensory and visual areas reported in the current study may contribute to performance on other tasks where significant visuospatial processing deficits are observed in AN, such as the object assembly subtest of the WAIS (Gillberg et al., 2007), the embedded figures test (Fonville et al., 2013; Jones et al., 1991) and visuospatial memory tasks of object location (Kemps et al., 2006). Furthermore, individuals with AN have been found to show a significant deficit in a size-weight illusion task, the Chapentier Illusion (Case, Wilson, & Ramachandran, 2012). During this task, two objects of equal weight but different sizes are held. Typically, individuals will experience a strong illusion that the smaller object feels heavier than the larger object, as an implicit assumption is held that weight scales with size. Individuals with AN have however been found to exhibit a diminished capacity to experience this illusion, suggesting poor visual and somatosensory integration in AN.

7.6.3 Summary and conclusions

The results of this study suggest intact functional connectivity of the default mode network in AN, despite reports of significant functional connectivity differences in other related psychiatric illnesses. This result suggests that the integration of brain regions contained in this network may not be involved in AN. This study found reduced connectivity of sensorimotor and visual areas in AN, which may be related to the inconsistency patients experience between how they think and feel they look, and the inability to accurately judge their own body size. Similarly, individuals with BN have been reported to display reduced functional connectivity between somatosensory and visual regions (Lavagnino et al., 2014).

A number of potential constraints in the way the data were analysed may have limited the findings. As the current study focused on two resting state networks which have the most relevance to AN and have also been previously investigated in this population, potential differences in other resting state networks were not explored. Additionally, it may have been instructive to assess functional connectivity between specific nodes and clusters of voxels throughout the entire brain, but would have reduced the statistical power of the study due to the increased number of comparisons.
The findings of the current study have important implications for our understanding of body image in AN. The results suggest that the deficit in body size perception that individuals with AN are reported to experience may be related to reduced functional connectivity between somatosensory and early visual processing areas of the brain. Therefore, treatments designed to strengthen the functional connectivity between these regions may assist in recovery. More specifically, monitoring the strength of functional connectivity between the areas of sensorimotor and visual network over the course of treatment, may assist in determining a reduction of body image distortion in individuals with AN. As the correlational analyses did not indicate a significant relationship between functional connectivity and the employed measures of body dissatisfaction, future research should first utilise a more sensitive measure of body image disturbance to confirm this relationship.

Body dissatisfaction is a significant issue in AN which often persists following recovery (Windauer, Lennerts, Talbot, Touyz, & Beumont, 1993), and is a significant risk factor for relapse (Carter, Blackmore, Sutandar-Pinnock, & Woodside, 2004). Body image therapies have been developed for the treatment of AN, but with limited efficacy (Key et al., 2002). Therefore, treatments specifically designed to increase functional connectivity between somatosensory and visual areas may improve treatment response. Transcranial magnetic stimulation (TMS) is a potentially useful tool for this purpose, though its clinical utility with the use of resting state findings remains unclear (M. D. Fox, Greicius, Fox, & Greicius, 2010). The development of body image therapies designed specifically to improve the perception of body size may also prove beneficial.
Chapter 8: Body Image

8.1 Body image in anorexia nervosa

A core feature of AN is a disturbance in the way in which an individual experiences their own body shape or weight, and this distortion of body image is indeed a diagnostic criterion for the disorder (American Psychiatric Association, 2013). Bruch (1962) first recognised a disturbance of body image as a common pathognomonic psychological factor in AN. She described this disturbance to be of delusional proportions and that even though patients were severely emaciated, they defended their appearance as ‘not too thin’. More recently, Garner and Garfinkel (1981) described two main elements of body image disturbance in AN: a perceptual disturbance in the way body shape or weight is perceived, and an attitudinal disturbance in the way the body is evaluated. The perceptual aspects of body image disturbance in AN have been of greater focus in quantitative investigations. One of the main methods utilised to assess perceptual body image disturbances in AN is the use of tasks of body size estimation. Studies have employed tasks of both estimation of individual body parts and whole bodies. However, inconsistent findings have been reported. In relation to estimating the size of their own body, some investigators have reported that individuals with AN do not differ from healthy individuals (Fernández-Aranda, Dahme, & Meermann, 1999; Fernández, Probst, Meerman, & Vandereycken, 1994; Probst, Vandereycken, Van Coppenolle, & Pieters, 1995, 1998), whilst other research has suggested that individuals with AN significantly overestimate their own body size (Collins et al., 1987; Slade & Russell, 1973; Smeets & Kosslyn, 2001; Tovée et al., 2000). One early study however reported an underestimation of own body size in AN (Gardner & Moncrieff, 1988). Furthermore, several studies have found greater variability in under- or over-estimating own body size in AN (Collins et al., 1987; Garfinkel, Moldofsky, & Garner, 1979; Garner, Garfinkel, Stancer, & Moldofsky, 1976; Probst et al., 1995; Touyz, Beumont, Collins, McCabe, & Jupp, 1984). When examining estimations of specific body areas, an overestimation in the size of the hips in AN has been reported (Sunday, Halmi, Werdann, & Levey, 1992), as well as a general overestimation of all body areas (Gila, Castro, Toro, & Salamero, 1998). However, Hennighausen, Enkelmann, Wewetzer, and Remschmidt (1999) found that individuals with AN were more likely to under- or over-estimate their own
body dimensions than healthy individuals, whereas studies by Button, Fransella, and Slade (1977) and Probst et al. (1998) both reported accurate body dimension estimations in their samples of AN participants. However, Probst et al. (1998) found that those with a more negative body attitude tended to overestimate their body dimensions. Furthermore, Sunday et al. (1992) reported improvements in body size estimation following treatment and weight-recovery.

The estimation of other people’s body size has been far less frequently investigated in AN as the disturbance in body perception has generally been held to be related solely to one’s own body. However, in a study by Smeets (1999) where participants were required to select when a morphing video of a female transitioned from thin to normal, to fat and to obese, the AN participants perceived earlier transitions than the healthy controls. In other words, what AN participants considered a thin, normal, overweight or obese body was thinner than what controls considered these body sizes to be. Furthermore, Tovée et al. (2000) reported not only an overestimation of body size in AN to female images displaying varying body sizes, but also a preference in AN participants to consider lower body mass as more attractive. This study also found that as the BMI of the observer decreased, the overestimation of body size increased.

The areas of the body upon which individuals with AN focus on has also been found to differ from healthy individuals. In a study of healthy individuals, Hewig, Trippe, Hecht, Straube, and Miltner (2008) showed that people make more fixations to and fixate longer on the face than any other body area. In relation to weight-recovered AN, Watson et al. (2010) reported reduced attention to face regions during a free-viewing task where participants were presented with whole body stimuli. R. Freeman et al. (1991) showed participants images of their own bodies photographed in a black leotard and reported that while healthy control participants spent relatively the same amount of time focusing on the four interest areas (the face, chest, abdomen and legs), individuals with AN spent more time looking at the their legs and abdomen and less time looking at their face. Furthermore, the areas of the body which were of greater focus in AN corresponded to the areas of the body with which the patients were most dissatisfied. Jansen, Nederkoorn, and Mulkens (2005) also found that participants with non-clinical eating disorder symptomatology spent more time
looking at their self-identified ‘ugly’ body parts than their self-identified ‘beautiful’ body parts, whereas individuals without eating disorder symptomatology were not found to show any difference in the amount of time focusing on their self-identified beautiful or ugly body parts. In a more recent study, Hewig, Cooper, et al. (2008) presented male and female participants scoring high and low on the drive for thinness scale of the Eating Disorders Inventory (Garner, Olmstead, & Polivy, 1983) with male and female body images. Participants scoring high on the measure were found to make more fixations to and fixate longer on the waist, hips, arms and legs, and less at the face and head area. The authors suggested that the results may reflect an attentional bias to areas that are associated with assessing body weight. Furthermore, the strength of the findings was dependent on the garments the models were wearing, with those in undershirts having the strongest effect, followed by those in underwear and swimwear, and nude individuals. These findings suggest that the clothing worn by models has an influence on which parts of the body people attend to. Therefore, it is necessary to control for these possible effects. Furthermore, personal characteristics of the model may draw more attention to certain body parts which would also need to be controlled for in studies. Rather than utilising drawings or computer-generated images of human figures which can be unrealistic and distracting, a potential tool is the human body biological motion task.

8.2 Biological motion

The term biological motion was first characterised by Johansson (1973) to describe the visual perception of animals and humans in locomotion. In this pioneering research, actors dressed completely in black with lights attached to their joints were filmed on an entirely black background so that only the lights were visible to the observer. It was found that observers were able to accurately identify different human motions such as walking, running or dancing purely from the pattern of motion created by the point-light displays. Point-light displays not only allow us to identify the type of movement made by a human, but also allow for the recognition of gender (Kozlowski & Cutting, 1977; Troje, 2002a), emotion (Dittrich, Troscianko, Lea, & Morgan, 1996) and even identifying individual people (Cutting & Kozlowski, 1977; Loula, Prasad, Harber, & Shiffrar, 2005). It has also been proposed that other
attributes such as body weight, age and personality traits could be identified from biological motion stimuli (Troje, 2002a).

The perception of body biological motion involves different areas of the brain in relation to general processing of body images. While the processing of static body images primarily involves the extrastriate body area (Downing, Jiang, Shuman, & Kanwisher, 2001) and the fusiform body area (Peelen & Downing, 2005), the processing of body biological motion involves, in addition to these areas (Peelen, Wiggett, & Downing, 2006), the superior temporal sulcus (Greze et al., 2001; Grossman & Blake, 2002; Grossman et al., 2000; Sokolov et al., 2012; Vaina, Solomon, Chowdhury, Sinha, & Belliveau, 2001), the cerebellum (Grossman et al., 2000; Jokisch, Troje, Koch, Schwarz, & Daum, 2005; Sokolov et al., 2012), area middle temporal (MT) (a motion-sensitive region), and the parietal cortex (Greze et al., 2001; Vaina et al., 2001).

The visual processing of biological motion stimuli has been of recent interest, particularly the areas of the stimulus that individuals focus their attention upon when observing these stimuli. In the only study to date utilising eyetracking in combination with the biological motion task, Saunders, Williamson, and Troje (2010) presented participants with two biological motion tasks consisting of humans walking: to determine the direction of the walker or to identify the gender of the walker. Three regions of interest were identified: the shoulders, pelvis and feet. Though participants fixated on the pelvic region more often in both conditions, the feet were more often fixated on in the direction condition and the shoulders in the gender task, suggesting that the shoulder region may be more important for gender discrimination. The study however has a number of limitations. Firstly, only the number of fixations was analysed and the duration of these fixations was not examined. Furthermore, the regions of interest were restricted to these three areas. This not only excluded areas such as the head, but also included unrelated features in the region of interest, such as the hands within the pelvic region. However, the study does support the notion that different task instructions result in differing eye movements to biological motion.

Recent research has also been interested in investigating how different psychiatric groups perceive biological motion stimuli.
8.3 Clinical populations

8.3.1 Autism spectrum disorder (ASD)

Individuals with ASD show marked impairments in social functioning and communication, which is thought to be attributed to a lack of theory of mind in these individuals (Baron-Cohen, Leslie, & Frith, 1985). As the biological motion task assesses aspects of social processing, several recent studies have employed the task to investigate social processing in ASD. Children as young as two years old with ASD have been reported to display deficits in biological motion perception. When presented with upright and inverted biological motion figures, typically developing children preferentially attended to the upright figures whereas children with ASD were found to be random in their viewing (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009). Furthermore, when simply presented with either biological motion or scrambled dots with incoherent motion and asked whether the sequence represented a person or not, children with ASD were found to show poorer discrimination, but were not found to differ from controls on a global-form task requiring the detection of a grouped figure against background noise (Blake, Turner, Smoski, Pozdol, & Stone, 2003). Although this deficit in biological motion discrimination was not correlated with chronological age, it was correlated with mental age which was suggested to likely contribute to this impairment. However, other recent studies have not reported a deficit in the general perception of biological motion stimuli, or the perception of actions such as kicking, jumping, etc., or motion direction, but deficits specifically related to the perception of emotion and attitudes from biological motion stimuli in ASD (Couture et al., 2010; Hubert et al., 2007; Moore, Hobson, & Lee, 1997; Murphy, Brady, Fitzgerald, & Troje, 2009; Parron et al., 2008; Rutherford & Troje, 2012).

Recent fMRI studies have also investigated activation differences in ASD to biological motion stimuli. When presented with coherent human movement and incoherent movement, Herrington et al. (2007) reported similar behavioural performance between ASD and control participants, but less activity of the inferior, middle and superior temporal regions, including area MT, in the ASD group. Similarly, Freitag et al. (2008) reported comparable behavioural performance between
a group of ASD participants and a typically developing group to biological motion compared to scramble motion stimuli. The ASD participants did show hypoactivation bilaterally in temporal and parietal areas, the ACC and inferior parietal lobule, in the right middle temporal gyrus, postcentral gyrus, medial and frontal gyri and occipital areas, claustrum, and the left anterior superior temporal fusiform and postcentral gyri, suggesting difficulties in higher-order motion perception or integration. Likewise, Koldewyn, Whitney, and Rivera (2011) found that in addition to having higher thresholds for biological motion perception, individuals with ASD also showed increased activity in the bilateral inferior temporal cortex, including the fusiform and lateral occipital gyri, and hypoactivation of the posterior temporal sulcus, DLPFC, ACC and parietal cortex. The ASD group, however, did not differ in area MT activity. These results were suggested to reflect impairments of higher-order social or attentional networks which may underlie the visual motion deficits observed in ASD rather than a deficit in lower-level motion processing.

8.3.2 Schizophrenia

Social functioning deficits are also apparent in individuals with schizophrenia (Couture, Penn, & Roberts, 2006), as are a range of visual processing deficits including poorer performance on visual search tasks (Lubow, Kaplan, Abramovich, Rudnick, & Laor, 2000) and visuospatial working memory tasks (Fleming et al., 1997). Furthermore, individuals with schizophrenia have also been found to display motion processing deficits, as shown by lower contrast sensitivity, or higher thresholds, on tasks of velocity discrimination and detection of motion direction (Chen, Nakayama, Levy, Matthysse, & Holzman, 2003; Chen et al., 1999). A disturbance in the perception of biological motion has also been reported in patients with schizophrenia. In a study undertaken by Couture et al. (2010), individuals with schizophrenia, individuals with ASD and a healthy control group were presented with biological motion stimuli and asked to report the emotion portrayed in the animations. Both clinical groups were found to show poorer performance on the task than healthy controls, but did not differ in performance from one another. In a more basic biological motion discrimination task where participants were presented with stimuli depicting motions such as running, jumping and throwing, and scrambled motion stimuli, participants were asked to respond to whether the stimulus was a biological or
The schizophrenia patients showed poorer biological motion discrimination, though they performed as well as controls on a global-form task. Furthermore, the deficit in biological motion perception was found to correlate with social functioning in schizophrenia. In a more recent study undertaken by the same group (J. Kim, Park, & Blake, 2011), participants completed three tasks. In the first, participants were required to detect biological motion embedded within masking noise; in the second, they were required to discriminate between two perturbed biological motion stimuli; and the third, involved distinguishing between biological motion and non-biological motion stimuli in an fMRI task. The authors reported that individuals with schizophrenia were poorer at both the discrimination and detection tasks, and showed similar levels of superior temporal sulcus activation to correctly perceived biological motion relative to correctly perceived scrambled motion, whereas the healthy control group showed greater activation in this area in response to biological motion stimuli. However, no group differences in area MT were found. These results may reflect a deficit in temporal integration which may contribute to the misinterpretation of others’ actions in individuals with schizophrenia and the difficulties experienced in social functioning.

8.3.3 Obsessive compulsive disorder (OCD)

Impairments in social functioning are also present in other mental illnesses such as OCD (American Psychiatric Association, 2013). Recent studies have investigated whether these social functioning deficits extend to the processing of social information, and specifically to the processing of biological motion. In a study by J. Kim et al. (2008), OCD and healthy control participants were presented with two biological motion tasks. One of the tasks involved detecting biological motion stimuli among the presence of scrambled stimuli (detection task), whereas the other involved discriminating between a biological motion and a scrambled stimulus in a forced-choice paradigm (discrimination task). During both tasks, participants with OCD showed poorer performance, though the deficit in performance was only correlated with degree of OCD symptomatology in the detection task. However, the OCD group did not differ to controls in performance on a global form task, suggesting that the deficit in integration of visual information was specific to biological motion.
Furthermore, Jung et al. (2009) reported differences in BOLD activity between OCD and healthy control groups during a biological motion task. Although both groups showed increased superior and middle temporal gyri activation to biological motion stimuli relative to scrambled motion stimuli, the OCD group showed increased activity of the right superior and middle temporal gyri, the left inferior temporal and fusiform gyri and the cerebellum, and reduced activity of the right postcentral gyrus, relative to controls. Together these results suggest an automatic and effortless processing of socially relevant stimuli in healthy individuals that is disturbed in individuals with OCD, which may be related to the more general social functioning difficulties experienced by these individuals.

8.3.4 Eating disorders

Although studies are yet to be undertaken in the ability to detect biological motion stimuli among scrambled stimuli in eating disorders, the ability to discriminate different emotions from such stimuli has been investigated. In a recent study by Zucker et al. (2013), individuals in the ill state of AN, individuals weight-recovered from AN and healthy control participants were presented with biological motion animations and were asked to verbally indicate the emotion portrayed in the clip from five emotional choices: happy, sad, afraid, angry and neutral. The currently ill AN group were found to be poorer at identifying sadness portrayed in the biological motion videos, but were more consistent with normative data when identifying anger in the animations. The weight-recovered group did not differ in performance to healthy controls. In the only other biological motion study in eating disorders (AN or BN) to date, Vocks, Legenbauer, Rüddel, and Troje (2007) asked participants with BN and BMI-matched healthy controls to estimate their body dimensions through a biological motion distortion technique and through the distortion of a photograph of their own body. In the static image task, participants were asked to distort the image of their own body in three conditions: to indicate their actual, felt and ideal body dimensions. The biological motion task was undertaken in the same manner as the static image task in that participants were required to distort the stimuli to indicate their actual, felt and ideal body dimensions. Both tasks were undertaken to identify whether body image distortion is present in static and dynamic conditions and whether these perceptual body image distortions are associated or separate constructs.
Furthermore, the biological motion task was utilised to reduce the confound of distorted body shape. In the static image condition, the BN group were found to overestimate their actual and felt body dimensions, whereas healthy participants underestimated their body dimensions in both conditions. Although there were no group differences in the ideal body condition, both groups reported ideal body dimensions that were slimmer than their undistorted photograph. In the biological motion task, groups again did not differ in the ideal body condition, but also did not significantly differ in the actual body condition. However, BN participants indicated significantly heavier bodies in the felt condition than control participants. Together these results suggest that individuals with BN feel heavier than healthy individuals, but their ideal body size does not differ. Furthermore, the discrepancy between BN participants’ perception of their actual body size in the static and biological motion conditions suggests that viewing distorted images of oneself may influence results. Therefore, utilising stimuli such as the biological motion task has the benefit of not influencing responses due to disturbances in physical distortion. Whether a disturbance exists in estimating body size in general, not specific to one’s own body, was however not reported in this study. Investigating this aspect of body size perception would be beneficial in understanding whether individuals with eating disorders have a general disturbance in the perception of physical size.

8.4 Current study aims and hypotheses

The aim of this study was to utilise a human biological motion task to investigate body size estimation of others in AN. An additional aim was to investigate visual scanpath characteristics to biological motion stimuli in AN, as well as to ascertain whether task instructions modify visual scanpaths. Participants were therefore presented with an implicit (gender discrimination) and an explicit (body size discrimination) task while eyetracking was performed. It was hypothesised that participants with AN would overestimate the size of the biological motion stimuli. It was also expected that participants with AN would focus on body size estimation areas (i.e. hips) more so than healthy individuals during the implicit task. Similarly to other clinical populations who show atypical scanpaths only during implicit processing (e.g. schizophrenia) (Delerue et al., 2010), it was expected that areas of attentional focus would not differ from healthy individuals when an explicit task was
undertaken. As hyperscanning behaviours are seen in response to anxiety-inducing and disorder-relevant stimuli in related clinical populations such as SAD (Horley et al., 2004), it was predicted that AN participants would show hyperscanning evident by increased fixations of shorter duration in both tasks, particularly to heavier stimuli. It was also expected that the overestimation of body size, hyperscanning in both tasks and the increased attention to areas related to body size estimation during the implicit task would be greater to female than male stimuli as the relevance of these stimuli to the processing of body image in females with AN would be expected to be greater.

8.5 Method

8.5.1 Participants

Twenty-four individuals with AN and 25 healthy control individuals completed the biological motion task behaviourally. Due to eyetracking difficulties in the behavioural set-up, one healthy control participants’ data could not be analysed. Therefore, the control group consisted of 24 participants. Demographic characteristics for the additional control participant who did not complete the entire study but completed the biological motion tasks are included in Appendix E.

8.5.2 Biological motion task

The biological motion task used in this study was developed by the BioMotionLab at Queen’s University, Ontario (Troje, 2002a). The stimuli consist of point-light displays in which the movement of lights placed at major joints results in the appearance of a moving organism. The task consisted of a human biological motion stimulus walking front on. The task was designed to allow the gender of the walker to be set as male or female, and the body size of the walker to be set along 13 different points. The gender was set as ‘most male’ or ‘most female’ for all body size selections. The animations were originally created with the use of 40 male and 40 female walkers. The gender and body weights were based on the true dimensions of the walker, rather than on rating data (Troje, 2002a, 2002b, 2008).
The biological motion task was undertaken as an implicit task requiring gender identification, and an explicit task requiring body size discrimination. The two conditions of the task were undertaken to determine whether visual scanpaths differ depending on the task at hand.

8.5.2.1 Implicit biological motion task

Participants were presented with 26 biological motion stimuli: 13 male and 13 female stimuli each displaying a different body size ranging from thin to heavy (see Figure 8.1). The stimuli were presented twice each in a pseudorandom order, yielding a total of 52 trials, with the same stimulus never being presented twice in a row. Prior to the presentation of each stimulus, a 1° black fixation cross appeared in the centre of a white screen for 500ms. The stimulus then followed for a period of 8000ms, followed by a screen asking participants to click whether they thought the walker they just saw was a male or female. The response screen was presented until participants made their decision. The biological motion stimuli were presented at a frame rate of 25Hz at 640x480 pixels. The size of the stimulus equalled approximately 2x16cm, or subtending 3.x10° at the viewing distance from the eye, varying slightly depending on the body size of the walker. Prior to the commencement of the task, participants also undertook a short practice task consisting of one male and one female stimulus of mid body size.

8.5.2.2 Explicit biological motion task

The explicit biological motion task was carried out essentially in the same manner as the implicit task. However, the purpose of this task was to estimate body size by clicking on a number along a Likert scale from 1 (very underweight) to 13 (very overweight) following the presentation of the walker. Again, the response screen remained presented until the participants made a response. Prior to the commencement of the task, participants also completed a short practice task consisting of a thin male and a heavy female.
8.5.2.3 Analysis

8.5.2.3.1 Behavioural data and eye movements

Behavioural and eyetracking data was analysed with SR Research’s analysis program, DataViewer. Discrete AOIs were created in the program and included the head, shoulders, hips, knees, feet and arms. ‘Trial reports’ and ‘interest area reports’ were generated in DataViewer and imported into Microsoft Excel for further analysis, prior to being imported into the study database in SPSS. The data was intentionally not cleaned to allow the analysis of raw scanpaths. Stimuli were grouped into body size categories for analysis, i.e. thin (stimuli 1-3), thin-mid (stimuli 4-5), mid (stimuli 6-8), mid-heavy (stimuli 9-10) and heavy (stimuli 11-13). As described in chapter 6, the FFI and FDI were also calculated for the biological motion task utilising the AOIs of the head, shoulders, hips, knees, feet and arms, as the salient features (see Figure 8.2). Indices ranged from -1 to +1, with positive values indicating more fixations or longer durations to salient features, and negative values indicating more visual attention to non-salient features. Fixation count and dwell times (total time fixating on an interest area during at trial) to each AOI were also calculated for each body size category.
8.5.3 Statistical analysis

Mixed design ANOVAs were carried out on the behavioural and eyetracking data following normality checking and the removal of outliers, with alpha set at 0.05 for all analyses. As the primary aim of the study was to investigate group differences, for brevity, only significant interactions with group are presented in detail in this chapter (see Appendix F for additional analyses).

8.5.4 Procedure

The two tasks were both completed during the ‘long MRI’ session following the MRI scan, in an interview room. Participants were informed that they would undertake two tasks, but were not informed of the tasks until just prior to their commencement. The implicit task always preceded the explicit task so that participants were not aware of the nature of the experiment. The implicit task was presented first so that participants were not explicitly aware that the different stimuli corresponded to different body sizes, and so that they would be somewhat familiar.
with the different stimuli for the next task, which required them to estimate body size. The tasks both began with a nine-point eyetracker calibration sequence, followed by a validation task requiring participants to look at different points on the monitor. Practice tasks were completed before the commencement of both the implicit and explicit tasks.

8.6 Results

8.6.1 Behavioural

A between groups ANOVA revealed that groups did not differ in gender discrimination in the implicit task \((F(1,11)= 0.47, p= 0.510)\). For the explicit biological motion task, a body size discrimination score was determined by subtracting participants’ responses by the correct scores for each body size (Table 8.1). A 2 (group) x 5 (body size category) x 2 (gender) mixed design ANOVA was conducted on the explicit biological motion task for this body size discrimination score. A significant main effect of body size category was found \((F(1.50,70.61)= 525.10, p < 0.001)\) with body size estimation decreasing (underestimating) as the stimulus size increased. A significant main effect of gender of the walker \((F(1,47)= 12.90, p < 0.001)\) was also found with greater underestimation of female stimuli. A significant interaction between body size category and gender was also found \((F(2.11,99.01)= 12.94, p < 0.001)\). No other significant interactions were found, and a significant main effect of group was also not revealed.

Exploratory Pearson’s correlation analyses were also conducted between body size discrimination scores and BMI, and scores of the FRS and EDE-Q. These analyses revealed no significant relationships for either group.
Table 8.1

*Body size discrimination scores, explicit biological motion task*

<table>
<thead>
<tr>
<th></th>
<th>AN Controls</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
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<td>Male stimuli</td>
<td>Female stimuli</td>
<td>Male Stimuli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
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<td>1.46</td>
<td>2.88</td>
<td>1.31</td>
<td>1.20</td>
</tr>
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<td>1.46</td>
<td>1.53</td>
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<td>0.90</td>
</tr>
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<td>1.29</td>
<td>-0.15</td>
<td>1.30</td>
<td>-1.30</td>
</tr>
<tr>
<td>Mid-heavy</td>
<td>-2.08</td>
<td>1.28</td>
<td>-2.08</td>
<td>1.28</td>
<td>-2.23</td>
</tr>
<tr>
<td>Heavy</td>
<td>-3.35</td>
<td>1.80</td>
<td>-3.35</td>
<td>1.40</td>
<td>-3.94</td>
</tr>
</tbody>
</table>

Note: AN= anorexia nervosa; discrimination scores over and under 0 indicate over- and under-estimation of body sizes, respectively.

8.6.2 Eyetracking

8.6.2.1 Scanpath characteristics

Two (group) x 5 (body size category) x 2 (gender) x 2 (task) mixed design ANOVAs were carried out for average fixation count, fixation duration and saccade amplitude separately (see Table 8.2).

For fixation count, a significant main effect of group was found with AN participants making more fixations than control participants (F(1,46)= 6.72, p= 0.013). Significant interactions were also found between body size category and task (F(3.25,149.53)= 3.580, p= 0.013), and between body size category, gender and group (F(4,184)= 2.65, p= 0.035) (Figure 8.3). Follow-up analyses revealed a significant difference between mid-heavy and heavy body sizes between male and female stimuli in AN relative to controls (F(1,46)= 9.41, p= 0.004). Fixation count for AN participants increased from the mid-heavy to heavy body size categories to male stimuli, but decreased to female stimuli. Fixation count to male stimuli did not differ between mid-heavy and heavy body size categories in controls, but decreased to female stimuli.
Figure 8.3. Fixation count for anorexia nervosa (AN) and control groups for each gender and body size category of biological motion stimuli over the implicit and explicit biological motion tasks (error bars= standard error)

For fixation duration, significant main effects were found for body size category (F(2.87,131.93)= 4.65, p= 0.005) with longer fixation durations to both thin and heavy stimuli than other body sizes. A significant main effect was also found for task (F(1,46)= 16.15, p < 0.001) with longer fixations during the implicit task; and a significant main effect was also found for group with AN participants displaying shorter fixation durations than controls (F(1,46)= 5.60, p= 0.022). No significant interactions were revealed.

For saccade amplitude, significant main effects were found for body size category (F(2.69,123.69)= 3.54, p= 0.020) with larger saccade amplitudes to thin and thin-mid body sizes; and gender (F(1,46)= 4.39, p= 0.042) with larger saccade amplitudes to male stimuli. There was also a significant main effect for group with AN participants making saccades of smaller amplitude than controls (F(1,46)= 5.89, p= 0.019). A significant interaction was also revealed for task by group: saccadic amplitudes decreased from the implicit to explicit tasks in AN, but increased between tasks in controls (F(1,46)= 5.70, p= 0.021) (Figure 8.4). Further analyses revealed a significant group difference during the implicit task with AN participants making...
smaller saccades than control participants ($F(1,46)= 12.63, p < 0.001$). However, groups were not found to differ in saccade amplitude during the explicit task.

*Figure 8.4.* Saccadic amplitude for anorexia nervosa (AN) and control groups for the implicit and explicit biological motion tasks (error bars= standard error)
Table 8.2

Scanpath data (means and standard deviations) to stimuli of different body sizes and gender during implicit and explicit biological motion tasks

<table>
<thead>
<tr>
<th></th>
<th>Fixation count</th>
<th>Fixation duration</th>
<th>Saccade amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AN Controls</td>
<td>AN Controls</td>
<td>AN Controls</td>
</tr>
<tr>
<td></td>
<td>Female Male</td>
<td>Female Male</td>
<td>Female Male</td>
</tr>
<tr>
<td>Implicit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin</td>
<td>18.50 18.26</td>
<td>13.37 13.37</td>
<td>424.67 386.94</td>
</tr>
<tr>
<td>(8.00) (6.55)</td>
<td>(3.07) (3.48)</td>
<td>(220.44) (187.49)</td>
<td>(184.82) (287.17)</td>
</tr>
<tr>
<td>Thin-mid</td>
<td>18.44 18.53</td>
<td>14.14 14.14</td>
<td>395.61 400.60</td>
</tr>
<tr>
<td>(7.00) (6.91)</td>
<td>(3.97) (3.52)</td>
<td>(231.99) (281.62)</td>
<td>(203.26) (160.38)</td>
</tr>
<tr>
<td>Mid</td>
<td>18.22 18.36</td>
<td>13.69 13.69</td>
<td>409.52 436.43</td>
</tr>
<tr>
<td>(7.49) (7.45)</td>
<td>(2.85) (3.72)</td>
<td>(254.46) (342.63)</td>
<td>(154.02) (206.66)</td>
</tr>
<tr>
<td>Mid-heavy</td>
<td>17.96 19.52</td>
<td>14.26 14.26</td>
<td>404.11 363.82</td>
</tr>
<tr>
<td>(6.89) (6.95)</td>
<td>(4.36) (3.25)</td>
<td>(210.69) (195.51)</td>
<td>(188.71) (146.83)</td>
</tr>
<tr>
<td>Heavy</td>
<td>18.21 17.65</td>
<td>14.17 14.17</td>
<td>495.44 402.63</td>
</tr>
<tr>
<td>(7.43) (6.50)</td>
<td>(2.53) (3.32)</td>
<td>(452.60) (218.00)</td>
<td>(184.44) (273.69)</td>
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<tr>
<td>Explicit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin</td>
<td>18.62 18.78</td>
<td>15.60 18.78</td>
<td>369.35 371.33</td>
</tr>
<tr>
<td>(7.19) (7.53)</td>
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<td>(141.28) (139.29)</td>
<td>(117.90) (108.70)</td>
</tr>
<tr>
<td>Thin-mid</td>
<td>18.40 18.98</td>
<td>16.20 16.20</td>
<td>377.01 348.64</td>
</tr>
<tr>
<td>(7.58) (7.21)</td>
<td>(3.79) (3.81)</td>
<td>(256.78) (163.24)</td>
<td>(102.61) (122.47)</td>
</tr>
<tr>
<td>Mid</td>
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<td>16.63 16.63</td>
<td>354.04 373.46</td>
</tr>
<tr>
<td>(7.73) (6.56)</td>
<td>(4.92) (4.74)</td>
<td>(145.44) (272.90)</td>
<td>(95.05) (121.58)</td>
</tr>
<tr>
<td>Mid-heavy</td>
<td>18.05 19.16</td>
<td>15.56 15.56</td>
<td>372.10 330.29</td>
</tr>
<tr>
<td>(6.81) (7.04)</td>
<td>(4.91) (4.36)</td>
<td>(152.00) (143.56)</td>
<td>(177.19) (120.10)</td>
</tr>
<tr>
<td>Heavy</td>
<td>19.20 18.92</td>
<td>15.58 15.67</td>
<td>372.01 416.53</td>
</tr>
<tr>
<td>(6.96) (6.91)</td>
<td>(4.42) (4.34)</td>
<td>(169.21) (318.48)</td>
<td>(122.68) (1557.69)</td>
</tr>
</tbody>
</table>

Note: AN=anorexia nervosa; fixation durations are reported in milliseconds; saccade amplitudes are reported in degrees
8.6.2.2 Areas of interest (AOIs)

A 2 (group) x 5 (body size category) x 6 (body area) x 2 (gender) x 2 (task) mixed design ANOVA was undertaken for fixation count and dwell time to AOIs (see Tables 8.3 and 8.4). For fixation count to salient features, significant main effects included body size category \( (F(2.75,120.80)= 26.221, p < 0.001) \) with increased fixations to larger body sizes, gender \( (F(1.44)= 7.98, p= 0.007) \) with increased fixations to female stimuli, and body area \( (F(1.97,86.78)= 63.44, p < 0.001) \) with more fixations to the hips than any region and fewest to the head. Significant interactions were found between task, body size category and gender \( (F(4,176)= 3.99, p= 0.004) \), task and body area \( (F(2.09,91.73)= 3.42, p= 0.035) \), body size category and body area \( (F(6.15,270.69)= 19.55, p < 0.001) \), gender and body area \( (F(2.31,101.79)= 29.59, p < 0.001) \), and body size, gender and body area \( (F(7.57,333.14)= 4.10, p < 0.001) \). There was no significant main effect of group or any significant group interactions.

For dwell time to salient features, there were significant main effects of body size category \( (F(2.95,129.93)= 17.60, p < 0.001) \) with increased dwell times to AOIs of larger body sizes; and body area \( (F(2.21,97.43)= 74.78, p < 0.001) \) with increased dwell times to the hip and shoulder regions and decreased dwell times to the head. There were also significant interactions between body size category and body area \( (F(7.17,315.63)= 16.58, p < 0.001) \), gender and body area \( (F(2.27,99.89)= 21.81, p < 0.001) \), and body size category, gender and body area \( (F(8.67,381.48)= 3.07, p= 0.002) \). There was no significant main effect of group or any significant group interactions.
Table 8.3

Fixation count (means and standard deviations) to areas of interest (AOIs) of stimuli of different body sizes and gender during implicit and explicit biological motion tasks

<table>
<thead>
<tr>
<th></th>
<th>AN Head</th>
<th>AN Shoulders</th>
<th>AN Hips</th>
<th>AN Knees</th>
<th>AN Feet</th>
<th>AN Arms</th>
<th>Controls Head</th>
<th>Controls Shoulders</th>
<th>Controls Hips</th>
<th>Controls Knees</th>
<th>Controls Feet</th>
<th>Controls Arms</th>
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<tr>
<td>** Implicit task**</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin</td>
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<td>1.13</td>
<td>1.90</td>
<td>0.99</td>
<td>0.47</td>
<td>0.80</td>
<td>0.10</td>
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<td>1.42</td>
<td>0.69</td>
<td>0.38</td>
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<tr>
<td></td>
<td>(0.20)</td>
<td>(1.12)</td>
<td>(1.42)</td>
<td>(0.84)</td>
<td>(0.61)</td>
<td>(0.60)</td>
<td>(0.22)</td>
<td>(0.69)</td>
<td>(0.86)</td>
<td>(0.49)</td>
<td>(0.45)</td>
<td>(0.31)</td>
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<td>Thin-mid</td>
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<td>2.34</td>
<td>0.90</td>
<td>0.37</td>
<td>0.53</td>
<td>0.07</td>
<td>1.11</td>
<td>2.17</td>
<td>0.53</td>
<td>0.21</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
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<td>(1.17)</td>
<td>(1.94)</td>
<td>(0.87)</td>
<td>(0.63)</td>
<td>(0.50)</td>
<td>(0.14)</td>
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<td>(0.75)</td>
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<td>1.06</td>
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<td>0.26</td>
<td>0.43</td>
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<td>(0.19)</td>
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<td>(1.10)</td>
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<td>(0.26)</td>
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<td>1.13</td>
<td>0.40</td>
<td>0.39</td>
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<td>(0.29)</td>
<td>(0.17)</td>
<td>(0.93)</td>
<td>(1.41)</td>
<td>(1.11)</td>
<td>(0.45)</td>
<td>(0.35)</td>
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<td>(1.27)</td>
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<td>(0.19)</td>
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<tr>
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<td>1.68</td>
<td>0.65</td>
<td>0.34</td>
<td>0.80</td>
<td>0.11</td>
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<td>(1.08)</td>
<td>(0.54)</td>
<td>(0.39)</td>
<td>(0.56)</td>
<td>(0.29)</td>
<td>(1.26)</td>
<td>(0.93)</td>
<td>(0.49)</td>
<td>(0.28)</td>
<td>(0.38)</td>
</tr>
<tr>
<td>Thin-mid</td>
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<td>0.70</td>
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<td>0.51</td>
<td>0.33</td>
<td>0.57</td>
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<td></td>
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<td>(1.30)</td>
<td>(1.97)</td>
<td>(0.92)</td>
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<td>(0.42)</td>
<td>(0.30)</td>
<td>(1.46)</td>
<td>(0.97)</td>
<td>(0.67)</td>
<td>(0.50)</td>
<td>(0.37)</td>
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<td>2.36</td>
<td>1.18</td>
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<td>0.47</td>
<td>0.11</td>
<td>1.69</td>
<td>1.92</td>
<td>0.61</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
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<td>(1.35)</td>
<td>(2.06)</td>
<td>(1.11)</td>
<td>(0.40)</td>
<td>(0.38)</td>
<td>(0.16)</td>
<td>(1.30)</td>
<td>(0.93)</td>
<td>(0.51)</td>
<td>(0.34)</td>
<td>(0.30)</td>
</tr>
<tr>
<td>Mid-heavy</td>
<td>0.28</td>
<td>2.62</td>
<td>2.60</td>
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*Note: AN= anorexia nervosa*
Table 8.4

Dwell times (means and standard deviations) to areas of interest (AOIs) of stimuli of different body sizes and gender during implicit and explicit biological motion tasks

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<td>(641.61)</td>
<td>(555.95)</td>
<td>(249.47)</td>
<td>(187.13)</td>
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</table>

Note: AN= anorexianervosa
Two (group) x 5 (weight category) x 2 (task) mixed design ANOVAs were also conducted on the FFI and FDI (Table 8.5). For the FFI, there was a significant main effect of body size category (F(3.30,145.30)= 13.82, p < 0.001) with more fixations to non-salient rather than salient features of heavy stimuli compared to thin stimuli, and a significant interaction between task and body size category (F(4,176)= 3.17, p= 0.015), but no significant main effect of group and no group interactions. For the FDI, a significant main effect of body size category was found (F(3.06,134.70)= 7.89, p < 0.001) with greater attention to non-salient features of mid-size stimuli, but there were no other main effects, or significant interactions.
Table 8.5

Feature fixation and duration indices (FFI; FDI) (means and standard deviations) to stimuli of different body sizes and gender during implicit and explicit biological motion tasks

<table>
<thead>
<tr>
<th></th>
<th>Feature fixation index</th>
<th>Feature duration index</th>
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<tbody>
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<td></td>
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<td>AN (Female) Male</td>
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<td>-0.12</td>
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<tr>
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<td>(0.24)</td>
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<td>Thin-mid</td>
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<td>-0.15</td>
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<tr>
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<td>(0.32)</td>
<td>(0.29)</td>
</tr>
<tr>
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<td>-0.12</td>
</tr>
<tr>
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<td>(0.30)</td>
<td>(0.21)</td>
</tr>
<tr>
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<td>-0.07</td>
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<tr>
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<td>(0.25)</td>
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<td>(0.28)</td>
<td>(0.30)</td>
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<td></td>
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<td>-0.04</td>
</tr>
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<td></td>
<td>(0.26)</td>
<td>(0.19)</td>
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<td>Thin-mid</td>
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<tr>
<td></td>
<td>(0.24)</td>
<td>(0.20)</td>
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</table>

Note: AN=anorexia nervosa; positive values indicate more fixations or longer durations to salient features, and negative values indicate more visual attention to non-salient features.
8.7 Discussion

The aim of this study was to utilise a human biological motion task to investigate how individuals with AN process biological motion stimuli of different body sizes, and to ascertain whether task instructions modify visual scanpaths. Specifically, we aimed to examine whether individuals with AN accurately perceive the size of human biological motion stimuli, and whether they demonstrate different scanning behaviours and visual attention to these stimuli. Participants were presented with an implicit (gender identification) and explicit (body size discrimination) task while undergoing eyetracking. The behavioural and eyetracking findings are discussed separately below.

8.7.1 Behavioural

Individuals with AN were hypothesised to overestimate the size of the biological motion stimuli, particularly female stimuli. However, contrary to expectations, the AN group did not differ from control participants in body size estimation of male or female biological motion stimuli, nor were participants’ estimations related to participants’ BMI or scores on the neuropsychological measures administered. These results are contrary to those reported by Smeets (1999) and Tovée et al. (2000) who found that AN participants overestimated body size of human stimuli relative to healthy individuals. Furthermore, Tovée et al. (2000) also found that the rate of overestimation was correlated with BMI; a result we did not find in our study. The current findings suggest that the perception of physical body size does not always differ between healthy individuals and those with AN, and the inconstancy with past research may reflect an influence of physical characteristics of real human stimuli on body size perception. The findings from the FRS, however, support the notion that individuals with AN may perceive their own physical size as larger, as the figure they thought they looked like did not significantly differ to controls, despite having significantly lower BMIs. Furthermore, a discrepancy between how AN participants thought and felt they looked was also apparent, with AN participants reporting feeling larger than they thought they appeared; a discrepancy which was not evident for healthy individuals. These results suggest that a distortion in the way the body is felt may be a more significant problem for individuals with AN than the way
the body is visually perceived. Further research utilising biological motion stimuli in the same manner as Vocks et al. (2007), where participants were required to set the stimulus to reflect their actual, felt and ideal bodies, would be valuable to investigate in AN.

8.7.2 Eyetracking

Participants with AN were hypothesised to display hyperscanning behaviours during both tasks, particularly to female stimuli and stimuli portraying a heavier body size. As hypothesised, groups were found to differ in scanpath behaviours. Specifically, AN participants demonstrated a tendency to hyperscan stimuli, evident by increased fixations of shorter duration. Scanning behaviours were however not found to differ depending on the gender or the body size of the stimulus alone, but were found to differ between body size categories of the two genders between groups. This was demonstrated by an increased rate of fixations to mid-heavy male stimuli in relation to female stimuli in AN. This rate of fixations decreased when observing heavy male stimuli, but increased when presented with heavy female stimuli; a relationship that was not evident in controls. As an increased rate of fixations is associated with hypervigilance and anxiety (Kimble et al., 2014), this finding may reflect increased anxiety to heavier female stimuli in AN relative to male stimuli. The AN group were also found to demonstrate hyperscanning during both biological motion tasks. Relative to healthy individuals, AN participants made more fixations of shorter duration to biological motion stimuli. The tendency for individuals with AN to show these behaviours when presented with human body biological motion stimuli may also reflect increased anxiety to disorder-relevant stimuli in general. However, it may also suggest an increased tendency to focus on details; this is further supported by the finding of smaller saccadic amplitudes, or a shorter distance between fixations, during the implicit task.

Perfectionism and a preoccupation with details is often reported in AN (Bastiani et al., 1995; Halmi et al., 2000; Tokley & Kemps, 2007). Furthermore, individuals with AN tend to focus on details and lose sight of the ‘big picture’. This is evident on tasks of central coherence where individuals with AN have demonstrated superior performance on tasks requiring local processing and poorer performance on
tasks requiring global processing (Gillberg et al., 2007; Lopez et al., 2008; Tokley & Kemps, 2007). Having said this, saccadic amplitudes did not differ between groups during the explicit task, suggesting that individuals with AN focused on relevant details to the same extent as healthy individuals when an explicit instruction was given. Furthermore, scanning behaviours are typically found to differ depending on task instruction in both healthy and clinical populations (Delerue et al., 2010; Yarbus, 1967). In schizophrenia, differences in scanpath characteristics change in the same direction as healthy controls between passive and active tasks (Delerue et al., 2010). This was not found in the current study for saccade amplitude. Saccade amplitude was found to increase in AN participants from the implicit to explicit tasks, but decrease between tasks in the control group. This result may reflect more global processing in AN when determining body size and more local processing in healthy individuals, relative to their implicit processing strategies.

The final hypothesis that AN participants would demonstrate a greater level of visual attention to body regions related to weight estimation, particularly during observations of female stimuli, was not supported. AN and healthy individuals did not differ in the number of fixations or the amount of time spent fixating on different body regions in either biological motion task. This result is contrary to the findings by R. Freeman et al. (1991) who reported increased visual attention to the legs and abdomen in AN. The stimuli used in the study by R. Freeman et al. (1991) were their own body images, and this may suggest that deviant attentional focus in AN is specific to viewing images of one’s own body. Furthermore, R. Freeman et al. (1991) did not investigate body size estimation of oneself in their study, though, other investigations have suggested an overestimation of own body size in AN (Collins et al., 1987; Slade & Russell, 1973; Smeets & Kosslyn, 2001; Tovée et al., 2000). Therefore, the overestimation of own body size commonly reported in AN may be related to increased visual attention to areas of one’s own body related to body weight estimation. Further investigations of visual scanpaths to own body biological motion stimuli, as described above, would also be beneficial for this reason. Furthermore, the use of eyetracking software that allows the creation of dynamic AOIs, where AOIs can be assigned to moving images, would be valuable in future research as the software utilised in this study only allowed for the creation of static AOIs which encompassed larger areas than necessary to ensure the body part was always in the
AOI created. A further limitation of the study was that areas such as the waist or thighs could not be specifically assigned to AOIs as these areas are not physically visible and are inferred by the observer.

8.7.3 Summary and conclusions

Overall, the study suggests that individuals with AN have intact perception of body size when presented with biological motion stimuli of different sizes, and the body areas attended to do not differ from healthy individuals. Together, these results suggest that individuals with AN are able to estimate the physical size of biological motion stimuli as accurately as healthy individuals and they visually attend to the same body areas when observing these stimuli. Visual scanning behaviours were however found to differ between groups. Individuals with AN were found to hyperscan stimuli relative to healthy individuals, which may reflect increased anxiety to body stimuli in AN or an increased focus on finer details rather than the bigger picture.

This is the first study to utilise biological motion stimuli in this manner in AN and demonstrates the utility of these stimuli in the exploration of visual processing deficits of human bodies. The benefit of using biological motion stimuli over real human stimuli is that personal characteristics or clothing of the model do not influence responses. However, the stimuli are limited as areas of the body that are highly relevant to body image, including the legs and waist, are inferred by the observer and the areas cannot be quantified. Importantly, these areas are among the top body concerns in AN patients, as described in Chapter 3. A potential solution to this problem would be to create a task in which participants trace the silhouette of the body following the observation period. By doing this, AOIs could be created for the regions that are inferred, and this would also allow the investigation of perceived size differences in these inferred regions. The current study also had limitations in the software utilised to present and analyse the task which did not allow for the creation of dynamic AOIs. This constraint may be overcome in future research with the use of other software designed for this purpose. Furthermore, investigating whether individuals with AN show processing deficits to biological motion stimuli reflecting their own actual, ideal and felt bodies would be valuable in increasing our
understanding of how individuals with AN visually process and perceive their own bodies.

As this is the first study to utilise biological motion stimuli in this manner in AN, the aim of this study was primarily exploratory and demonstrated the utility of the biological motion task in examining visual perception of body processing in AN. Although a number of confounds existed in the way the task was administered, the study suggests that the stimuli may be useful in the investigation of visual processing of the human body. Together, these results suggest that individuals with AN are able to estimate the physical size of human body biological motion stimuli as accurately as healthy individuals. This implies that although individuals with AN may perceive themselves as larger, their perception of body size for other individuals is intact. Therefore, a distorted perception of body size may be specific to oneself in the condition. Furthermore, although AN participants fixated the same body areas when observing these stimuli, scanpath behaviours differed from healthy controls. Individuals with AN were found to hyperscan stimuli relative to healthy individuals, which may reflect a preoccupation with detail or increased anxiety induced by disorder-relevant stimuli in AN. A number of reports have suggested a relationship between anxiety and AN (e.g. W. H. Kaye et al., 2004) and the findings of the current study may provide further support for this association. Furthermore, as the current study indicates a potential role of anxiety related to body stimuli, future research examining scanning behaviour to own body stimuli may provide information about increased anxiety to self-body stimuli in AN. Additionally, these scanning behaviours may be monitored over the course of treatment to investigate potential improvements which may be indicative of reduced anxiety to disorder-relevant stimuli, and correspondingly, improved body image in AN.
Chapter 9: Square Wave Jerks and Anxiety as Distinctive Biomarkers for Anorexia Nervosa

This chapter has been published in the journal *Investigative Ophthalmology & Visual Science* (Phillipou, Rossell, Castle, Gurvich, & Abel, 2014). The task undertaken in this manuscript was completed at the beginning of the ‘long MEG’ session during a resting state MEG task. The results of the resting state MEG analysis are not presented in this thesis, and only the results of the concurrent fixation task are discussed.
Eye Movements, Strabismus, Amblyopia, and Neuro-Ophthalmology

Square Wave Jerks and Anxiety as Distinctive Biomarkers for Anorexia Nervosa

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Submitted: October 6, 2014
Accepted: October 14, 2014

Anorexia nervosa (AN) is a psychiatric illness characterized by a pervasive fear of body weight, a fear of weight gain, and a disturbance in the experience of one’s own body weight or shape. A disturbance of body image is a common pathognomonic psychological factor in AN, and perceptual disturbances in the way body shape and weight are perceived are often reported. Anorexia nervosa is associated with significant morbidity and has a mortality rate among the highest of any mental illness, though the factors involved in the cause and maintenance of the illness remain unclear. A wide range of neurobiological findings have been reported in AN, though these are not consistent and a biomarker for the illness has not been identified (for a review see Ref. 7). Eye movements are a potentially useful tool in aiding our understanding of the neurobiology of AN as they utilize identifiable brain circuits. Of particular interest in psychiatric illnesses has been the examination of saccadic eye movement. As humans we use a “saccade and fixate” strategy when viewing our surroundings, typically making three to four saccades every second of our waking lives. There is a substantial literature which has examined saccadic eye movement execution in a range of psychiatric illnesses including mood, anxiety, and psychotic disorders (see Refs. 7 and 8 for reviews).

During attempted fixation, saccadic intrusions occur in small numbers in healthy individuals. The most widely studied saccadic intrusions are square wave jerks (SWJs), which are pairs of saccades moving the eyes away and returning them to fixation, typically with an intersaccadic interval (ISI) of approximately 200 ms and an amplitude ranging from 0.5° to as high as 5°. An increased rate of SWJs has been associated with a range of neurodegenerative movement disorders including Huntington’s disease, Parkinson’s disease, and a variety of cerebellar disorders. Thus, the neural mechanisms involved in the production of SWJs, and fixation stability in general, appear rather non-specific, with areas of the cerebral hemispheres, basal ganglia, and cerebellar cortex involved in both.
cerebellum, and superior colliculus potentially involved. Additionally, SWJs can also occur during smooth pursuit.11,18

Few studies have examined the rate of SWJs during fixation in psychiatric populations. An early study by Lestin and colleagues50 reported increased saccadic intrusions during fixation in a group of people with schizophrenia. Although the description of these saccadic intrusions closely resembled SWJs, the authors failed to identify them as such.20 A more recent study by Clementz et al.21 however, reported no group differences in SWJ rate at central or eccentric fixation between participants with schizophrenia and healthy controls (HCs). In contrast, Sweeney et al.20 reported an increased rate of SWJs at central and eccentric fixation in individuals with depression, and although Tien et al.24 reported a trend for obsessive compulsive disorder (OCD) patients to make more SWJs than healthy individuals, statistical significance was not reached. Furthermore, Sweeney et al.18 found significantly more SWJ during pursuit in OCD patients than in controls. It is of interest that studies often report considerable OCD comorbidity in individuals with AN.24,25

The aim of the current study was to identify whether individuals with AN demonstrate difficulties in fixation stability relative to healthy individuals. Given the lack of research in SWJ rate in psychiatric conditions, we proposed an exploratory comparison of SWJ rate between individuals with AN and control participants. An additional aim of the study was to undertake further exploratory analyses between SWJ rate and clinical variables to identify potential relationships between them.

Methods

This study was approved by the human research ethics departments at The University of Melbourne, Swinburne University of Technology, The Melbourne Clinic, The Austin Hospital, and St Vincent's Hospital, all in Melbourne, Australia. Informed written consent was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Participants were 24 right-handed females with AN and 24 HCs matched for age and premorbid intelligence quotient (IQ). Technical eye tracking difficulties resulted in the data of one AN and two HC participants being excluded, allowing analyses to be conducted on 23 AN and 22 HC participants. Healthy controls were recruited through public advertisements, whereas AN participants were recruited through public advertisements, the Body Image and Eating Disorders Treatment and Recovery Service at the Austin and St Vincent's hospitals, and The Melbourne Clinic, all in Melbourne, Australia.

All participants were English speaking, had no history of significant brain injury or neurological condition, no significant ocular pathology and normal (or corrected to normal) visual acuity. Controls were required to have no history of an eating disorder or other mental illness; they were also required to not be taking any medications apart from hormonal contraceptives (10 HC participants were taking this medication). Anorexia nervosa participants were instructed to continue with their normal medications, which were: selective serotonin reuptake inhibitors (SSRIs; 10), atypical antipsychotics (10), benzodiazepines (5), serotonin norepinephrine reuptake inhibitors (SNRIs), hormonal contraceptives (3), melatoninergic antidepressants (2), noradrenergic and specific serotonergic antidepressant (NASSA, 1), and cyclopentolones (1).

The Mini International Neuropsychiatric Interview, 5.0-0 (MNI)20 was used to screen participants for major Axis I psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). It was also used to confirm diagnoses of AN, with the exception of the anorexia nervosa criterion, which is no longer included in the current DSM-5. Anorexia nervosa was required to be the primary diagnosis of the AN group. Anorexia nervosa participants with comorbid psychiatric conditions, other than psychotic conditions, were not excluded as this would not have represented a typical AN sample.

Premorbid intellect was estimated using the Wechsler Test of Adult Reading.27 Eating disorder symptomatology was investigated with the Eating Disorders Examination Questionnaire (EDE-Q),28 and negative emotional states with the Depression Anxiety Stress Scale (DASS).59

Fixation Task

The fixation task consisted of asking participants to fixate on a one degree white fixation cross against a black background, presented on a rear-projected screen measuring 23" x 115 cm in front of the participant. They were instructed to fixate for the entire duration of the task (i.e., 5 minutes). The extended duration was used as the data presented here were part of a magnetoencephalographic study of resting state activity, whose results will be presented elsewhere. Eye tracking was recorded using a remote view eye tracker, the Eyelink1000 (SR Research, Ontario, Canada), monocularly at 500 Hz. Data were bandpass filtered between 1.5 and 60 Hz to eliminate slow baseline drift and high frequency noise. Analysis was performed with a custom-made program under Matlab R2014a (Mathworks, Natick, MA, USA). Threshold criteria for SWJ detection included saccade pairs occurring within 200 ms, with amplitudes ranging between 0.1 and 5° (see Fig. 1 for an example).30 Square wave jerks were analyzed for rate, ISI, and amplitude of the first and second saccade of the SWJ pair.

Results

To minimize the effects of fatigue resulting from maintaining constant fixation on a single point, only the first 60 seconds of the fixation task was analyzed. A summary of the results is presented in the Table.
### Table: Summary of Results

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>22.94</td>
<td>5.25</td>
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<tr>
<td>Prenatal IQ</td>
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</tr>
<tr>
<td>BMI</td>
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<tr>
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<td>3.65</td>
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<td>3.55</td>
</tr>
<tr>
<td>EDE-Q restraint</td>
<td>4.02</td>
<td>1.39</td>
</tr>
<tr>
<td>EDE-Q eating concern</td>
<td>3.94</td>
<td>1.23</td>
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<td>EDE-Q shape concern</td>
<td>5.05</td>
<td>0.50</td>
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<td>EDE-Q weight concern</td>
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<td>EDE-Q global score</td>
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<tr>
<td>DASS depression</td>
<td>22.52</td>
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<tr>
<td>DASS anxiety</td>
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<td>9.65</td>
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<tr>
<td>DASS stress</td>
<td>25.32</td>
<td>10.39</td>
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<tr>
<td>SWJ rate</td>
<td>11.77</td>
<td>12.19</td>
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<td>SWJ ISL</td>
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<td>SWJ amplitude first saccade</td>
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<td>0.28</td>
</tr>
<tr>
<td>SWJ amplitude second saccade</td>
<td>0.51</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Square wave jerk ISL is reported in seconds; SWJ amplitudes are reported in degrees; SWJ ISL and amplitudes are not reported for 1 AN and 4 control participants who made too few or no SWJs. Prenatal IQ, standardized Wechsler Test of Adult Reading Score; BMI, Body mass index; Age, age of illness onset and duration illness are reported in years.*

Following data screening and normality checking one outlier was removed from the AN group and two from the HC group, and a between groups analysis of variance (ANOVA) was performed comparing rate of SWJs. Participants with AN were found to make a significantly increased number of SWJs relative to controls (F(1,40) = 9.979, P = 0.005; Fig. 2).

Pearson's correlation analyses were performed between the rate of SWJs and each of the DASS subtypes. One further outlier was removed from the HC group who scored high on the depression and anxiety subscales of the DASS (see Fig. 3 for anxiety score distributions). The DASS measures were not found to correlate with the rate of SWJs in the HC control group. The rate of SWJs did not correlate with the depression or stress scores on the DASS in the AN group. However, a significant negative relationship was found for the AN group between SWJ rate and anxiety score (r = —.637, P < 0.001; Fig. 4).

A discriminant function analysis on the entire sample revealed that 87% of AN participants and 95.5% of HC participants were correctly classified based on SWJ rate and anxiety scores (Wilk's Lambda = 0.399; χ²(2) = 45.085, P < 0.001).

**Discussion**

Individuals with AN were found to produce a significantly greater number of SWJs during attempted fixation than healthy individuals. In the only other study to examine SWJ rate in AN, Pillarin and colleagues did not report a significant difference relative to HCs during a smooth pursuit task. However, this study used electrooculography with inadequate resolution to detect SWJs with amplitudes as small as were seen in our study. An increased rate of SWJs has not been shown for other psychiatric disorders such as schizophrenia, affective disor-

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**Figure 2.** SWJ rate for AN and HC participants.

**Figure 3.** Anxiety scores on the DASS for AN and HC participants.
depression, autism, or anxiety during smooth pursuit. One previous study found SWJ rate to be modestly and significantly elevated in OCD during a smooth pursuit task. As earlier noted, some studies have found appreciable comorbidity between AN and OCD. In contrast, elevated SWJ rates have been reported in progressive supranuclear palsy, essential tremor, and after unilateral pallidotomy as a treatment for Parkinson's disease. The findings have been attributed to defects in the projections from the fastigial nucleus of the cerebellum to the superior colliculus, but such lesions are also associated with saccadic hypermetria, which was not seen in our AN group (these results are to be reported elsewhere). SWJs have also been associated with a range of cerebral lesions and cerebellar conditions such as Friedreich's ataxia.

As an increased rate of SWJs may be attributed to a number of areas of the brain, it is not necessarily clear which area underpins this in our AN participants. Areas such as the frontal eye fields (FEFs) and the posterior parietal cortex contain fixation neurons, and defects in these areas may lead to increased SWJs. The superior colliculus is specifically involved in the inhibition and distribution of saccades, with excitatory inputs from the rostral SC projecting to the omnipause neurons, which inhibit the excitatory burst neurons, giving rise to saccades. This mechanism is also thought to play a role in the production of SWJs. Furthermore, the injection of the γ-aminobutyric acid (GABA) agonist muscimol into the rostral superior colliculus in monkeys has been found to result in difficulty maintaining fixation and in the production of unwanted saccades.

The potential role of GABAergic function is further supported by the finding that SWJs were found to correlate negatively with state anxiety. GABA appears to play a significant role in anxiety, leading to anxiolytic treatments such as benzodiazepines being used to enhance GABA transmission in these individuals. Therefore, the findings may be explained by higher GABA activity in non-anxious relative to highly anxious individuals; if this higher GABA activity occurred in areas containing fixation neurons such as the superior colliculus, PEF, or posterior parietal cortex, it could result in an increased rate of SWJs in non-anxious individuals. As we found no significant correlation between SWJ rate and anxiety in HC, this GABAergic effect may be specific to AN. Alternatively, insufficient between-subject variability in SWJ rate and state anxiety in HC may have prevented significant correlations in this group.

The classification of groups based on these results, as can be seen in Figure 4, suggests they distinctly differ on these measures and the rate of SWJs relative to state anxiety levels may be a biomarker of AN. It is striking that the AN and control groups can be so well separated using only these two measures. As treatment for AN prioritizes weight-restoration, we set out to determine whether these patterns persist into recovery or whether those recovered from AN perform more similarly to controls. Furthermore, as structural brain changes are often found to improve following weight restoration and recovery, we investigated the rate of SWJs in individuals recovered from AN will also allow us to examine whether the state effects of starvation have an influence on results.

A limitation of this study is that spectroscopy was not performed to ascertain the concentrations of GABA and hence its potential role in these findings. To date, the only published studies examining GABA in AN have determined GABA levels in cerebrospinal fluid, and no differences have been reported. Future research combining the techniques used in this study with spectroscopy would increase the value of this research and assist in explaining the findings. Another limitation is that AN patients were not medication-free. Benzodiazepines and atypical antipsychotics have both been found to reduce saccadic peak velocity and gain as well as increase latency, but neither has been reported to induce SWJs. However, to the best of our knowledge, whether benzodiazepines or atypical antipsychotics induce SWJs has not been specifically investigated. Therefore, these medications, particularly benzodiazepines that enhance GABA transmission, may have influenced the findings. Studies of SWJ rate in other clinical populations receiving these medications could help resolve this question.

The results of this study have important implications for our understanding of AN. It appears to share with OCD an increase in SWJ rate but shows in addition a relationship between the rate of these saccadic intrusions and levels of state anxiety. Furthermore, the findings suggest that AN may be related to a dysfunction in a specific brain area or neurotransmitter system, and may help explain some of the difficulties experienced by these individuals. Specifically, the findings suggest a potential role of GABA in brain areas containing fixation neurons such as the superior colliculus, PEF, or the posterior parietal cortex in the psychopathology of AN. Further research into the role of GABA in AN will assist in confirming the areas of dysfunction in these individuals, and has the potential to lead to the development of more effective treatments specifically targeting these dysfunctions.

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References

Chapter 10: General Discussion

The aim of this thesis was to investigate the neurobiological and cognitive features of AN through an extensive battery of eyetracking, functional neuroimaging and cognitive tasks. This chapter will discuss the key findings.

10.1 Summary

A summary of the thesis findings are presented in Table 10.1 below. Overall, the study suggests a different profile in AN compared with other psychiatric illnesses in terms of cognitive performance, eye movement characteristics, emotion processing and functional neuroimaging. The aim of this chapter was to integrate the key findings of the study and to discuss the potential relationships between results.
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<th>Finding</th>
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<td>Increased</td>
</tr>
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</tr>
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<td>Weight concern</td>
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</tr>
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<td></td>
<td>Global</td>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
<td></td>
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<td>Higher feel than think; no difference between think and feel in controls</td>
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<td>Anxiety</td>
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</tr>
<tr>
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</tr>
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<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Attention</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Cognitive instability</td>
<td>Increased</td>
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<td>Task/Measure</td>
<td>Component</td>
<td>Finding</td>
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<tr>
<td></td>
<td>Difficulty describing feelings</td>
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<tr>
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<tr>
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</tr>
<tr>
<td></td>
<td>Rate</td>
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<tr>
<td></td>
<td>Gain</td>
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<tr>
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</tr>
<tr>
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<tr>
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<tr>
<td></td>
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</tr>
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<tr>
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<td>Antisaccade error rate</td>
<td>No group difference</td>
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Table 10.1 cont’d

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<thead>
<tr>
<th>Task/Measure</th>
<th>Component</th>
<th>Finding</th>
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</tr>
<tr>
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<tr>
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<td>Higher frequency of reporting as sad</td>
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<td></td>
</tr>
<tr>
<td>Fixation count to all faces (Ekman &amp; own)</td>
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<td></td>
</tr>
<tr>
<td>Fixation duration to all faces (Ekman &amp; own)</td>
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<td></td>
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Table 10.1 cont’d

<table>
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<tr>
<th>Task/Measure</th>
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<th>Finding</th>
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<td></td>
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<td><strong>Eyetracking</strong></td>
<td></td>
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</tr>
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<td>Saccade amplitudes to</td>
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<td>No group difference</td>
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<tr>
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<td><strong>fMRI</strong></td>
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<tr>
<td>Own &gt; neutral</td>
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<td>Increased activity in right inferior and middle temporal gyri, and right lingual gyrus</td>
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<td>Default mode network</td>
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<tr>
<td></td>
<td>associative visual cortices; and</td>
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<td>associative visual cortices</td>
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<td>Task/Measure</td>
<td>Component</td>
<td>Finding</td>
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<td>------------------------------------------------</td>
<td>-------------------------------------------------------</td>
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<tr>
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<td>Saccade amplitude (all body sizes)</td>
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</tr>
<tr>
<td></td>
<td>FDI</td>
<td>No group difference</td>
</tr>
<tr>
<td>Fixation</td>
<td>SWJ rate</td>
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<tr>
<td></td>
<td>Intersaccadic interval of SWJ pair</td>
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</tr>
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<td></td>
<td>SWJ amplitude</td>
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</tr>
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<td></td>
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</tbody>
</table>

Note: AN= anorexia nervosa; WTAR= Wechsler Test of Adult Reading; EDE-Q= Eating Disorder Examination Questionnaire; FR= Figure Rating Scale; DASS= Depression Anxiety Stress Scale; BIS-11= Barratt Impulsiveness Scale; TAS-20= Toronto Alexithymia Scale; MATRICS= Management and Treatment Research to Improve Cognition in Schizophrenia consensus cognitive battery; fMRI= functional magnetic resonance imaging; Ekman faces= Ekman Faces of Facial Affect stimuli; FFI= feature fixation index; FDI= feature duration index; AOIs= areas of interest; SWJ= square wave jerk
Performance on the cognitive battery suggested that individuals with AN have largely intact general cognitive abilities, unlike the findings of widespread cognitive deficits in a number of other psychiatric illnesses (Heinrichs & Zakzanis, 1998; Sweeney et al., 2000). Performance was similar to that reported in OCD (Purcell et al., 1998), as was performance on a number of other measures which will be discussed in this chapter. Although the AN group showed mostly intact performance on the cognitive battery, a trend for poorer performance on one component was identified. Individuals with AN demonstrated poorer performance on the backward component of the Spatial Span task, but not the forward component. This finding suggests that individuals with AN displayed poorer performance on a visuospatial working memory task that requires the manipulation of visuospatial information. As groups were not found to differ in performance on the forward component of the task, it may suggest the individuals with AN have intact visuospatial memory of tasks requiring low cognitive demand. This hypothesis is supported by the finding of intact latency and gain during the memory-guided saccades task, which requires visuospatial processing of simple stimuli. The memory-guided saccade task, however, resulted in an increased rate of inhibitory errors specifically to targets presented at 10°, a finding similar to that reported in OCD (Rosenberg, Averbach, et al., 1997). This finding reflects a potential role of the SC and GABA in AN. When GABA is injected into the SC of monkeys it has been found to result in an increased rate of inhibitory errors on the memory-guided saccade task (Munoz & Wurtz, 1993b). As the SC is topographically organised (Sparks, 2002), this finding may reflect increased GABA in a specific area of the SC, therefore resulting in more inhibitory errors to this specific amplitude. The potential role of the SC and GABA in AN is further supported by the findings of the PAN saccade task.

The results of the PAN saccade task indicated that individuals with AN performed similarly to controls on most measures. Increased rates of antisaccade or no-go errors were not observed, nor were group differences between antisaccade latency or gain. These findings largely differ to those reported in patients with other psychiatric conditions who are often reported to make increased antisaccade and no-go errors, and display increased latency and reduced gain of correct antisaccades (see Hutton & Ettinger, 2006 for a review). Though the findings in OCD are somewhat inconsistent, intact performance on these measures, as observed in the current sample
in AN, has been reported by some (Kloft et al., 2011; Maruff et al., 1999; McDowell & Clementz, 1997; Spengler et al., 2006; van der Wee et al., 2006). These findings suggest adequate functioning of the brain areas involved in volitional saccade production including the FEF, SEF, ACC and DLPFC. This finding was further supported by the lack of group differences observed in the fMRI findings. The AN group were, however, found to make prosaccades of shorter latency than healthy individuals. This finding further supports the potential role of GABA in the SC in AN, as GABA injected into the SC has been found to result in shorter prosaccade latencies (Munoz & Wurtz, 1993b). Furthermore, the results from the fixation task also provide support for potential role of the SC and GABA in AN.

The findings of the fixation task were somewhat unexpected. Though rarely studied, individuals with psychiatric conditions have typically been found to show intact fixation stability (Clementz et al., 1994; Tien et al., 1992). Neurodegenerative disorders such as Parkinson’s disease and Huntington’s disease, have been found to produce more spontaneous saccades during fixation in the form of SWJs (Bollen et al., 1986; White et al., 1983). The brain areas responsible for the production of SWJs appear rather non-specific with areas of the cerebral hemispheres containing fixation neurons such as the FEF and posterior parietal cortex, cerebellum, BG, and SC potentially involved. The potential role of the SC is supported by the finding that GABA injected into the rostral SC results in difficulty maintaining fixation and the production of unwanted saccades (Munoz & Wurtz, 1993b). The potential role of GABAergic function in AN is further supported by the negative correlation found between SWJs and state anxiety. As decreased levels of GABA are associated with higher anxiety (Tallman, Paul, Skolnick, & Gallager, 1980), this finding may be explained by increased GABA in non-anxious AN patients, which if also occurring in areas containing fixation neurons such as the SC, also results in an increased rate of SWJs.

The role of anxiety, and potentially the role of GABA transmission, in AN was also implicated through the visual scanpath findings. The AN group were found to demonstrate hyperscanning behaviours to all types of stimuli presented, including the Ekman Faces of Facial Affect, their own faces and the biological motion stimuli. Increased scanning behaviours have been reported when observing anxiety-inducing
stimuli (Horley et al., 2003; Kimble et al., 2014), and although the results of the current study may suggest increased anxiety to disorder-relevant stimuli, these results may alternatively suggest a distinctive scanpath strategy in AN. As hyposcanning behaviours are not limited to face stimuli in individuals with schizophrenia, but are also observed to a range of other stimuli (de Wilde, Bour, Dingemans, Boerée, & Linszen, 2007; Minassian, Granholm, Verney, & Perry, 2005), individuals with AN may utilise hyperscanning strategies even when not viewing disorder-relevant stimuli. Therefore, further research is required to assess whether hyperscanning strategies are a fundamental feature of AN. The findings of the visual scanpath tasks also provided information about the processing of body stimuli, self-images and emotion in AN.

Emotion identification in images of other individuals’ faces was found to be intact in the AN group. This finding differs to other reports of poorer emotion identification in AN (Jänsch et al., 2009; Kessler et al., 2006; Kucharska-Pietura et al., 2004; Pollatos et al., 2008), and may reflect differences in methodology between studies. Other psychiatric conditions such as schizophrenia and ASD are however associated with emotion identification difficulties (Bolte & Poustka, 2003; Deruelle et al., 2004; Humphreys et al., 2007; Kohler et al., 2000; Kohler et al., 2003; Salem et al., 1996; Wallace et al., 2008). These conditions are also associated with poorer attention to salient facial features (de Wit et al., 2008; E. Gordon et al., 1992; M. J. Green et al., 2003; Hernandez et al., 2009; Loughland et al., 2002b; Pelphrey et al., 2002; L. M. Williams et al., 1999), which was not found to the faces of facial affect in the current AN group. Therefore, the emotion identification difficulties experienced in these groups may be related to the reported findings that they do not visually attend to the correct facial areas when identifying emotions. Although the lack of emotion identification deficits in the current sample of AN participants and the lack of significant fMRI findings suggests that the perception of emotion in others is intact in AN, the findings from the TAS-20 suggest that individuals with AN have difficulties in identifying and describing emotions specific to oneself. A difference in the processing of oneself in AN was also found during the faces task. When presented with neutral self-images, individuals with AN were most likely to report their own face as neutral, but nonetheless were more likely than healthy individuals to report their face as sad. The AN group were also found to show more attention to non-salient features of their own face images, thereby devoting less visual attention to salient
features. This finding may reflect an avoidance of salient features of one’s own face in AN as they find self-images anxiety-inducing. The AN group were also found to show increased BOLD activity in areas related to the processing of one’s own face and higher order visual perception, suggesting atypical processing of self-images in AN. Increased activity was also found in the lingual gyrus, which together with the finding of greater scanning of irrelevant features of own face stimuli, may suggest greater local feature processing in AN.

Greater local processing was also found in AN during the implicit biological motion task, evident by saccades of smaller amplitude than controls. As this finding was specific to the implicit biological motion task, and was not apparent during the explicit task, it suggests that increased local processing of these stimuli may only be evident when an explicit instruction is not provided and participants are able to view the stimuli in a more natural manner. The findings of the biological motion task also suggested that individuals with AN visually attend to the same areas of a body as healthy individuals, and the estimation of body sizes of others is intact in AN. Similarly to the finding of self-processing deficits to faces and emotion in AN, the findings of the FRS suggest that individuals with AN have a specific deficit in the estimation of their own body size, overestimating how they think and feel they look. A discrepancy was also found between how large patients felt and thought they looked, with AN participants reporting feeling larger than they looked; whereas controls did not demonstrate this discrepancy. The inability to accurately judge own body size in AN and the discrepancy between the size patients think and feel they look may be related to the findings of the resting state study. Though groups were not found to differ in functional connectivity of the default mode network, the AN group were found to have reduced connectivity within the sensorimotor and visual network. The reduced functional connectivity specifically between primary somatosensory and motor cortices, and visual regions of the brain in AN may contribute to this distorted body image of oneself in AN and may also be related to the trend in visuospatial processing difficulties reported in the cognitive battery.

10.2 Methodological considerations

AN is associated with a range of structural brain differences during the underweight state of the illness, some of which improve and others which persist
following weight-recovery (Phillipou, Rossell, & Castle, 2014). Whether structural brain differences are as a result of malnourishment, or are innate differences that contribute to the development of AN, is unclear. Nevertheless, structural brain abnormalities, though not specifically investigated in the current study, are likely to have been present in the current sample of patients. Therefore, these structural changes would inevitably have an impact on findings. However, this is true of all research in AN, and is perhaps unavoidable in an illness which results in significant physical complications. However, a significant strength of the current study was that the majority of patients were outpatients and all patients were medically stable at the time of testing. Studies in AN often utilise samples of current inpatients as they are often easily accessible to the researcher. However, these patients are typically very physically unwell, which is likely to have a significant impact on task performance.

Psychiatric comorbidities were also not controlled for in the current study. AN was the primary diagnosis for all patients in the study, with only one participant meeting criteria for AN-BP according to the MINI. As the results of this patient did not significantly differ to the rest of the AN sample, her data was included in the larger AN group. Although AN was the primary diagnosis for all patients, they were found to have a number of comorbidities which may have influenced findings. Comorbid mood disorders were common, as were anxiety disorders. The great majority of AN participants met criteria for at least one anxiety disorder. As a number of the findings in this thesis suggest a relationship with anxiety and GABAergic function in AN, these comorbid conditions may have contributed to the results. Alternatively, this may suggest a significant role of anxiety in AN. As individuals with AN typically present with a number of comorbidities, a sample free of any psychiatric comorbidities would not be representative of a typical AN population. Furthermore, a number of participants were taking GABAergic medications such as benzodiazepines, as well as a variety of other medications, which may have influenced the findings. To cause minimal disruption to current treatment, patients were instructed to continue with their medications as advised by their practitioner. Due to the wide range of medications taken by patients, accurate investigation into whether specific medications influenced findings could not be explored. However, medications are likely to have influenced findings and their specific effects on these tasks in AN should be explored in future research.
10.3 Future research

Although the findings of the study have provided a greater level of insight into a number of deficits in AN, further research is required to further explore these findings. Of particular benefit would be to further explore visuospatial processing of highly cognitively demanding stimuli in AN, and whether they utilise the same hyperscanning strategies when viewing stimuli other than the types used in this study. As deficits in the processing of oneself were apparent in AN participants, it would also be of benefit to further explore the processing of own face and own body stimuli in AN to examine activation differences to these stimuli and how individuals with AN perceive images related to themselves. Of great interest would also be to further investigate the potential role of GABA and the SC in AN. As a number of findings implicated GABAergic function in this area of the brain, it would be imperative to further explore this. The investigation of GABAergic function in AN could potentially be achieved through methods such as magnetic resonance spectroscopy, with a particular focus on areas such as the SC. Further investigations are also however required to investigate whether other areas of the brain are potentially involved in these findings in AN, and may require tasks such as the memory-guided task to also be undertaken during fMRI. Furthermore, as malnutrition is a likely confound in all AN research, it would also be of benefit to investigate performance on the tasks undertaken in the current study in patients who have recovered from AN and whose structural brain differences may have normalised to some extent; as well as patients with a primary diagnosis of BN who display similar psychopathology to AN but whose illness is not associated with starvation and extensive weight loss. Additionally, as the current findings suggested similar results to those reported in some anxiety disorders, particularly OCD, it would be beneficial to investigate the overlap between AN and these conditions, and how these illnesses may differ from or be similar to AN in terms of performance on these tasks.

10.4 Clinical implications

The findings of this thesis have important implications for our understanding of AN and potential directions for the development of improved treatments. Individuals with AN were found to demonstrate a range of visuospatial processing
deficits which may relate to the distorted self-image experienced by these individuals. The atypical processing of own face images emphasises the importance of therapies such as CBT to address distorted perceptions of oneself in AN. Furthermore, remediation techniques designed to train individuals to focus on the correct areas of one’s own face may lead to improved attention to salient facial features and consequently, improved recognition of emotions related to oneself. In addition to atypical processing of own face images, individuals with AN were also found to show reduced functional connectivity within the sensorimotor and visual network. This finding suggests that the deficit in own body size perception reported in AN may be related to decreased functional connectivity between somatosensory and early visual processing areas of the brain. In other words, a deficit in multisensory integration between somatosensory and visual processes may contribute to the body image disturbances in AN. Treatments designed to strengthen the functional connectivity between these regions may assist in recovery, and monitoring the strength of connectivity between these areas may aid in determining a reduction of body image distortion in individuals with AN.

The AN group were also found to demonstrate similar task performance to that reported in patients with anxiety disorders, particularly OCD. Specifically, individuals with AN showed a similar pattern of cognitive performance to the reported literature in OCD, in which general cognitive abilities largely remain intact (Krishna et al., 2011). Similarly to SAD (Horley et al., 2003), the AN group also demonstrated hyperscanning behaviours to disorder-relevant stimuli. Whether individuals with OCD similarly display hyperscanning behaviours to disorder-relevant stimuli is unclear as detailed investigations are yet to be undertaken. AN participants were, however, found to demonstrate similar performance to that reported in OCD on a memory-guided saccade task. Specifically, the current study found that AN participants made a greater number of inhibitory errors to targets presented at 10°, whereas a study by Rosenberg, Averbach, et al. (1997) reported increased inhibitory errors to a similar amplitude (i.e. 9°) in OCD. This finding is potentially related to GABA in the SC in AN. The potential role of GABA in the SC is further supported by the findings of shorter prosaccade latencies and an increased rate of SWJs during fixation in AN. Furthermore, SWJ rate together with state anxiety discriminated groups with exceptionally high accuracy. As GABA appears to play a significant role in anxiety,
leading to anxiolytic treatments such as benzodiazepines being used to enhance GABA transmission in anxious individuals (Tallman et al., 1980), these findings support the potential role of GABA in the SC in AN. Therefore, these findings suggest that therapies designed to modulate GABA transmission in specific brain regions such as the SC may be beneficial for the treatment of AN.

As a number of the findings in this thesis have indicated overlap with reported findings in anxiety disorders, particularly OCD, it suggests these disorders share similar phenomenology and potentially similar neurobiological underpinnings. The potential relationship between AN and anxiety disorders may have specific implications for our categorisation of AN in the DSM-5. In the DSM-5, AN is listed under feeding and eating disorders, along with conditions such as pica whereby individuals have an appetite for non-food items such as paper and metal (American Psychiatric Association, 2013). These disorders differ greatly, and their categorisation together as feeding and eating disorders may require reconsideration. AN is indeed associated with restricted food intake. However, this is not as a consequence of disordered eating, per se. AN is associated with a distortion of body image which leads to a restriction in energy intake in order to lose weight. Categorising AN with disorders related specifically to disturbances in feeding may therefore not be the most suitable classification. As the findings of this thesis suggest distinctive overlap with anxiety disorders, particularly OCD, in terms of phenomenology and potential neurobiological underpinnings of the conditions, it may be appropriate to consider the categorisation of AN under anxiety disorders.

10.5 Conclusions

Overall, the study has provided a greater level of understanding of not only a number of deficits experienced by individuals with AN, but also a number of areas of intact functioning in these individuals. The findings of the study suggest that processing related to oneself may be dysfunctional in AN, though the perceptual processing of other individuals may remain intact. These findings emphasise the importance of treatments directed at addressing a distorted self-image in AN. Potentially related to this deficit in the processing of oneself in AN, decreased functional connectivity was found between primary somatosensory and visual areas of
the brain, which may contribute to the body image distortions experienced by these individuals. This finding also has important implications for treatment as the strength of this connectivity may assist in monitoring body image distortion in AN and subsequently, recovery from the illness. The findings of this thesis also suggest an overlap between performance on a number of measures in AN and reported task performance in individuals with anxiety disorders, particularly with OCD, providing support for the long-proposed hypothesis that AN and OCD share overlapping psychopathology (Holden, 1990). Furthermore we were also able to distinguish between individuals with AN and healthy individuals with very high accuracy, using two seemingly unrelated measures (SWJ rate and state anxiety), which together provided an accurate biomarker for AN. The findings of this task and a number of the other tasks have implicated the potential role of GABA and the SC in AN, suggesting a possible neurobiological underpinning of the illness. These findings have important implications for our current understanding of AN and may lead to the development of improved treatments in the future specifically targeting these dysfunctions.
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307


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Appendix A
The neurobiology of anorexia nervosa: A systematic review

Andrea Phillipou1,2,3, Susan Lee Rossell4,5,6 and David Jonathan Castle2,6

Abstract

Objective: Recent advances in neuroimaging techniques have enabled a better understanding of the neurobiological underpinnings of anorexia nervosa (AN). The aim of this paper was to summarise our current understanding of the neurobiology of AN.

Methods: The literature was searched using the electronic databases PubMed and Google Scholar, and by additional hand searches through reference lists and specialist eating disorders journals. Relevant studies were included if they were written in English, only used human participants, had a specific AN group, used clinical populations of AN, group comparisons were reported for AN compared to healthy controls and not merely AN compared to other eating disorders or other psychiatric groups, and were not case studies.

Results: The systematic review summarises a number of structural and functional brain differences which are reported in individuals with AN, including differences in neurotransmitter function, regional cerebral blood flow, glucose metabolism, volumetrics and the blood oxygen level dependent response.

Conclusion: Several structural and functional differences have been reported in AN, some of which reverse and others which persist following weight restoration. These findings have important implications for our understanding of the neurobiological underpinnings of AN, and further research in this field may provide new direction for the development of more effective treatments.

Keywords

Eating disorders, neuroimaging, neurotransmitters, MRI, PET, SPECT

Introduction

Anorexia nervosa (AN) is a serious psychiatric condition with a 12-month prevalence rate of 0.4% among females, and approximately one-tenth of that among males (American Psychiatric Association, 2013). The crude mortality rate of individuals admitted into US university hospitals with AN is approximately 5% per decade (American Psychiatric Association, 2013), among the highest mortality rate of any psychiatric disorder (Harris and Barraclough, 1998; Sullivan, 1995). Furthermore, AN is associated with exceptionally high relapse rates (Eckert et al., 1995; Löwe et al., 2001; Norring and Solberg, 1993; Strober et al., 1997; Zippel et al., 2000). A major contributing factor for the high rates of morbidity and mortality experienced by individuals with this condition is that the cause or causes of the illness are not clear, and although treatment modalities such as cognitive behaviour therapy and family therapy have emerging evidence for efficacy, many patients remain under- or unresponsive. With increasing advances in technology, particularly with...
development of sophisticated neuroimaging techniques, we are able to gain a better understanding of the neurobiological underpinnings of this condition.

A large number of structural neuroimaging studies have been undertaken in AN since the mid-1980s, and with the emergence of more advanced neuroimaging techniques, the number of functional imaging studies in AN has grown rapidly. Therefore, the aim of this systematic review was to summarise our current understanding of the neurobiology of AN. Specifically, differences in neurotransmitter function, regional cerebral blood flow, glucose metabolism, volumetrics and the blood oxygen level dependent (BOLD) response in AN will be reviewed.

Methods

The literature was searched using the electronic databases PubMed and Google Scholar, and additional hand searches were conducted in specialist eating disorder journals. Journals were searched from 1980 to July 2013. Search terms included anorexia nervosa coupled with one or more of the following: neurobiology, neuronal, neurotransmitters, serotonin, dopamine, neuropeptides, SPECT, PET, MRI, fMRI, functional, structural, neuroimaging. The search resulted in an unmanageable number of hits (N > 100,000) and so only relevant studies meeting the eligibility criteria were included. For studies to be included they had to meet the following criteria: written in English; used only human participants; had a specific AN group and not combined with other eating disorder patients; group comparisons were reported for AN compared to healthy controls, not merely AN compared to other eating disorders or psychiatric groups; used clinical populations and not non-clinical populations with AN symptoms; not case studies.

Results and discussion

Our search strategy yielded a total of 29 and 81 publications meeting the above eligibility criteria reporting structural and functional brain imaging in AN, respectively, all of which are included in this review. Of the 29 studies reporting structural data in AN, the three earliest studies utilised computerised tomography (CT), while the remaining studies utilised magnetic resonance imaging (MRI). Of the 81 functional imaging studies in AN, 15 investigated differences in neuronal systems: one utilising blood samples, five using lumbar puncture techniques, one utilising single photon emission tomography (SPECT) and eight employing positron emission tomography (PET). Fifteen of the 81 functional imaging studies reviewed utilised SPECT, seven employed PET to investigate glucose metabolism, and 44 of the studies reviewed utilised fMRI to study functional brain differences in AN. A summary of the results of these studies are presented in Tables 1 to 4.

Structural brain differences

Structural changes are frequently observed in the brains of individuals with AN, and are generally thought to reflect the effects of malnutrition and starvation. The illness is associated with enlargement of the cortical sulci and ventricles (Artmann et al., 1986; Dolan et al., 1988; Kingston et al., 1996; Swartz et al., 1996), and enlargement of the inter-hemispheric fissure (Artmann et al., 1985). Cerebral atrophy changes have been found to correlate with weight loss, and the reversal of these changes has also been found to correlate with the normalisation of body weight (Artmann et al., 1986; Golden et al., 1996; Kingston et al., 1996; Swartz et al., 1996). However, one study found no significant change in ventricular size, but a significant degree of sulcal widening after patients had attained normal body weight (Dolan et al., 1988). A more recent study found no differences in ventricular size of AN patients, but enlarged external cerebral spinal fluid (CSF) spaces when compared to controls (Palszczok et al., 1999). Individuals with AN have been reported to have larger total CSF volumes in the ventricles and sulci, and significantly reduced grey and white matter volumes (Boigi et al., 2011; Castro-Fornieles et al., 2009; Gautier et al., 2011; Katzman et al., 1996, 1997; Lambé et al., 1997; Mainz et al., 2012; Mühlau et al., 2007; Roberts et al., 2011). Differences in white matter volume have not been consistently found (Castro-Fornieles et al., 2009; Mainz et al., 2012; Mühlau et al., 2007). Follow-up studies in weight-recovered patients have reported elevated CSF volumes and persistent grey but not white matter deficits (Katzman et al., 1997; Lambé et al., 1997; Roberto et al., 2011). However, two studies have reported normalisation of grey matter and CSF volume in weight-recovered AN patients (Castro-Fornieles et al., 2009; Cowdrey et al., 2012b; Mainz et al., 2012). Furthermore, a recent study by Lázaro et al. (2012) found no difference in grey or white matter volume between weight-recovered AN patients who were at >6% of their expected body mass index (BMI) for at least one month, and a group of healthy controls.

Specific brain structures have also been found to differ between AN patients and controls, including reduced size of the pituitary gland (Doraß et al., 1991), and a reduction of total hippocampal-amygdala formation volume (Giordano et al., 2001). Individuals with AN have also been found to have decreased grey matter in the anterior cingulate cortex (ACC) (Mühlau et al., 2007), and significantly reduced ACC volume whose degree of normalisation during treatment is related to outcome (McConnochie et al., 2008). A more recent study has also reported a reduction of grey matter volume in both individuals currently ill with AN and weight-recovered patients (Friedrich et al., 2012). This study also reported reduced grey matter volumes of the amygdala and putamen in ill individuals, and the supplementary motor area in both weight-recovered...
<table>
<thead>
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<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
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<tr>
<td>Amiunto et al. (2013)</td>
<td>12 AN-R, 12 BN, 10 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: reduced grey matter bilaterally in the lateral cerebellum, precuneus, frontal orbital cortex and cingulate cortex.</td>
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<tr>
<td>Frank et al. (2013)</td>
<td>19 AN-R, 24 rec-AN-R, 20 BN, 24 HC</td>
<td>All participants were tested once.</td>
<td>Rec-AN-R vs HC: increased insula and reduced inferior parietal volumes. All ED vs HC: increased gyrus rectus volume. AN-R and rec-AN-R vs HC: reduced inferior temporal white matter.</td>
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<td>Lazarro et al. (2013)</td>
<td>35 rec-AN, 17 HC</td>
<td>All participants were tested once.</td>
<td>Rec-AN vs HC: no difference in grey or white matter volume.</td>
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<tr>
<td>Yau et al. (2013)</td>
<td>12 rec-AN-R, 10 HC</td>
<td>Diffusion tensor imaging was performed.</td>
<td>Rec-AN vs HC: no significant differences in fractional anisotropy, lower mean diffusivity in frontal, parietal and cingulum white matter tracts.</td>
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<tr>
<td>Cowdrey et al. (2012)</td>
<td>15 rec-AN, 15 HC</td>
<td>All participants were tested once.</td>
<td>No group differences in grey matter.</td>
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<tr>
<td>Friederich et al. (2012)</td>
<td>12 AN (6 AN-R, 6 AN-BP), 13 rec-AN, 14 HC</td>
<td>All participants were tested once.</td>
<td>AN and rec-AN vs HC: decreased grey matter volume in ACC and supplementary motor area. AN vs HC: decreased grey matter volume in amygdala and putamen. AN vs rec-AN: reduced grey matter volume in the left amygdala, putamen and bilateral inferior temporal cortex.</td>
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<tr>
<td>Frieling et al. (2012)</td>
<td>21 AN (12 AN, 9 rec-AN), 20 HC</td>
<td>Diffusion tensor imaging was performed.</td>
<td>AN vs HC: regional decrease in fractional anisotropy in the white matter of the posterior thalamic radiation bilaterally and mediodorsal thalamus, parts of the left superior longitudinal fasciculus and bilateral posterior corona radiata and the left middle cerebellar peduncle. AN vs rec-AN: no difference.</td>
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<td>Maiz et al. (2012)</td>
<td>T1: 19 AN (13 AN-R, 6 AN-BP), 19 HC T2: 18 AN</td>
<td>Tested shortly after admission and at discharge (mean between T1 and T2 = 15 weeks).</td>
<td>T1: higher CSF volumes, reduced cerebral grey matter and no difference in total cerebral volume in AN. T2: grey matter volumes no longer differ.</td>
</tr>
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<td>Bogli et al. (2011)</td>
<td>10 AN-R first presentation, 11 AN-R more than 9 years treatment, 27 HC</td>
<td>All participants were tested once.</td>
<td>AN-R vs HC: reduced total white matter volume and local grey matter atrophy in the hypothalamus, caudate nucleus, cerebellum, and frontal, parietal and temporal areas.</td>
</tr>
<tr>
<td>Gaudio et al. (2011)</td>
<td>16 AN-R, 16 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: reduced global grey matter volume and grey matter volume bilaterally of the middle cingulate cortex, precuneus, and inferior and superior parietal lobes.</td>
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<tr>
<td>Kazbiski et al. (2011)</td>
<td>16 AN (6 AN-BP, 10 AN-R), 17 HC</td>
<td>Diffusion tensor imaging was performed.</td>
<td>AN vs HC: reduced fractional anisotropy in the bilateral thalamus-formica, fronto-occipital fasciculus and posterior cingulum.</td>
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<td>Roberto et al. (2011)</td>
<td>T1: 32 AN, 21 HC T2: 32 AN, 21 HC</td>
<td>T1: within 2 weeks of hospitalisation. T2: before discharge.</td>
<td>Grey and white matter volume increased from T1 to T2 in AN. Grey matter volume did not normalise by T2.</td>
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<th>Procedure</th>
<th>Key findings</th>
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<td>Suchan et al. (2010)</td>
<td>13 AN, 15 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: reduced grey matter volume of the extrastriate body area.</td>
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<td>Castro-Fornieles et al. (2009)</td>
<td>T1: 12 AN, 9 HC T2: 12 AN, 9 HC</td>
<td>Tested at baseline and 6 month follow-up.</td>
<td>T1: higher CSF volumes in ventricles and sulci; reduced grey matter volume; no difference in white matter volume in AN. T2: normal CSF volumes, and grey and white matter volumes.</td>
</tr>
<tr>
<td>McCormick et al. (2008)</td>
<td>T1: 18 AN, 18 HC T2: 14 AN, 18 HC</td>
<td>Tested soon after admission and after weight restoration.</td>
<td>T1: right dorsal ACC was reduced in AN. T2: ACC volume normalized.</td>
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<td>Mühle et al. (2007)</td>
<td>22 rec-AN, 37 HC</td>
<td>Recovery was defined as a BMI above 1.7 kg/m² and regular menses for at least 6 months.</td>
<td>Rec-AN vs HC: global grey matter volume was decreased; no differences in white matter volume; grey matter decrease in bilateral ACC.</td>
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<tr>
<td>Constan et al. (2006)</td>
<td>16 AN, 16 HC</td>
<td>Tested once during treatment.</td>
<td>AN vs HC: bilateral reduction in hippocampal volume.</td>
</tr>
<tr>
<td>Giordano et al. (2001)</td>
<td>20 AN, 20 HC</td>
<td>Tested once during treatment.</td>
<td>AN vs HC: reduction of total hippocampus-amygdala formation volume.</td>
</tr>
<tr>
<td>Næmark et al. (2004)</td>
<td>T1: 18 AN, 25 HC T2: 18 AN T3: 18 AN</td>
<td>AN participants tested at three different time points: at admission to treatment (T1), with 50% weight restoration (T2) and with normal weight (T3). HC were tested at one time point.</td>
<td>T1: significantly reduced volume of the lateral ventricles and the fissure of the Sylvius between AN and HC. The size of the mesencephalon was also markedly reduced in AN. T2 and 3: reduced mesencephalon size persisted.</td>
</tr>
<tr>
<td>Katzman et al. (1997)</td>
<td>T1: 14 AN, 34 HC T2: 8 AN</td>
<td>AN participants were tested at low weight (T1) and 2–3 years later when weight-recovered. HGs were tested once.</td>
<td>T1: grey and white matter deficits and elevated CSF volume in AN. T2: persistent grey matter deficit and elevated CSF volume. White matter deficits no longer evident.</td>
</tr>
<tr>
<td>Lambe et al. (1997)</td>
<td>13 AN, 12 rec-AN, 10 HC</td>
<td>All participants were tested at one time point. Weight recovery ranged from 1 to 23 years.</td>
<td>Rec-AN vs HC: significantly greater CSF volume and smaller grey matter volume. Rec-AN vs AN: smaller CSF volumes and larger grey and white matter volumes.</td>
</tr>
<tr>
<td>Golden et al. (1996)</td>
<td>T1: 12 AN, 12 HC T2: 12 AN</td>
<td>AN participants were tested during hospitalization and following nutritional rehabilitation. HC were tested once.</td>
<td>T1: reduced total ventricular volume was decreased in AN. T2: following re-feeding, ventricular volume returned to the normal range.</td>
</tr>
<tr>
<td>Katzman et al. (1996)</td>
<td>13 AN, 8 HC</td>
<td>All participants were tested at one time point.</td>
<td>AN vs HC: larger total CSF volumes, and reduced total grey and white matter volume.</td>
</tr>
<tr>
<td>Kingston et al. (1996)</td>
<td>T1: 36 AN, 41 HC T2: 33 rec-AN, 41 HC</td>
<td>AN participants were tested while underweight, and after having gained at least 10% of their body weight. HC controls were tested on two occasions with a similar time interval.</td>
<td>T1: AN had enlarged lateral ventricles and dilated sulci. T2: enlarged ventricles and dilated sulci in AN returned to normal levels.</td>
</tr>
<tr>
<td>Authors</td>
<td>Participants</td>
<td>Procedure</td>
<td>Key findings</td>
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<tr>
<td>Swayne et al. (1996)</td>
<td>T1: 10 AN, 10 HC T2: 16 rec-AN</td>
<td>AN participants were tested within a mean of 3.9 days following admission and at weight recovery (BMI of at least 10). HC were tested once.</td>
<td>T1: AN had significantly larger ventricles at and did not differ in total brain volume from HC. T2: ventricular volume decreased and brain volume increased significantly.</td>
</tr>
<tr>
<td>Dasariwami et al.</td>
<td>14 AN, 12 BN, 14 HC</td>
<td>All participants were tested once.</td>
<td>AN and BN vs HC: reduced pituitary gland size.</td>
</tr>
</tbody>
</table>

AN anorexia nervosa; BN: bulimia nervosa; rec-AN: weight-recovered AN; HC: healthy controls; CSF: cerebrospinal fluid; BMI: body mass index; T1: time 1; T2: time 2; T3: time 3; ACC: anterior cingulate cortex.

**Table 2.** Structural brain differences in anorexia nervosa utilising computed axial tomography.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palazidou et al. (1990)</td>
<td>17 AN, 9 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: enlarged extramural CSF spaces; ventricular size did not differ.</td>
</tr>
<tr>
<td>Dolan et al. (1988)</td>
<td>T1: 25 AN, 17 HC T2: 14 rec-AN</td>
<td>AN participants were tested while underweight and after weight recovery.</td>
<td>T1: AN had enlarged ventricles and zuki widening. T2: Sylveol widening lessened after weight recovery but ventricular appearance did not significantly change.</td>
</tr>
<tr>
<td>Artmann et al. (1985)</td>
<td>T1: 35 AN T2: 26 AN T3: 3 AN</td>
<td>AN participants were tested during hospital admission (T1), following 3 weeks to 10 months (T2) and 2–3 months after first examination for participants with early T2 times.</td>
<td>T1: enlargements of CSF spaces, zuki and ventricles, and expansion of interhemispheric and Sylvian fissures in AN. T2 and T3: changes in CSF spaces, zuki and ventricles reverse.</td>
</tr>
</tbody>
</table>

AN anorexia nervosa; rec-AN: weight-recovered AN; HC: healthy controls; CSF: cerebrospinal fluid; T1: time 1; T2: time 2; T3: time 3.

**Table 3.** Functional brain differences in AN utilising functional magnetic resonance imaging.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amianto et al. (2013)</td>
<td>12 AN, 12 BN, 10 HC</td>
<td>Resting state scans were performed.</td>
<td>AN vs HC: intrinsic connectivity networks in the cerebellum were more restricted to vermis areas; greater medial and less lateral connectivity in the cerebellum; more connectivity with the bilateral temporal pole, posterior cingulate cortex and left insula, and less connectivity with the parietal lobe.</td>
</tr>
<tr>
<td>Fonville et al. (2013)</td>
<td>35 AN (20 AN-R, 7 AN-BP), 37 HC</td>
<td>Participants completed the embedded figures test where a target geometric shape and two more complicated figures are presented and the participant is required to indicate which of the two figures contains the target shape.</td>
<td>AN vs HC: poorer on the simple and complex trials and had greater activation of the fusiform gyrus irrespective of task condition. HC showed greater precuneus activation than AN.</td>
</tr>
</tbody>
</table>
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lao-Kaem et al. (2013)</td>
<td>31 AN (24 AN-R, 7 AN-BP), 31 HC</td>
<td>Participants completed a letter n-back task.</td>
<td>AN vs HC: no difference in accuracy or response time at any task difficulty; no significant difference in activations at each level of difficulty.</td>
</tr>
<tr>
<td>Oberndorfer et al. (2013)</td>
<td>14 rec-AN, 14 rec-BIN, 14 HC</td>
<td>Sucrose and saccharine solutions were delivered to participants while undergoing functional magnetic resonance imaging.</td>
<td>Rec-AN vs HC: sucrose and saccharine resulted in decreased right anterior insula activation.</td>
</tr>
<tr>
<td>Sato (2013)</td>
<td>15 AN (9 AN-R, 6 AN-BP), 15 HC</td>
<td>The Wisconsin Card Sort Test was administered during scanning.</td>
<td>AN vs HC: lower right ventrolateral prefrontal cortex and bilateral parahippocampal cortex activity during set shifting.</td>
</tr>
<tr>
<td>Strigo et al. (2013)</td>
<td>12 rec-AN, 12 HC</td>
<td>Painful heat stimuli were administered and different colours indicated the intensity of the upcoming trial.</td>
<td>Rec-AN vs HC: greater activity of the right anterior insula, DLPFC and cingulate cortex during pain anticipation; increased activity during pain stimulation in the DLPFC and decreased activity in the posterior insula.</td>
</tr>
<tr>
<td>Suchan et al. (2013)</td>
<td>10 AN, 15 HC</td>
<td>Passive viewing of images of bodies and chairs.</td>
<td>AN vs HC: effective connectivities between the middle occipital gyrus and the fusiform body area and the fusiform body area and the extrastriate body area; reduced connectivity of the fusiform body area and extrastriate body area.</td>
</tr>
<tr>
<td>Suda (2013)</td>
<td>20 AN, 15 HC</td>
<td>Participants were presented with images of “body checking” and control images of other active tasks, and were asked to imagine they were performing the action portrayed in the image.</td>
<td>AN vs HC: reduced activity of the anteromedial prefrontal cortex and right fusiform gyrus. The prefrontal cortex activity was negatively correlated with state concern; increased activation of the right parietal lobe to the body checking images compared to the neutral images in AN.</td>
</tr>
<tr>
<td>Bar et al. (2012)</td>
<td>19 AN-R, 19 HC</td>
<td>Pain processing was investigated by delivering thermal painful stimuli to the right arm.</td>
<td>AN vs HC: increased activity in the ipsilateral parietal lobe during heat pain perception.</td>
</tr>
<tr>
<td>Brooks et al. (2012)</td>
<td>18 AN (11 AN-R, 7 AN-BP), 24 HC</td>
<td>Presented with high- and low-calorie food and non-food images and required to imagine eating the food or using the non-food items.</td>
<td>AN vs HC: increased activity of the right visual cortex, and reduced activity of the bilateral cerebellar vermis when thinking about eating food.</td>
</tr>
<tr>
<td>Castelnuo et al. (2012)</td>
<td>18 AN-R, 19 HC</td>
<td>Passive viewing of images of their own body and digitally distorted images of their own body as underweight and overweight. Control stimuli were images of houses.</td>
<td>AN vs HC: increased activity in the middle temporal gyrus in the underweight-normal weight contrast, and increased inferior frontal gyrus activity in the overweight-normal weight comparison.</td>
</tr>
<tr>
<td>Cowdrey et al. (2012a)</td>
<td>16 rec-AN, 15 HC</td>
<td>Resting state scans were performed while participants had their eyes open. Resting state networks of interest included medial visual, lateral visual, auditory, sensory-motor, default mode network, cognitive control, and fronto-parietal (left and right).</td>
<td>Rec-AN vs HC: increased temporal coherence between the default mode network functional connectivity map and the right precuneus close to the border of the posterior cingulate gyrus and the prefrontal cortex/ inferior frontal gyrus.</td>
</tr>
</tbody>
</table>

(Continued)
<table>
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<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowdrey et al. (2012b)</td>
<td>16 rec-AN-R, 16 HC</td>
<td>Presented with happy and fearful emotional faces and required to undertake a gender-decision task.</td>
<td>No difference between groups.</td>
</tr>
<tr>
<td>Favaro et al. (2012a)</td>
<td>33 AN, 30 HC</td>
<td>Resting state scans were performed while participants had their eyes closed. Three visual networks (medial, lateral and ventral) and one somatosensory network were identified.</td>
<td>AN vs HC: groups did not differ in functional connectivity of the prefrontal cortex. AN MET homocysteine vs AN Val carriers: higher positive correlation of the DLPFC and ventromedial prefrontal cortex seeds, and lower negative correlation for the DLPFC, ventromedial prefrontal cortex and ventrolateral prefrontal cortex.</td>
</tr>
<tr>
<td>Favaro et al. (2012b)</td>
<td>29 AN, 16 rec-AN, 26 HC</td>
<td>Resting state scans were performed while participants had their eyes closed. Three visual networks (medial, lateral and ventral) and one somatosensory network were identified.</td>
<td>AN vs HC: decreased connectivity in the left occipitotemporal junction; significantly increased correlation within the somatosensory network in the left superior parietal cortex; Rec-AN vs HC: decreased activation in the right middle frontal gyrus.</td>
</tr>
<tr>
<td>Frank et al. (2012)</td>
<td>21 AN-R, 19 obese, 23 HC</td>
<td>Participants performed a reward-conditioning task that involved learning the association between conditioned visual stimuli (geometric shape) and unconditioned taste stimuli (juice solution, no solution or artificial saliva), and unexpected violations of the learned associations.</td>
<td>AN-R vs HC: greater right ventral putamen activation; AN-R vs HC and obese: greater left orbitofrontal cortex activation in the positive prediction error condition; reduced activation of the bilateral putamen and left orbitofrontal cortex for the negative prediction error condition.</td>
</tr>
<tr>
<td>Holsen et al. (2012)</td>
<td>12 AN-R, 10 rec-AN (8 AN-R, 2 AN-BP), 11 HC</td>
<td>Presented with images of high- and low-calorie foods and objects (control) before and after a meal. Participants were asked to press a button when images changed.</td>
<td>AN vs HC: reduced hypothalamus, amygdala, hippocampus, anterior insula and orbitofrontal cortex activity to high-calorie foods pre-meal; reduced amygdala and insula activity post-meal; Rec-AN vs HC: decreased activity of the hypothalamus, amygdala and anterior insula pre-meal.</td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td>18 AN (6 AN-R, 12 AN-BP), 20 BN, 20 HC</td>
<td>Passive viewing of food and non-food images.</td>
<td>AN vs HC: increased activity of the left anterior insula and significant interactions with the right insula and inferior frontal gyrus.</td>
</tr>
<tr>
<td>McAdams et al. (2012)</td>
<td>18 rec-AN, 18 HC</td>
<td>Presented with written appraisals statements in social and physical tasks that required the evaluation of the self, a friend and a reflection of what is believed by one’s friend.</td>
<td>Rec-AN vs HC: self-knowledge and perspective-taking showed decreased activity of the precuneus, and reduced left middle frontal gyrus activation.</td>
</tr>
<tr>
<td>Miyake et al. (2012)</td>
<td>30 AN, 30 HC</td>
<td>Presented with negative words concerning interpersonal relationships and neutral words.</td>
<td>AN vs HC: higher activations in the left insula, and right superior temporal and inferior frontal gyrus.</td>
</tr>
<tr>
<td>Brooks et al. (2011)</td>
<td>18 AN (11 AN-R, 7 AN-BP), 8 BN, 24 HC</td>
<td>Presented with high- and low-calorie food and non-food images. Participants were required to imagine eating the food or using the non-food items.</td>
<td>AN-R vs HC: increased activation of the cerebellum, left visual cortex, right DLPFC and parietal lobe to food images compared to non-food images; AN-BP vs HC: increased activity in the bilateral cerebellum and supplementary motor area in to food images; AN vs HC: results not presented.</td>
</tr>
<tr>
<td>Authors</td>
<td>Participants</td>
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<td>Key findings</td>
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<tr>
<td>Cowdrey et al. (2011)</td>
<td>15 rec-AN, 16 HC</td>
<td>Participants were delivered an oral stimulus of either a pleasant chocolate taste or an aversive unpleasant taste during the visual presentation of a picture of chocolate, mallow strawberries or a grey control image, or a tasteless liquid coupled with a grey screen (control).</td>
<td>Rec-AN-R vs HC: increased activation of the insula, cingulate, occipital and medial prefrontal cortices to the taste of chocolate, increased activation of the ACC, lateral posterior insula, caudate, putamen and DLPFC in response to the aversive image and taste condition.</td>
</tr>
<tr>
<td>Joca et al. (2011)</td>
<td>11 AN-R, 11 HC</td>
<td>Passive viewing of food and non-food items.</td>
<td>AN-R vs HC: decreased activity of the posterior middle cingulate cortex and increased activity of the right amygdala to food images.</td>
</tr>
<tr>
<td>Oberndorfer et al. (2011)</td>
<td>12 rec-AN, 12 HC</td>
<td>Completed a stop signal task.</td>
<td>AN vs HC: similar activity between groups when inhibitory demand is low; reduced medial prefrontal cortex activity during hard trials.</td>
</tr>
<tr>
<td>Vocks et al. (2011)</td>
<td>12 AN-R, 12 HC</td>
<td>Participants drank chocolate milk and water via a tube in hungry and satiated state.</td>
<td>AN-R vs HC: increased activations when drinking chocolate milk in the right amygdala and left medial temporal gyrus when hungry, no differences in the satiated condition; increased activity of the inferior temporal gyrus (including the extrastriate body area), whereas HC showed increased activation of the left insula when comparing the hungry and satiated conditions.</td>
</tr>
<tr>
<td>Castro-Fornieles et al. (2010)</td>
<td>T1: 14 AN, 14 HC, T2: 9 rec-AN</td>
<td>Testing was completed during admittance and after 7 months of treatment and weight recovery. Participants complete a number n-back task.</td>
<td>T1: increased activation of temporal and parietal areas in AN. T2: rec-AN showed reduced activity of the ACC and frontal and parietal regions compared to T1, but did not differ in activations relative to HC.</td>
</tr>
<tr>
<td>Fladung et al. (2010)</td>
<td>14 AN, 14 HC</td>
<td>Presented with computer-generated images of overweight, normal weight and normal weight female bodies. Asked to process stimulus in a self-referring way or estimate body weight (control).</td>
<td>AN vs HC: increased activity to overweight relative to normal weight stimuli; increased ventral striatal activity to normal weight stimuli compared to overweight stimuli in HC.</td>
</tr>
<tr>
<td>Friederich et al. (2010)</td>
<td>17 AN, 18 HC</td>
<td>Compare self with slim idealized female bodies (active condition) or compare their room design with images of interior home designs (control condition).</td>
<td>AN vs HC: increased activity of the right insula and premotor cortex, and less activity of the rostral ACC in response to the active condition.</td>
</tr>
<tr>
<td>Gizewski et al. (2010)</td>
<td>12 AN-R, 12 HC</td>
<td>Presented with images of high-calorie foods and neutral stimuli in satiated and hungry states.</td>
<td>AN-R vs HC: increased activation of the central cortex and to food stimuli in the hungry state, and the ACC and insula in the HC; increased posterior cingulate cortex activation in the hungry state; increased activity of the left insula during the satiated state.</td>
</tr>
<tr>
<td>Miyake et al. (2010)</td>
<td>12 AN-R, 12 AN-BP, 12 BN, 12 HC</td>
<td>Presented with negative body-image words, non-specific emotional words and neutral words</td>
<td>AN-R and AN-BP vs BN and HC: higher activation of the right amygdala to negative body-image words.</td>
</tr>
</tbody>
</table>
### Table 3. (Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohr et al. (2010)</td>
<td>16 AN, 16 HC</td>
<td>Images of the individual’s body were created that were thinner and fatter than their actual body. Task 1: rate how much image corresponds to their real body. Task 2: rate how much image represents the ideal body.</td>
<td>AN vs HC: increased activity of the insula and middle frontal gyrus for thin images in Task 1 compared to thin images of Task 1; lower activation of the precuneus for all body sizes in Task 1, and the fatter images for Task 1 relative to Task 2.</td>
</tr>
<tr>
<td>Vocles et al. (2010a)</td>
<td>13 AN, 15 BN, 27 HC</td>
<td>Passive viewing of images of their own body and another woman’s body.</td>
<td>AN vs HC: reduced activity of the inferior parietal lobule when viewing their own body. AN vs BN and HC: higher amygdala activity.</td>
</tr>
<tr>
<td>Vocles et al. (2010b)</td>
<td>5 AN</td>
<td>Passive viewing of their own body. Tested before and after body image therapy.</td>
<td>Increased activity pre- to post-treatment in the right middle temporal gyrus (including the extrastriate body area). Increased activity pre- to post-treatment in the left precuneus, posterior cingulate gyrus, fusiform gyrus, right inferior and superior frontal gyri, parahippocampal gyrus and bilateral inferior parietal lobule.</td>
</tr>
<tr>
<td>Zastrow et al. (2007)</td>
<td>15 AN (7 AN-R, 8 AN-BP), 15 HC</td>
<td>Presented with a visual target-detection task consisting of images of geometric shapes. Participants were required to classify shapes as target, non-target or standard shapes.</td>
<td>AN vs HC: reduced activity of the dorsal ACC and ventral putamen in the correct target-shift trials; reduced activity of the rostral ACC and middle and dorsal striatum in the target maintain trials; incorrect trials, relative to correct trials, resulted in decreased activity of the dorsal ACC extending to the medial frontal gyrus. AN: decreased activity in the bilateral thalamus, rostral cingulate, sensorimotor region and cerebellum to target trials compared to standard trials, independent of task performance.</td>
</tr>
<tr>
<td>Redgrave et al. (2006)</td>
<td>6 AN, 6 HC</td>
<td>Emotional Stroop task consisting of fat, thin and neutral words and words consisting of XXXXs.</td>
<td>AN vs HC: greater activity of the middle and medial frontal gyrus, and the junction of the insula, frontal and temporal lobes in the thin-XXXX contrast; reduced activity of the DLPFC in the fat-XXXX contrast.</td>
</tr>
<tr>
<td>Sachdev et al. (2006)</td>
<td>10 AN, 10 HC</td>
<td>Presented with self and non-self body images in a passive viewing task.</td>
<td>AN vs HC: less activity in the frontal gyrus, insula, precuneus and occipital regions when processing self-images but did not differ when processing non-self images.</td>
</tr>
<tr>
<td>Wager et al. (2007a)</td>
<td>16 rec-AN-R, 16 HC</td>
<td>Presented with a sucrose solution or distilled water.</td>
<td>Rec-AN-R vs HC: reduced activation to both tastes in the insula, and ventral and dorsal striatum.</td>
</tr>
<tr>
<td>Wager et al. (2007b)</td>
<td>13 rec-AN-R, 13 HC</td>
<td>Completed a simple monetary reward task.</td>
<td>Region-of-interest analysis: rec-AN-R showed decreased activity in the caudate than HC. HC showed increased activity in the left anterior ventral striatum for wins than for losses, whereas rec-AN-R did not differ.</td>
</tr>
<tr>
<td>Authors</td>
<td>Participants</td>
<td>Procedure</td>
<td>Key findings</td>
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<tr>
<td>Sante et al. (2006)</td>
<td>13 AN, 10 HC</td>
<td>Participants rated food and non-food images for pleasantness in hungry and satisfied states.</td>
<td>AN vs HC: decreased activity of the left inferior parietal cortex when satiated and the right visual occipital cortex to food images when hungry; compared to the hungry state, satiety in AN was associated with increased activity of the right occipital cortex.</td>
</tr>
<tr>
<td>Uher et al. (2005)</td>
<td>13 AN, 9 BN, 18 HC</td>
<td>Presented with line drawings of underweight, overweight and normal weight female bodies and houses [control], and asked to think how acceptable the body/house would be for them.</td>
<td>AN vs BN and HC: weaker activation of the occipitotemporal cortex (including the extrastriate body area), fusiform gyrus and parietal cortex to all body shapes.</td>
</tr>
<tr>
<td>Uher et al. (2004)</td>
<td>16 AN, 10 BN, 19 HC</td>
<td>Presented with images of food, and non-food items and asked to think how hungry it makes them, and emotional aversive and neutral images and asked to think about how it makes them feel.</td>
<td>AN vs HC: more activity in the lingual gyrus and reduced activity in the inferior parietal lobule and cerebellum in the food–non-food contrast; reduced activity in the right cerebellum but increased activity of the left cerebellum in the aversive-neutral contrast.</td>
</tr>
<tr>
<td>Uher et al. (2003)</td>
<td>8 AN-R, 9 AN-R, 9 HC</td>
<td>Presented with images of food and non-food items and asked to think how hungry it makes them, and emotional aversive and neutral images and asked to think about how it makes them feel.</td>
<td>Rec-AN-R vs HC: increased medial prefrontal and ACC, and reduced inferior parietal lobule activity in responses to food versus non-food images. Rec-AN-R vs AN-R: increased activation of dorsal ACC, right lateral and apical prefrontal cortex. No difference in emotional aversive and neutral comparison between groups.</td>
</tr>
<tr>
<td>Wagner et al. (2003)</td>
<td>13 AN, 10 HC</td>
<td>Presented with distorted images of their own body with subjective maximum unacceptability (target), subjective unacceptability of another woman’s body (non-target), and abstract images consisting of participant’s own body (neutral).</td>
<td>AN vs HC: increased activity of the inferior parietal lobule and prefrontal cortex in relation to target versus neutral stimuli.</td>
</tr>
<tr>
<td>Seeger et al. (2002)</td>
<td>3 AN, 3 HC</td>
<td>Presented with distorted images of their own body with subjective maximum unacceptability (target), subjective unacceptability of another woman’s body (non-target), and abstract images consisting of participant’s own body (neutral).</td>
<td>AN vs HC: target versus non-target and neutral contrast revealed increased activity of the right amygdala, fusiform gyrus and brainstem.</td>
</tr>
<tr>
<td>Ellison et al. (1998)</td>
<td>6 AN, 6 HC</td>
<td>Presented with images of high- and low-calorie drinks.</td>
<td>AN vs HC: increased activity of the left insula, ACC and left amygdala-hypocampal region to high-versus low-calorie drinks.</td>
</tr>
</tbody>
</table>

AN: anorexia nervosa; AN-R: anorexia nervosa restricting subtype; AN-BP: anorexia nervosa binge-purge subtype; rec-AN: weight-recovered AN; BN: bulimia nervosa; HC: healthy controls; DLPPC: dorsolateral prefrontal cortex; ACC: anterior cingulate cortex; T1: time 1; T2: time 2; T3: time 3.
<table>
<thead>
<tr>
<th>Modality</th>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>Baillet et al. (2012)</td>
<td>10 rec-AN, 9 HC</td>
<td>Participants were scanned pre-amphetamine administration and 3 hours post-amphetamine administration.</td>
<td>Rec-AN vs HC: positive association between anxiety and DA release in the dorsal caudate.</td>
</tr>
<tr>
<td></td>
<td>Galusca et al. (2006)</td>
<td>8 AN-R, 9 rec-AN-L, 7 HC</td>
<td>All participants were tested once, 2 hours after lunch. Recovery was defined as a BMI &gt; 18.5 kg/m² for at least 1 year.</td>
<td>AN-R vs HC: increased S-HT1A receptor binding in the right superior temporal gyrus, inferior frontal gyrus, parietal operculum and tempoparietal junction.</td>
</tr>
<tr>
<td></td>
<td>Baillet et al. (2005a)</td>
<td>15 AN, 29 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: increased S-HT1A receptor binding in prefrontal and lateral orbitofrontal regions, medial and lateral temporal lobes, parietal cortex, and dorsal raphe nuclei. S-HT2A was normal.</td>
</tr>
<tr>
<td></td>
<td>Baillet et al. (2005b)</td>
<td>8 rec-AN-R, 7 rec-AN-BP, 9 rec-BN, 10 HC</td>
<td>All participants were tested once. Recovery was defined as having maintained a weight above 85% average body weight, regular menstrual cycles, and not having binged, purged, or engaged in significant restrictive eating patterns for at least 1 year before the study.</td>
<td>Rec-AN-R vs rec-AN-BP: increased S-HT binding potential in the dorsal raphe and anteroventral striatum. Rec-AN-R vs rec-BN: decreased S-HT binding potential in the anteroventral striatum. ED vs HC: no differences.</td>
</tr>
<tr>
<td></td>
<td>Baillet et al. (2005)</td>
<td>13 rec-AN-R, 12 rec-AN-BP, 18 HC</td>
<td>All participants were tested once.</td>
<td>Rec-AN-BP vs HC: increased S-HT1A binding in cingulate, lateral and medial temporal, lateral and medial orbitofrontal, parietal, and prefrontal cortical regions, and dorsal raphe. AN-R vs HC: no significant differences.</td>
</tr>
<tr>
<td></td>
<td>Frank et al. (2005)</td>
<td>10 rec-AN, 12 HC</td>
<td>All participants were tested during the first 10 days of the follicular phase of the menstrual cycle. Recovery was defined as 1 year of normal weight, regular menstrual cycles and no binging or purging behaviours.</td>
<td>Rec-AN vs HC: higher DA D3/D3 receptor binding in antero-ventral striatum.</td>
</tr>
<tr>
<td></td>
<td>Baillet et al. (2004)</td>
<td>10 rec-AN-BP, 16 HC</td>
<td>All participants were tested during the first 10 days of the follicular phase of the menstrual cycle. Recovery was defined as 1 year of normal weight, regular menstrual cycles and no binging or purging behaviours.</td>
<td>Rec-AN-BP vs HC: had significantly reduced S-HT2A binding potential the left subgenual cingulate, left parietal cortex, and right occipital cortex.</td>
</tr>
<tr>
<td></td>
<td>Frank et al. (2002)</td>
<td>16 rec-AN-R, 23 HC</td>
<td>All participants were tested once. Recovery was defined as 1 year of normal weight, regular menstrual cycles and no binging or purging behaviours.</td>
<td>Rec-AN-R vs HC: had significantly reduced S-HT2A binding in the amygdala, hippocampus and cingulate.</td>
</tr>
<tr>
<td></td>
<td>Frank et al. (2007)</td>
<td>10 rec-AN-R, 8 rec-AN-BP, 9 rec-BN, 8 HC</td>
<td>All participants were tested once. Recovery was defined as 1 year of normal weight, regular menstrual cycles and no binging or purging behaviours.</td>
<td>rCBF was similar across groups.</td>
</tr>
</tbody>
</table>

(Continued)
Table 4. (Continued)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG</td>
<td>Gordon et al. (2001)</td>
<td>8 AN, 8 HC</td>
<td>Participants were presented with high- and low-caloric foods, and non-food names.</td>
<td>AN vs HC: greater rCBF in the medial temporal lobe; increased activity of the left occipital and right temporo-occipital cortex; for high-calorie images relative to low-calorie images.</td>
</tr>
<tr>
<td></td>
<td>Delvenne et al. (1999)</td>
<td>10 AN, 10 BN, 10 HC</td>
<td>All participants were tested once.</td>
<td>AN vs BN and HC: lower absolute global cortical glucose activity, and higher relative activity in the inferior frontal cortex, basal ganglia, putamen and caudate.</td>
</tr>
<tr>
<td></td>
<td>Delvenne et al. (1997)</td>
<td>10 AN, 10 low-weight depressive disorder, 10 HC</td>
<td>All participants were tested once.</td>
<td>AN vs HC: absolute global and regional glucose activity was lower; lower relative metabolism of glucose in the parietal cortex.</td>
</tr>
<tr>
<td></td>
<td>Delvenne et al. (1996)</td>
<td>T1: 10 AN, 10 HC, T2: 10 rec-AN</td>
<td>All participants were scanned during rest, eyes closed and with low ambient noise. The AN participants were scanned on two occasions, when ill (and underweight) and when weight-recovered</td>
<td>T1: AN participants demonstrated a regional hypometabolism of glucose. T2: Regional hypometabolism of glucose normalized with weight gain.</td>
</tr>
<tr>
<td></td>
<td>Delvenne et al. (1998)</td>
<td>10 AN, 10 HC</td>
<td>All participants were scanned during rest, eyes closed and with low ambient noise.</td>
<td>AN vs HC: regional hypometabolism of glucose in cortical regions, with the most significant differences found in the frontal and the parietal cortices.</td>
</tr>
<tr>
<td></td>
<td>Hertolz et al. (1987)</td>
<td>T1: 5 AN, 10 HC, T2: 5 rec-AN</td>
<td>AN participants were tested during the ill AN state and following weight recovery.</td>
<td>T1: AN had significant hypermetabolism of the caudate, temporal cortex, lentiform nucleus, thalamus and brainstem. T2: When weight-recovered, there were no differences in comparison to HC.</td>
</tr>
<tr>
<td>SPECT</td>
<td>Frampton et al. (2011)</td>
<td>T1: 13 AN, T2: 9 rec-AN</td>
<td>Participants were tested when ill and when weight-recovered, with an average of 4.2 years following the first session.</td>
<td>T1: unilateral temporal hypoperfusion, predominantly in the antero-medial temporal region. T2: hypoperfusion persisted.</td>
</tr>
<tr>
<td></td>
<td>Komatsu et al. (2010)</td>
<td>T1: 10 AN, T2: 10 AN</td>
<td>Participants were tested when ill, and after weight loss and normal eating behaviour improved with an average duration of 120 days following the first session.</td>
<td>Increased rCBF in the bilateral parietal lobe and right posterior cingulate gyrus after weight gain.</td>
</tr>
<tr>
<td></td>
<td>Beato-Fernandez et al. (2009)</td>
<td>9 AN-R, 13 BN, 12 HC</td>
<td>Results were compared during a rest condition, following a video of a landscape (neutral), and following a video of the participant’s own body filmed unclothed</td>
<td>AN vs HC: increased activity of the left parietal and right superior frontal cortices when viewing one’s own body compared to the neutral condition.</td>
</tr>
<tr>
<td></td>
<td>Yonesawa et al. (2008)</td>
<td>13 AN-R, 13 AN-BP, 10 HC</td>
<td>All participants were tested once.</td>
<td>AN-R and AN-BP vs HC decreased perfusion bilaterally of subcortical gyrus, midbrain and posterior cingulate.</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Mortality</th>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key et al. (2006)</td>
<td>11 AN, 11 HC</td>
<td>All participants were tested once.</td>
<td></td>
<td>Hypoperfusion was demonstrated in the anterior temporal lobe and/or caudate nuclei in 8 of 11 AN patients. There was no hypoperfusion in HC.</td>
</tr>
<tr>
<td>Matsumoto et al. (2006)</td>
<td>8 AN</td>
<td>All participants were tested within 2 weeks of hospital admission and prior to being discharged.</td>
<td></td>
<td>rCBF increases post-treatment were observed in the DUPFC, medial prefrontal cortex, posterior and AOC and the precuneus.</td>
</tr>
<tr>
<td>Kojima et al. (2003)</td>
<td>T1: 12 AN-R, 11 HC, T2: 12 rec-AN-R</td>
<td>Control participants were tested once, whereas AN participants were tested following weight recovery.</td>
<td></td>
<td>T1: AN-R had lower rCBF in the bilateral anterior lobes, including the AOC, right parietal lobe, insula and occipital lobes. T2: AN-R showed increases in the right parietal lobe, and decreases in the basal ganglia, cerebellum and AOC compared to HC.</td>
</tr>
<tr>
<td>Audernert et al. (2003)</td>
<td>15 AN, 11 HC</td>
<td>All participants were tested once.</td>
<td></td>
<td>Significantly reduced 5-HT₁A binding potential in the left fronto-temporal cortex, left and right parietal cortex, and left and right occipital cortex.</td>
</tr>
<tr>
<td>Chowdhury et al. (2003)</td>
<td>15 AN</td>
<td>All participants were tested once.</td>
<td></td>
<td>11 of 15 participants showed hypoperfusion in at least one area including the temporal lobe, parietal lobes, frontal lobes, thalamus and the caudate nucleus.</td>
</tr>
<tr>
<td>Naruse et al. (2001)</td>
<td>7 AN-R, 7 AN-BP, 7 HC</td>
<td>All participants were tested once.</td>
<td></td>
<td>AN-R vs AN-BP and HC: hypoperfusion of frontal areas, mainly the ACC.</td>
</tr>
<tr>
<td>Talano et al. (2001)</td>
<td>14 AN, 8 HC</td>
<td>All participants were tested once.</td>
<td></td>
<td>AN vs HC: had hypoperfusion in the medial prefrontal cortex and AOC, and hypoperfusion in the thalamus and amygdala hippocampus complex.</td>
</tr>
<tr>
<td>Naruse et al. (2000)</td>
<td>7 AN-R, 7 AN-BP, 7 HC</td>
<td>All participants were tested once before breakfast.</td>
<td></td>
<td>AN-BP vs HC: increased rCBF in the right inferior prefrontal, superior prefrontal and parietal regions.</td>
</tr>
<tr>
<td>Gordon et al. (1997)</td>
<td>T1: 15 AN, T2: 3 rec-AN</td>
<td>15 participants were tested when ill with childhood AN. 3 of these patients were retested after weight restoration.</td>
<td></td>
<td>T1: 13 of the 15 patients had unilateral temporal lobe hypoperfusion. T2: temporal lobe hypoperfusion persisted in the three patients tested at follow-up.</td>
</tr>
<tr>
<td>Nisose et al. (1994)</td>
<td>8 AN, 5 BN, 9 HC</td>
<td>SPECT was performed before and after food intake.</td>
<td></td>
<td>AN vs BN and HC: rCBF activity was lower in all cortical regions pre-meal. AN vs HC: left parietal rCBF was significantly lower pre-meal. Post-meal, the three groups did not differ.</td>
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</tbody>
</table>
### Table 4. (Continued)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar puncture</td>
<td>Kaye et al. (1999)</td>
<td>19 rec-AN, 13 rec-BN, 19 HC</td>
<td>All participants were tested during the first 10 days of the follicular phase of the subject’s menstrual cycle</td>
<td>AN-R vs AN-BP, BN and HC had significantly lower CSF HVA.</td>
</tr>
<tr>
<td></td>
<td>Kaye et al. (1991)</td>
<td>17 rec-AN, 15 HC</td>
<td>All participants were tested during the early follicular phase of the menstrual cycle</td>
<td>Rec-AN vs HC: elevated concentrations of CSF increased 5-HIAA levels; no difference was found for CSF HVA levels.</td>
</tr>
<tr>
<td></td>
<td>Kaye et al. (1988)</td>
<td>T1: 15 AN, 10 HC, T2: 11 AN following 2–6 weeks of a weight-restoration programme</td>
<td>All participants were tested during the early follicular phase of the menstrual cycle, between 8am and 9am.</td>
<td>T1: CSF 5-HIAA levels were significantly reduced in AN compared to HC. T2: CSF 5-HIAA levels increased in AN.</td>
</tr>
<tr>
<td></td>
<td>Kaye et al. (1984a)</td>
<td>8 AN (5 AN-BP, 3 AN-R), 8 recently rec-AN (5 AN-BP, 3 AN-R), 8 long-term rec-AN (6 AN-BP, 2 AN-R), 8 HC</td>
<td>All participants were administered a lumbar puncture between 8am and 9am (pre-probenecid). Probenecid was infused over 15 minutes and another lumbar puncture was performed 8 hours later (post-probenecid). Underweight AN participants were continuously below 75% of ideal body weight for a minimum of 6 months; the same patients were tested 3–4 weeks after weight correction (recently rec-AN), and a separate group with AN who were weight-recovered with a mean of 20 months (long-term rec-AN).</td>
<td>AN-BP vs AN-R: no difference in CSF 5-HIAA or HVA. Long-term rec-AN is recent rec-AN: higher post-probenecid than pre-probenecid CSF HVA; similar 5-HIAA. Combined rec-AN vs HC: no difference in CSF HVA pre- or post-probenecid; no difference in CSF: 5-HIAA pre-probenecid; rec-AN-BP had higher 5-HIAA than AN-R or HC post-probenecid.</td>
</tr>
<tr>
<td></td>
<td>Brambilla et al. (2001)</td>
<td>8 AN-R, 8 AN-BP, 7 BN, 8 HC</td>
<td>All participants were administered a lumbar puncture between 8am and 9am, and a second following 8 hours.</td>
<td>T1: ill AN had lower CSF 5-HIAA and HVA. T2: CSF 5-HIAA and HVA returned to normal with weight restoration. Rec-AN-R had a higher concentration of 5-HIAA than rec-AN-BP.</td>
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</table>

**Blood samples**

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<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Procedure</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brambilla et al. (2001)</td>
<td>8 AN-R, 8 AN-BP, 7 BN, 8 HC</td>
<td>All participants were tested once.</td>
<td>Reduced D2 receptor sensitivity in AN-R compared to other groups.</td>
</tr>
</tbody>
</table>
patients and patients with a current diagnosis. Furthermore, in comparison to weight-recovered individuals, individuals ill with AN were found to have reduced grey matter volumes of the left amygdala and putamen, and the bilateral inferior temporal cortex. Frank et al. (2013) on the other hand reported increased grey matter volume of the gyrus rectus and decreased insula volume compared to healthy controls. This study also reported reduced grey matter volume of the caudate and putamen and reduced inferior parietal white matter volume in weight-recovered AN, as well as reduced temporal white matter volume in both weight-recovered and ill AN. Other recent studies have also found decreased grey matter volumes in ill AN patients of the extrastriate body area (Sancha et al., 2010), and the middle cingulate cortex, precuneus, and inferior and superior parietal cortex (Gadri et al., 2011). A recent study by Arriano et al. (2013) reported decreased grey matter in the lateral cerebellum, precuneus and frontal orbital and cingulate cortices. Furthermore, a study by Boghi et al. (2011) found reduced grey matter of the frontal and parietal cortices, caudate nucleus, hypothalamus and cerebellum. Additionally, in this study the AN group was divided into two subgroups based on illness duration: those who had a diagnosis of more than nine years, and those who were being treated at first presentation of the illness. The group with shorter disease duration were found to have more evident hypothalamic atrophy, whereas the cerebellum was more affected in the group with longer disease duration, in comparison to healthy controls. Additionally, individuals with AN have been found to have reduced hippocampal volumes in comparison to healthy controls (Coman et al., 2006), and the size of the mesencephalon has also been found to be markedly reduced in ill AN patients, which remains reduced in weight-restored individuals (Neuhammer et al., 2006).

Several recent studies have also utilised diffusion tensor imaging (DTI) to assess white matter pathways in AN. Kazzouki et al. (2011) reported poorer white matter integrity in the bilateral lenticulostriate, fronto-occipital fasciculus and posterior cingulum in AN, irrespective of AN subgroup. The AN group also showed higher mean diffusivity in these areas, in addition to frontal, parietal, temporal and occipital areas. However, in a more recent study by Vu et al. (2013), the authors reported lower mean diffusivity in frontal, parietal and cingulum white matter tracts in weight-recovered AN, unlike the study by Kazzouki et al. (2011) who found higher mean diffusivity in these areas. Vu et al. (2013) reported poorer white matter integrity in weight-recovered AN who had a history of more severe illness. Frielings et al. (2012), on the other hand, investigated white matter integrity in a group of individuals with a current diagnosis of AN combined with individuals weight-recovered from the illness, and a sample of healthy participants. This study reported decreases in white matter of the posterior cingulate, bilateral thalamus and the mesodiencephalic thalamic and the combined AN group. Decreases were also reported in the left superior longitudinal fasciculus, bilateral posterior corona radiate and left middle cerebellar peduncle. Additionally, no differences were found between the two subgroups of AN, currently ill or weight-restored.

Functional differences

Neural systems

A neuronal system of particular interest in relation to the neurobiology of AN is the serotonergic (5-HT) system. Research in AN has mainly focused on the main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and the 5-HT receptors 5-HT1A and 5-HT2A. Individuals with AN in the ill state have significantly lower CSF basal concentrations of the 5-HT metabolite 5-HIAA (Kaye et al., 1984b, 1988). However, those recovered from AN have significantly increased 5-HIAA levels in comparison to healthy controls (Kaye et al., 1991), particularly those recovered from the binge-eating purging subtype of AN (AN-BP) (Kaye et al., 1984a).

Recent neuroimaging studies have investigated 5-HT binding differences in the brain. In a study undertaken by Bailer and colleagues (2007b), the investigators reported that ill AN individuals had increased 5-HT1A binding in the subgenual, medial temporal, orbital frontal and rostral prefrontal brain regions, and the prefrontal, lateral temporal, ACC and parietal regions. Similar findings have been reported for 5-HT1A binding in ill participants (Bailer et al., 2007b; Galvele et al., 2008), whereas recovered AN individuals have been reported to have diminished binding potential for 5-HT2A and increased binding potential of 5-HT1A. Audenaert et al. (2003) reported significantly reduced 5-HT2A binding in the left frontal cortex as well as the left and right parietal and occipital cortices of individuals with AN compared to control participants. Bailer et al. (2005), on the other hand, reported increased 5-HT1A binding potential of the dorsal raphe, and the cingulate, lateral and medial temporal, lateral and medial parietal, parietal and prefrontal cortices in weight-recovered AN. Studies investigating the specific subtypes of AN found that weight-restored restricting subtype AN (AN-R) participants had reduced 5-HT2A receptor activity in the subgenual and pregenual cingulate cortex, and mesial temporal and parietal cortices (Frank et al., 2002), whereas reduced 5-HT2A receptor activity in the subgenual cingulate, and the mesial temporal, lateral temporal, parietal and occipital cortices has been reported for recovered AN-BP participants, in comparison to controls (Bailer et al., 2004). A further study, however, found no difference in 5-HT binding potential between AN subgroups and controls, but increased 5-HT binding potential in the dorsal raphe and anteroventral striatum in recovered AN-R compared to recovered AN-BP participants, and decreased 5-HT binding potential in the anteroventral...
neurotransmitter system largely related to the serotonergic system which has also been implicated in the etiology and course of AN is the dopaminergic system. Homovanillic acid (HVA), the major metabolite of dopamine (DA) in humans, has been found to be decreased in the CSF of individuals with AN in the ill state (Kaye et al., 1984a). Two related studies have reported that HVA returns to normal levels following weight restoration (Kaye et al., 1984a, 1984b). However, a more recent study undertaken by the same investigators examining the HVA levels in individuals recovered from AN utilizing more stringent criteria than purely weight restoration (including over 2 years of normal weight, regular menstrual cycles, no restricting eating patterns or binging or purging) found that individuals recovered from AN-R had significantly lower CSF HVA than AN-BP, bulimia nervosa (BN) participants and healthy controls (Kaye et al., 1999).

In related work, Frank et al. (2005) used positron emission tomography (PET) imaging with radiolabeled [11C]raclopride to assess D(2)/D(3) receptor function in recovered AN individuals. The investigators reported significantly higher [11C]raclopride binding potential in the antero-ventral striatum than control participants, providing support for the possibility that AN is associated with decreased striatal dopamine concentration or increased D(2)/D(3) receptor density; the authors suggest this may contribute to the disturbed reward processing exhibited in AN. Another study using an amphetamine challenge and PET found that recovered AN participants exhibited a positive association between endogenous DA release and anxiety in the dorsal caudate, possibly explaining why food-related DA release produces anxiety in AN but is pleasurable in healthy individuals (Bailer et al., 2012).

Additionally, AN has been associated with altered D(2) receptor sensitivity demonstrated by significantly reduced growth hormone response to growth hormone releasing hormone administered with apomorphine, a selective D(1) and D(2) receptor agonist (Irons & Bailer et al., 2005). A study indirectly investigating dopaminergic function in AN also revealed a deficit in this group (Lawrence et al., 2003). Participants were administered a task which involved the learning of a series of two-alternative forced-choice visual discriminations. This is analogous to tasks that activate DA neurons in primates and is sensitive to neurotransmission, including L-Dopa treatment in Parkinson's disease. The AN group was found to show deficits in learning during the early stages of the task when DA activity should be at a maximum, providing indirect evidence for altered DA neurotransmission in AN.

Neuropeptides have also been of interest in AN as they are involved in the regulation of feeding behaviors. Abnormalities in the illness state of AN have been found for a variety of neuropeptides including opioid peptides, oxytocin, neuropeptide-Y and leptin, although the differences observed appear to normalize after weight restoration, suggesting a state rather than trait effect (for a review see Bailer and Kaye, 2003).

**Regional cerebral blood flow**

Functional neuroimaging is relatively new technology which has allowed the indirect measurement of brain activity. Early functional studies utilized single-photon emission computed tomography (SPECT) and showed hypoperfusion at rest in a number of brain areas in the ill state of AN. Kuroglu et al. (1983) reported hypoperfusion in frontal, parietal and frontal-temporal areas, which normalized following weight restoration. Another study reported unilateral temporal lobe hypoperfusion which persisted in a subgroup who had a follow-up at a following weight restoration (Gordon et al., 1997). A more recent study by Chowdhury et al. (2003) revealed hypoperfusion in the temporal, parietal and frontal lobes, thalamus, and caudate nuclei. Other recent studies found hypoperfusion in the medial prefrontal cortex, the ACC (Takano et al., 2001), the posteriort cingulate gyrus, the subcallosal gyrus, the midbrain (Yonezawa et al., 2008), the anterior temporal lobe and caudate nuclei (Key et al., 2006), and hypoperfusion in the thalamus and the amygdala-hypothalamus complex (Takano et al., 2001). Hypoperfusion specific to AN-R has also been found in frontal areas, mainly the ACC (Naruo et al., 2001), and hypoperfusion specific to AN-BP in the right hemisphere, including inferior and superior prefrontal and parietal regions (Naruo et al., 2000). Changes in regional cerebral blood flow (rCBF) at rest have been reported by some to normalize following weight restoration and remission (Kurogulu et al., 1985), though others have found persistent changes (Frampton et al., 2011). One study reported that, in comparison with healthy controls, individuals with AN-R prior to treatment had lower cerebral blood flow in the ACC, right parietal lobe, insula and occipital lobes. Following treatment and weight gain, normalization in a number of brain areas occurred, but decreased rCBF persisted in the ACC (Kojima et al., 2005). Another study by Matsumoto et al. (2006) found AN patients had increased rCBF post-treatment relative to pre-treatment in the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex, anterior and posterior cingulate and precuneus. A more recent study by Komata et al. (2010), however, reported increased rCBF in the right posterior cingulate gyrus and bilateral parietal lobe following weight recovery. Differences in rCBF have also been reported in AN relative to different conditions. Prior to eating a meal, AN participants have been found to show significantly decreased rCBF in the left parietal cortex in comparison to controls. Post-meal, however, AN participants were found to not differ in rCBF relative to healthy controls or BN patients (Naruo et al., 1995). Individuals with AN have also...
been found to show differences in rCBF when viewing stimuli of their own bodies. In a study by Beato-Fernández et al. (2009), healthy individuals, patients with BN and patients with AN viewed videos of themselves and landscapes. When viewing videos of one’s own body, increased rCBF of the left parietal and right superior frontal cortex was found in AN, whereas healthy controls showed decreased activation in these areas, suggesting a possible dysfunction in somatosensory integration in AN.

**Glucose metabolism**

Findings similar to those reported with the use of SPECT have also been found with PET. Individuals with AN have been shown to display global hypometabolism as well as relative hypometabolism of glucose in cortical regions, most significantly in the frontal and parietal cortices (Delvenne et al., 1995, 1997), which have been found to normalize with weight gain (Delvenne et al., 1996). The same authors also reported hypometabolism in the inferior frontal cortex and basal ganglia when compared to controls, as well as increased glucose metabolism in the caudate and putamen when compared to patients with EN (Delvenne et al., 1999); whereas AN individuals in remission have been shown to display normal glucose metabolism in the brain (Delvenne et al., 1996; Frank et al., 2007; Herholz et al., 1987). Furthermore, individuals with AN have been shown to have greater regional cerebral blood flow within the bilateral medial temporal lobes in comparison to healthy controls (Gordon et al., 2001), an area heavily involved in memory processes (Squire and Zola-Morgan, 1991) and an area which has also been associated with increased blood flow in schizophrenia (Friston et al., 1992). Additionally, the study by Gordon et al. (2001) reported increased occipital and tempo-occipital cortex activity of AN patients relative to controls when viewing images of high- compared to low-calorie foods. These areas are related to the processing of visual information and increased activity of related visual processing areas has been found in individuals with specific phobias when presented with phobic stimuli (Wik et al., 1993).

**Blood oxygen level dependent (BOLD) response**

Changes in neural activity in response to different conditions that were initially explored with PET have typically been explored with functional magnetic resonance imaging (fMRI) since the technology became widely available. In the first fMRI study in AN, Ellison et al. (1991) presented individuals with images of high- and low-calorie drinks. The authors reported that the group of AN participants showed increased activity of the left insula, ACC and amygdala-hippocampal region in response to high- versus low-calorie drinks, relative to controls. In response to images of food and non-food items on the other hand, Jooe et al. (2011) found increased right amygdala activity and decreased posterior middle cingulate cortex activity in AN-R compared to controls, whereas Kim et al. (2012) reported increased left anterior insula activity in AN, and significant interactions between the right insula and inferior frontal gyrus. However, it must be noted that the studies by Kim et al. (2012) and Jooe et al. (2011) involved passive viewing of images. In a study undertaken by Brooks et al. (2011), the investigators asked participants to imagine they were eating the food in the images presented to them and were using the objects in the control images. Increased activity of the cerebellum, left visual cortex, right DLPFC and parietal lobe was reported in AN-R to food compared to non-food items, and in the bilateral cerebellum and supplementary motor area in AN-BP. However, this study only reported within-group comparisons for AN participants and did not present between-group comparisons with healthy controls. Utilising the same paradigm, a more recent study by the group, which reported results compared to healthy individuals, increased right visual cortex activity and reduced bilateral cerebellar vermis activity was reported in AN-R when thinking about eating food (Brooks et al., 2012). When the investigators examined AN-R and AN-BP separately in comparison to healthy controls, increased right visual cortex and DLPFC activity, and reduced left cerebellar vermis and right insular activity was found when thinking about eating food in AN-R. Similar results were reported for the AN-BP group, although no increase in right DLPFC activity was found. When comparing the two AN subgroups to one another, the AN-R group showed increased activity of the visual cortex, left parahippocampal gyrus and left ACC, suggesting a possible difference in the processing of food-related information between the two AN subgroups.

BOLD activity differences in response to images of food have also been found between patients currently ill with AN and weight-recovered patients. Holen et al. (2012) presented ill AN, weight-recovered AN and healthy controls with images of food and non-food items before and after a meal. Pre-meal, the two patient groups showed reduced hypothalamus, amygdala and anterior insula activity when viewing images of high-calorie foods compared to controls. Additionally, the ill AN group also showed increased hippocampus and orbitofrontal cortex activity. Post-meal, the group with active illness persisted to show reduced amygdala and anterior insula activity, whereas the weight-recovered individuals did not. Other studies assessing AN participants in a hungry and satiated state have reported increased posterior cingulate (Grzeski et al., 2010), and inferior parietal and visual cortex activity (Santel et al., 2006) in a hungry state when viewing food images. When satiated, increased activity of the left insula to food images has been reported in AN in comparison to controls (Grzeski et al., 2010). In relation to a hungry
state, however, increased occipital cortex activity has been reported in AN when viewing food images (Santel et al., 2006). Different neural responses in AN when hungry and satiated have also been investigated with the use of oral stimuli. In a task where participants were required to drink chocolate milk or water through a tube while undergoing fMRI, the group of AN-R participants showed increased right amygdala and left medial temporal gyrus activity relative to controls when drinking the flavoured milk (Woolfe et al., 2011). Although groups did not differ in response to the chocolate milk in the satiated condition, when comparing the hungry to the satiated condition the AN group displayed increased inferior temporal gyrus activity, which included the extrastriate body area, whereas the control group showed increased left insula activity. In a study by Wagner et al. (2007a), on the other hand, where participants were administered either a sucrose solution or water, the investigators reported reduced activation to both stimulus types in the insula, and ventral and dorsal striatum in AN. A similar finding was reported by Orendorff et al. (2013), who reported reduced right insula activity in AN to both sucrose and saccharin in a group of weight-recovered AN participants relative to healthy controls. Furthermore, differences in striatum and insula activity have also been reported in a study by Cowdrey et al. (2011). In this study the investigators administered a pleasant chocolate taste or an aversive unpleasant taste coupled with the presentation of chocolate, moldy strawberries or a grey control image, or a grey screen coupled with a tasteless liquid which acted as a control condition, to healthy individuals and individuals weight-recovered from AN-R. The weight-recovered AN group was found to show increased ventral striatum and cingulate cortex activity to the taste of chocolate, and increased activity of the cingulate, medial prefrontal and occipital cortices in response to the sight of chocolate. When presented with the moldy strawberry picture, however, no group differences were apparent, although increased activation of a number of areas was evident when the oral stimulus was administered alone or with the corresponding aversive image, including the ACC, DLPFC, lateral posterior insula, putamen and caudate.

Furthermore, in a series of studies undertaken by Uher and colleagues (Uher et al., 2003, 2004), the investigators presented participants with images of food and non-food items and asked them to think about how hungry the images made them; and emotional aversive and neutral images which required participants to think about how the images made them feel. In the food/non-food contrast, individuals with AN demonstrated more activity of the lingual gyrus and lower activity of the inferior parietal lobule and cerebellum when compared to controls (Uher et al., 2004); whereas individuals weight-recovered from AN showed increased prefrontal and ACC activity, and reduced inferior parietal activity in the same contrast compared to healthy individuals (Uher et al., 2003). Relative to individuals with a current diagnosis of AN-R, the weight-recovered group were found to show heightened activation of the dorsal ACC and the prefrontal cortex. In this earlier study, group differences were specific to food stimuli and no difference in activation was apparent for the emotional aversive stimuli for either AN-R or weight-recovered AN compared to controls. In the later study, however, which contained a larger sample size, AN participants were found to show reduced right cerebellar activity but increased left cerebellar activity when viewing the emotional aversive images compared to healthy individuals. Individuals with AN have also been found to show differences in brain activation when presented with negative words related to interpersonal relationships. Specifically, AN has been associated with increased left insula, and right superior temporal and inferior frontal gyrin activity, relative to healthy controls (Miyake et al., 2012). In an earlier study, the same group investigated neural responses to negative body-image words (Miyake et al., 2010). AN-R was associated with more activity of the right amygdala and inferior parietal lobule, whereas AN-BP was associated with higher activity of the amygdala and left ventromedial prefrontal cortex, relative to a healthy comparison group. Responses to negative body-image words have also been investigated in AN, utilizing an Emotional Stroop task consisting of fat, thin and neutral words, and words comprised of XXXXs (Redgrave et al., 2008). This study revealed increased activation at the junction of the left insula, and frontal and temporal lobes, and the left middle and medial frontal gyri to thin versus XXXX words in AN compared to controls; whereas the fat versus XXXX contrast revealed lower activity of the DLPFC and parietal areas in comparison to controls. These findings suggest that individuals with AN process positive and negative body image words differently to healthy individuals, with increased activation to thin words and decreased activation to fat words in areas related to executive function.

Furthermore, body image in AN has also been explored by examining responses to images of human bodies. A recent study involving passive viewing of body images and images of chairs, which acted as control conditions, aimed to investigate the connectivity within the core network for body processing (Suzhan et al., 2013). The findings of the study revealed a different network in AN during the processing of human bodies. In healthy controls, effective connectivity was found between the middle occipital gyrus and extrastriate body area, and the extrastriate body area and fusiform gyrus. In AN, however, effective connectivity was evident between the middle occipital gyrus and fusiform body area, and the fusiform body area and the extrastriate body area. Furthermore, reduced connectivity between the fusiform body area and extrastriate body area was found in the group of AN patients. Differences in the extrastriate body area and fusiform body area function between AN and healthy individuals have also been reported in a study...
involving the presentation of underweight, overweight and normal weight female bodies. Uher et al. (2005) reported reduced activation of the occipitotemporal cortex (including the extrastriate body area), the fusiform gyrus and the parietal cortex in a group of AN participants to all body shapes, relative to both BN and healthy controls. This task required participants to think about how acceptable the body of a house (control image) would be for them. In a similar study utilizing stimuli of computer-generated nude females depicting underweight, overweight and normal body weights, participants were asked to process the stimuli during two conditions: one in which they were required to imagine how it would feel to be the body shape presented, and the other where they needed to estimate the body weight of the stimuli, which acted as the control condition (Flachsland et al., 2010). Greater activity of the ventral striatum to normal weight compared to underweight stimuli was evident in healthy controls, whereas individuals with AN were found to show greater activity to underweight stimuli in the same contrast. However, groups were not found to differ in response to overweight stimuli. In another study, Friederich et al. (2010) presented participants with images from magazines of either slim idealized female bodies or interior home designs in which participants were asked to compare their body shape or room design with the presented image. Group comparisons revealed that in response to the body images, individuals with AN showed decreased activity of the rostral ACC and greater activity of the right insula and premotor cortex. In a recent study by Suda et al. (2013), the investigators presented individuals with AN and healthy individuals with images of "body checking," such as images of measuring leg width with a measuring tape and pinching skin folds, and neutral active images such as using a computer or writing. The authors reported increased right parietal cortex activity in the AN group to the body checking images compared to the neutral images, and lower activity of the anteromedial prefrontal cortex and right fusiform gyrus relative to controls.

Rather than displaying images of other people's bodies, several studies have focused on responses to images of one's own body. Sachdev et al. (2008) found that in comparison to a group of healthy participants, AN participants showed less activity of the frontal gyrus, insula, precuneus and occipital regions when processing own body images, but did not differ when processing non-self body images. Voesk et al. (2010a), on the other hand, reported higher amygdala activity in AN compared to BN and controls when viewing another woman's body, and reduced inferior parietal lobule activity when viewing own body image compared to controls alone. In a related study, the same authors presented AN patients with own body stimuli before and after undergoing body image therapy and found increased pre- to post-treatment activity in the right middle temporal gyrus (including the extrastriate body area); whereas decreased pre- to post-treatment activity in the left prefrontal, posterior cingulate gyrus, fusiform gyrus, and right inferior and superior frontal gyri, para-hippocampal gyrus, and bilateral inferior parietal lobule was reported in AN (Voesk et al., 2010b). Furthermore, other studies have not only presented individuals with images of their own body, but also distorted images of their own body. Castellani et al. (2013) asked participants to passively view images of their own body undistorted, their own body digitally distorted, and control of images of houses. The authors reported that in comparison to healthy controls, individuals with AN showed reduced inferior frontal gyrus activity when presented with overweight stimuli relative to normal weight stimuli, and greater activity of the middle temporal gyrus in the underweight–normal weight contrast. In another study with similarly distorted images, participants were asked to either rate how much the image corresponded to  their real body, or how much it represented their ideal body (Mohrs et al., 2010). In the ideal body condition, increased activity of the insula and middle frontal gyrus was found for thin images in comparison to thin images of the real body condition. Additionally, the AN group were found to show decreased prefrontal activity for all body sizes in the real body condition compared to controls, and the heavier images in the real body condition relative to the ideal body condition in comparison to healthy individuals. Furthermore, in an early fMRI study in AN undertaken by Seeher et al. (2002) presented distorted own body images of maximum subjective unacceptability to the participant, subjective unacceptability of another woman's body and abstract images consisting of the participant's own body. This study reported that AN participants showed increased activity of the right amygdala, fusiform gyrus and brainstem to distorted own body images compared to distorted images of other bodies and the abstract images. However, this study was only comprised of three individuals with AN and three companion participants. In a follow-on study by the same group of investigators, the same task was performed in a larger sample and was found to lead to increased inferior parietal lobule and prefrontal cortex activity in the same comparison mentioned above (Weigert et al., 2003).

Although the great majority of fMRI studies have presented individuals with disorder-relevant stimuli such as bodies and food, other aspects of the disorder have also been investigated. A number of cognitive tasks have been performed while undergoing fMRI, including tasks of inhibition, working memory, visuospatial processing, cognitive flexibility and reward. During the completion of a stop-signal task, groups of AN patients and healthy controls demonstrated similar neural activity when the inhibitory demand was low. However, when the inhibitory demand was high, individuals with AN showed decreased prefrontal cortex activity in comparison to controls (Obendorfer et al., 2011). However, during a number is-back task, a task assessing working memory, individuals with AN were reported to show increased activation of temporal and
parietal areas compared to controls. A subgroup of the same AN patients were tested following seven months of treatment and weight restoration and were found to show reduced activity in the ACC, and frontal and parietal regions compared to the results from the original test session. As follow-up, the AN patients no longer differed from the control group (Castro-Pomales et al., 2013). However, in a more recent study by Lao-Kaim et al. (2013), the authors reported no difference in performance or brain activity between groups of AN participants and healthy controls on a letter n-back task, suggesting that verbal working memory may be intact in AN. During a visual-spatial processing task, on the other hand, participants were not to identify a target shape within more complicated figures, the AN group not only performed better on the task but also showed greater fusiform gyrus activity, whereas controls showed greater precuneus activity (Fonville et al., 2013). These findings suggest that unlike healthy individuals who utilize visuospatial search strategies to complete such tasks, individuals with AN may utilize strategies related to object recognition. During a visual-spatial response shifting task, on the other hand, participants were required to respond to targets and classify images as targets, non-targets or standard shapes. Zastrow et al. (2009) described that individuals with AN showed decreased bilateral thalamus, rostral cingulate, sensorimotor region and cerebellum activity to target trials, independent of performance. The AN group also showed reduced activity of the dorsal ACC and ventral putamen in the correct shift target trials, and reduced activity in the rostral ACC and dorsal middle striatum in the correct maintain target trials, relative to controls. Incorrect trials relative to correct trials, on the other hand, were associated with lower activity of the dorsal ACC, which extended to the medial frontal gyrus in AN. Together, the findings by Zastrow et al. (2009) indicate that during tasks of behavioral response shifting, individuals with AN may have altered fronto-striatal-thalamic function. Additionally, during the Wisconsin Card Sort Test, a task of behavioral response shifting and cognitive flexibility, individuals with AN are also found to show differences in neural response. In a study by Sato et al. (2013), the authors reported poorer performance on the task in AN, and lower right ventrolateral prefrontal cortex and bilateral parahippocampal cortex activity relative to healthy controls.

Differences in responses to stimuli related to reward have also been recently investigated in AN. In a study by Frank et al. (2012), participants performed a reward-conditioning task where they not only learned specific associations, but they would receive or be deprived of one of two association stimuli, therefore causing an unexpected violation of these learned associations. When an unexpected stimulus was received, AN participants had greater left ventral putamen activation compared to controls, and greater left orbitofrontal cortex activity in comparison to a sample of obese participants and the healthy control group combined. When a stimulus was unexpectedly deprived, AN participants showed reduced activation of the bilateral putamen and left orbitofrontal cortex compared to the two comparison groups. Additionally, in a study presenting a simple monetary reward task to individuals weight-recovered from AN and a healthy comparison group, the healthy controls were found to show increased left anterior ventral striatum activity for wins than for losses, whereas the patient group did not differ and had similar responses to both conditions, suggesting a possible difficulty in differentiating positive and negative feedback in AN (Wagner et al., 2007b).

A range of other BOLD studies have been undertaken in AN. One study aiming to assess emotion processing in AN presented individuals with happy and fearful human faces (Cowdrey et al., 2012b). The study revealed no difference in neural response between groups. However, this result may be due to the fact that appropriate comparisons between conditions could not be made as a neutral control condition was not presented. A study investigating the processing of identity in AN, on the other hand, found reduced precuneus dorsal ACC and left middle frontal gyrus activity when presented with stimuli related to self-knowledge and perspective taking (McAdams and Krawczyk, 2012). Two recent studies have also looked at pain perception in AN. In the earlier study, Bar et al. (2012) administered a painful thermal stimulus to the right arm of participants and found that AN participants had an increased heat pain threshold and increased right fronto-insula activity in comparison to controls. The later study undertaken by Strigo et al. (2013) investigated pain processing and anticipation in weight-recovered AN. The authors reported increased DLPFC and decreased posterior insula activity during pain stimulation in the AN group. During pain anticipation, however, the AN group displayed greater right anterior insula, DLPFC and cingulate cortex activity anticipation, relative to controls, suggesting a potentially intensified stress response.

Recently, studies have begun to investigate functional connectivity in individuals with AN. During resting state scans of individuals weight-recovered from AN, increased temporal coherence has been reported between the default mode network functional connectivity map and the right precuneus and the DLPFC/inferior frontal gyrus (Cowdrey et al., 2010). Decreased connectivity in the right middle frontal gyrus has also been reported for weight-recovered AN, and decreased connectivity of the left occipitotemporal junction within the ventral visual network (Favaro et al., 2013). Favaro et al. (2013) also reported increased connectivity in the left superior parietal cortex within the somatomotor network for individuals with AN. In another study, the same authors described increased frontal functional connectivity in individuals with AN who were Met-Met carriers of the COMT gene, compared to AN patients who were Val carriers of the gene (Favaro et al., 2012). In a more recent study by Amianto et al. (2013), the
investigators reported intrinsic connectivity networks in the cerebellum in AN which were more restricted to vermal areas, and showed greater medial and less lateral connectivity in the cerebellum relative to healthy individuals. The AN group also demonstrated less cerebellar connectivity with the parietal lobe, but more cerebellar connectivity with the posterior cingulate cortex, bilateral temporal pole and insula. Furthermore, the anterior insula showed more connectivity in AN, in contrast to individuals with BN who showed hyperconnectivity with the posterior portion of the insula.

Conclusion

The objective of this review was to provide a summary of the current literature on the neurobiology of AN. It is apparent that structural and functional changes occur during the ill state of AN, some of which have been found to reverse with weight restoration, and others which persist following weight recovery. A number of structural brain differences have been reported in AN. The enlargement of cortical sulci and ventricles is commonly reported, as are deficits in grey and white matter volumes. Although reduced grey matter volumes are frequently found to persist in weight recovery, the findings regarding white matter volumes in both weight-recovered and ill AN patients remain inconsistent. Recent DTI studies have suggested poorer white matter integrity in a number of brain areas in AN, although a limited number of studies utilizing this technique have thus far been undertaken. Grey matter deficits in specific brain areas have also been reported, particularly areas of the limbic system including the amygdala, hippocampus and cingulate cortex, areas heavily involved in emotion (LeDoux, 2000). Reduced grey matter volumes have also frequently been reported in the putamen, a structure of the basal ganglia involved in learning, as well as the regulation of DA (Packard and Knowton, 2002).

Deficits in DA function have been reported in AN, specifically, reduced levels of CSF HVA and altered DA receptor function. DA plays an important role in eating behaviours, motivation, reinforcement and reward (Bassano and Di Chiara, 1999; Holroyd and Coles, 2002; Phillips et al., 2008; Rostain et al., 2004; Schultz et al., 1997; Volkow et al., 2003; Wise, 2004); behaviours which are also found to be disturbed in AN (e.g. Flaherty et al., 2010; Scheurink et al., 2010; Wagner et al., 2007b; Watson et al., 2010). Similarly, deficits in 5-HT function have also been reported in AN, namely, increased 5-HT1A and decreased 5-HT2 binding in ill and weight-recovered AN, and decreased CSF 5-HIAA in ill patients but increased levels in weight-recovered patients. 5-HT plays a role in a number of symptoms and behaviour which are evident in the condition, including obsessive-compulsive behaviours, anxiety, impulse control, inhibition, attention and mood (Bahor, 1997; Higley and Linnola, 1997; Luchi, 1997; Soubie, 1986). It is also involved in regulating feeding behaviour such as playing an inhibitory role in eating, regulating meal size and controlling eating rate (Blundell, 1984; Leibowitz and Alexander, 1990; Samsalay, 1995).

SPECT studies have revealed that individuals with AN show hyperfusion in several brain areas, although whether these rCBF differences persist into weight recovery remains unclear. Similarly, PET studies have demonstrated global hypometabolism in individuals ill with AN, but this change in glucose metabolism is no longer evident in weight-recovered individuals. Functional differences in the brains of these individuals have however tended to be investigated with more sophisticated neuroimaging techniques such as fMRI.

Recent fMRI studies have provided us with a better understanding of the areas of the brain potentially responsible for the onset or maintenance of the illness. The function of the insular and cingulate cortices, in particular, have been regularly reported to differ in AN. The cingulate cortex is particularly involved in motivation, goal-directed behaviour and emotional processes (Devinsky et al., 1995); whereas the insula also plays a key role in emotional processes (Jones et al., 2010), particularly in the processing of disgust (Wicker et al., 2003), which AN patients have been reported to have particular difficulty recognising (Pollatos et al., 2008).

Due to inconsistencies across study procedures, findings are not always consistent and can be difficult to interpret. A major issue in all AN research is that it remains unclear whether changes occur as a result of the condition and are due to the effects of starvation, or whether they are innate differences that contribute to the development of the illness. This is a very challenging issue to address as it would be difficult, if not impossible, to test individuals before the onset of illness symptoms. This is one of the reasons why recovered AN patients are often researched. However, the findings observed at recovery may be state effects, reflecting damage due to starvation, rather than trait effects of AN. Additionally, the length of time in which patients are weight-recovered varies between studies as a standard minimum timeframe for what constitutes someone who is in recovery does not exist. Furthermore, patients with varying illness severity and duration are often included in the same analysis. Although particularly difficult to control due to small patient numbers and often limited information regarding illness duration, more systematic recruitment protocols would provide a better understanding of how these factors may contribute to neurobiological findings. Furthermore, information is gathered about illness duration and severity, correlational analyses could be performed with neurobiological data.

The results of this review suggest a number of structural and functional deficits in the brains of individuals with AN as revealed with the use of a number of neuroimaging modalities. It is important to note that some modalities were not included.
in this review, such as electromyography (EEG), as they were beyond the scope of this paper. However, a number of recent papers have suggested EEG and event-related potential differences in AN (e.g., Hase et al., 2010, 2011, for a review see Jastrebofo-Loboaro, 2012), and further studies utilizing more sophisticated neuroimaging techniques such as magnetoencephalography will provide further information regarding differences in the time course of activity in AN.

The findings of this review have important implications for the treatment of AN, however, more systematic research with larger sample sizes is required. Of great benefit would also be research which utilizes tasks that are known to employ the areas which are disturbed in AN, such as emotion processing tasks which employ areas such as the insula and limbic system, as well as sacro-coccygeal eye movement tasks which involve the insula, cingulate cortex, basal ganglia, DLPC, and striatum, among other areas. With further investigation into the neurobiology of AN, a better understanding of the mechanisms involved in the development and maintenance of the illness will be established which will have the potential to provide new direction for the development of effective treatments.

Acknowledgements
The authors would like to thank Larry Abel, PhD, for his contribution to the manuscript.

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Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


d216.


Appendix B
Dr Larry Abel  
Department of Optometry & Vision Sciences  
The University of Melbourne  
Parkville VIC 3010

Dear Dr Abel,

HREC-A Protocol number: 057/12

*Investigating the neurobiological and cognitive features of Anorexia Nervosa.*

The St Vincent's Hospital (Melbourne) Human Research Ethics Committee-A has reviewed and approved the aforementioned study.

**Approval Status: FINAL**

**Period of Approval: 4 June 2012 – 4 June 2016**

Ethical approval is given in accordance with the research conforming to the National Health and Medical Research Council Act 1992 and the National Statement on Ethical Conduct in Human Research (2007).

Ethical approval is given for this research project to be conducted at the following sites:

- Body Image Eating Disorders and Recovery Treatment Service (BETHS)  
  St Vincent's Hospital (Melbourne)

**Approved documents**
The following documents have been reviewed and approved:

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<td>Research Protocol</td>
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Approval is subject to:

- The Principal Researcher is to ensure that all associate researchers are aware of the terms of approval and to ensure the project is conducted as specified in the application and in accordance with the National Statement on Ethical Conduct in Human Research (2007).
- Immediate notification to the Research Governance Unit of any serious adverse events on participants.
- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
- Notification and reasons for ceasing the project prior to its expected date of completion;
- Notification of proposed amendments to the study;
- Submission of an annual report, due on the anniversary date of approval, for the duration of the study.
- Submission of reviewing HREC approval for any proposed modifications to the project;
- Submission of a final report and papers published on completion of project;
- Projects may be subject to an audit or any other form of monitoring by the Research Governance Unit at any time.

Please note: Any Serious Adverse Events (SAEs) relating to patient information and/or data management must reported to HREC-A within 24 hours (for information only).

The HREC wishes you and your colleagues every success in your research.

Yours sincerely,

[Signature]

Ms Anita Arndt
Senior Administrative Officer and HREC-A Secretary
Research Governance Unit
St Vincent’s Hospital (Melbourne)
Human Research Ethics Committee  
Research Ethics Unit  
Henry Buck Building  
Austin Hospital

TO: Dr Larry Abel  
Department of Optometry & Vision Sciences  
The University of Melbourne Parkville Vic 3010

PROJECT: Investigating the neurobiological and cognitive features of anorexia nervosa

PROTOCOL NO: H2012/04648

PROJECT NO:

FROM: Ms Jill Davis, Research Ethics Unit Manager

DATE: 13 June 2012

RE:  
- Protocol Version 3 dated 22 May 2012  
- Participant Information and Consent Form Version 3 dated 24 May 2012  
- Parent Information and Consent form Version 3.1 dated 7 June 2012  
- Child Assent form Version 3 dated 7 June 2012  
- MRI pre-scan Information and Consent Form Version 2 dated  
- MEG pre-scan Information and Consent Form Version dated 18 January 2012  
- Databank Information and Consent Form Version 6 dated 29 September 2010  
- Advertisement 2 dated 30 April 2012  
- Letter of invitation Version 1 dated 1 May 2012  
- Letter of invitation for parent Version 1 dated 1 May 2012

Questionnaires:  
- Clinical demographic record  
- Depression Anxiety Stress Scale (DASS)  
- Eating Disorders Inventory (EDI-3)  
- Edinburgh Handedness Inventory  
- Montgomery Asberg Depression Rating Scale (MADRS)  
- Mini International Neuropsychiatric Interview (MINI)  
- Stunkard Figure Rating Scale  
- Toronto Alexithymia Scale (TAS-20)  
- Wechsler Test of adult reading (WTAR)  
- Personality Diagnostic Questionnaire (PDQ-4)
Approval Period: 13 June 2012 to 13 June 2015

Further to my letter dated 24 May 2012 concerning the above detailed project, I am writing to acknowledge that your response to the issues raised by the Human Research Ethics Committee at their meeting on 17 May 2012 is satisfactory. This project now has full ethical approval for a period of three years from the date of this letter.

Before the study can commence you must ensure that you have:

- For trials involving radiation it is your responsibility to ensure the research is added to the Austin Health Management Licence issued by Department of Human Services - Radiation Safety Section prior to study commencement should it be required (check your Medical Physicist Report). The HREC must be notified when the research has been added to the licence.
- It is a requirement that a progress report is submitted to the Committee annually, or more frequently as directed. Please note a final report must be submitted for all studies. Should you plan for your study to go beyond the 3-year ethics approval, please request in writing an extension of ethics approval prior to its lapsing. If your study will not commence within 12 months, a request must be forwarded to the HREC justifying the delay beyond 12 months. Should such a request not be received, ethics approval will lapse and a resubmission to the HREC will then be necessary.
- After commencement of your study, should the trial be discontinued prematurely you must notify the HREC of this, citing the reason.
- Any changes to the original application will require a submission of a protocol amendment for consideration as this approval only relates to the original application as detailed above.
- Please notify the HREC of any changes to research personnel. All new investigators must be approved prior to performing any study related activities.
- It is now your responsibility to ensure that all people (i.e. all investigators, sponsor and other relevant departments in the hospital) associated with this particular study are made aware of what has been approved.

The Committee wishes to be informed as soon as practicable of any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers. The HREC has adopted the NHMRC Australian Health Ethics Committee (AHEC) Position Statement 'Monitoring and reporting of safety for clinical trials involving therapeutic products' May 2009

Please ensure you frequently refer to the Research Ethics Unit website http://www.austin.org.au/Page.aspx?id=415 for all up to date information about research and ethical requirements.
DETAILS OF ETHICS COMMITTEE:
It is the policy of the Committee not to release personal details of its members. However I can confirm that at the meeting at which the above project was considered, the Committee fulfilled the requirements of the National Health and Medical Research Council in that it contained men and women encompassing different age groups and included people in the following categories:

Chairperson
Ethicist
Lawyer
Lay Man
Lay Woman
Person fulfilling a Pastoral Care Role
Person with Counselling Experience
Person with Research Experience

**Additional members include:**
- Chairs of all sub committees, or nominees
- Other persons as considered appropriate for the type/s of research usually being considered

I confirm that the Principal Investigator or Co-Investigators were not involved in the approval of this project. I further confirm that all relevant documentation relating to this study is kept on the premises of Austin Health for more than three years.

The Committee is organised and operates according to the National Statement on Ethical Conduct in Human Research (NHMRC The National Statement) and the Note for Guidance on Good Clinical Research Practice (CPMP/ICH/135/95) annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Records Act 2001.

PLEASE NOTE: The Committee requests that the Research Ethics Unit (ethics@austin.org.au) is informed of the actual starting date of the study as soon as the study commences. A written notice (e-mail, fax or letter) is considered the appropriate format for notification.

_Jill Davis_
Manager, Research Ethics Unit

This HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice. The process this HREC uses to review multi-centre research proposals has been certified by the NHMRC.
Dr Larry Abel  
Department of Optometry & Vision Sciences  
The University of Melbourne  
PARKVILLE 3010  
11 December 2013

Dear Dr Abel

Re Project 235: Investigating the neurobiological and cognitive features of Anorexia Nervosa.

I confirm that at the meeting of The Melbourne Clinic Research Ethics Committee held on the 11 December 2013 your letter dated 22 Nov 2013 and the following study documents:

1. TMC Application Form
3. Investigators Relationship to the Research
4. Scales to be used in the study:
   - MCCB Administrators Form and Respondents Booklet
   - Attachment Style Questionnaire
   - Barratt Impulsiveness Scale (BIS-11)
   - Demographic Record
   - DASS 42
   - EDE-Q
   - Edinburgh Handedness Questionnaire
   - Figure Rating Scale
   - Intolerance of Uncertainty Scale
   - MADRS
   - M.I.N.I
   - Need Threat Scale
   - Personality Diagnostic Questionnaire (PDQ-4)
   - Sensitivity to punishment and reward questionnaire
   - Social Anhedonia Questionnaire (revised)
   - Toronto Alexithymia Scale (TAS-20)
   - Wechsler Test of Adult Reading (WTAR).
6. Patient Consent Form (Version_ not dated)
7. MEG Pre-Scan Information, Checklist and Consent Form for Participants (Version_ dated 18.01.2012)
8. MRI-15 checklist and Consent Form for Participants no contrast (Version 2, not dated)
9. TMC Consultants Permission Form
10. Cognitive and Genetic Explanations of Mental Illnesses (CAGEMIS) Bio-Databank PICF  
    (Version 9, dated 30.4.12)
11. Advertising Flyer
12. CV of the PI
13. Letter of Approval from other HRECs
   1. Austin Health (dated 13 June 2012)
   3. Austin Health amendment to the Letter of Invitation (dated 26 Sept 2012)
   4. Austin Health amendment to the Protocol (dated 28 Sept 2012)
   5. Austin Health amendment to the Protocol, PICF, advertisement (dated 21 Dec 2012)
   6. Austin Health amendment to the Protocol & addition of a scale (dated 16 April 2013)
   7. Letter of Acknowledgement of St Vincent’s HREC approval from the HREC of the University of Melbourne (dated 24 Jan 2013)
8. Letter of Acknowledgement of St Vincent’s HREC approval from the HREC of the Swinburne ethics (undated)
9. St Vincent’s - final Approval (dated 4 June 2012)
10. St Vincent’s - amendments to the Protocol, PICF and reimbursement (dated 27 August 2012)
11. St Vincent’s - amendment to the advertisement (dated 28 August 2012)
12. St Vincent’s - amendment to the Protocol (dated 15 October 2012)
13. St Vincent’s - amendment to the Protocol, eye movement tasks, scales, patient reimbursements and study personnel (dated 11 Dec 2012)
15. St Vincent’s - amendment to the Protocol (dated 24 April 2013)
16. St Vincent’s - amendment to the advertisement (dated 2 July 2013)

Were tabled, discussed and approved with the proviso that in the PICF (Version 1, dated 22.11.13) first paragraph under point 1. Introduction; there is a fuller explanation to patients, in particular with regards to "different strategies" and "certain tasks."

Enclosed is the "Acceptance of Researchers Requirements Form." The Acceptance of Research Requirements Form outlines the terms and conditions of The Melbourne Clinics Research Ethics Committees approval of your project. Please sign and return this form to the Secretariat as soon as possible.

I confirm for the record that although we do not list Committee members by name that the Committee is constituted and functions in accordance with the National Statement on Ethical Conduct in Research Involving Humans (2007) issued by the National Health and Medical Research Council (NHMRC) in accordance with the NHMRC Act, 1992.

We wish you success with the research and look forward to hearing from you further on its progress.

Yours sincerely,

Dr Harry Derham
Chair
Research Ethics Committee
To: Prof Susan Rossell, BPsyC, FLSS
Dear Susan

SUHREC Project 2012/277 Investigating the neurobiological and cognitive features of Anorexia Nervosa

Prof Susan Rossell, BPsyC/FLSS et al
(UofMelb Cl: Dr Larry Abel; Student: Ms Andrea Philippou. SVH HREC-A Protocol 057/12)

Approved Duration to 01/05/2015 [Adjusted]

I refer to the application for Swinburne ethics clearance for Swinburne involvement in the above collaborative project involving St Vincent’s Hospital, Melbourne and the University of Melbourne and given ethics clearance by St Vincent’s Hospital Human Research Ethics Committee (SVH HREC-A) (Protocol 057/12).

Relevant documentation pertaining to the application was emailed by you on 20 November 2012 with attachments, then a full set of updated and additional information forwarded on your behalf by Ms Andrea Philippou in two emails on 19 December 2012. The original documentation was given expedited ethical review by a delegate of Swinburne’s Human Research Ethics Committee (SUHREC) significantly on the basis of the prior SVH HREC-A ethical review and a recommendation to approve given on the basis of further clarification/information needed as now contained in Ms Philippou’s emails of 19 December 2012.

I am pleased to advise that, as submitted to date, Swinburne ethics clearance has been given in line with standard on-going ethics clearance conditions here outlined (as applicable) and on the understanding that appropriate insurance arrangements are in place to cover the Swinburne-sanctioned research activity. (No SVH HREC-A may need to be apprised of the Swinburne ethics clearance.)

- All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the current National Statement on Ethical Conduct in Human Research and with respect to secure data use, retention and disposal.

- The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

- The above project has been approved as submitted for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants and any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

- At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project. (A copy of any progress, annual or final report submitted to SVH also being submitted to my office should meet these requirements, all things being equal; similarly with any request to modify the approved protocol.)

- A duly authorised external or internal audit of the project may be undertaken at any time.

Please contact me if you have any queries about Swinburne on-going ethics clearance and if you need a signed Swinburne ethics clearance certificate, citing the SUHREC project number. Copies of clearance emails should be retained as part of project record-keeping.

Best wishes for the project, including for Ms Philippou’s research.

Yours sincerely

Keith

Keith Wilkins
Secretary, SUHREC & Research Ethics Officer
Swinburne Research (H68)
Swinburne University of Technology
P O Box 218
HAWTHORN VIC 3122
Tel +61 3 9214 5218
Fax +61 3 9214 5267
24 January 2013

Dr L.A. Abel  
Optometry and Vision Sciences  
The University of Melbourne

Dear Dr Abel

I am writing to advise you that this project has been registered at this University as approved by St Vincent’s HREC which is the Responsible Human Research Ethics Committee for this project. Please take note of the University ethics ID Number below.

Project title: Investigating the neurobiological and cognitive features of anorexia nervosa  
Researchers: Dr L A Abel, A Phillipou, Dr C Keating, Professor D J Castle, Associate Professor R Newton, Mr R Nibbs, Dr W Woods, Miss R Batty, Professor S Rossell  
Ethics ID: 1239068

Please note the following conditions of registration:

1. The St Vincent’s HREC approval must be current for the life of the project.
2. You are required to keep the Health Sciences Human Ethics Sub-Committee informed of any subsequent variations or modifications made to the project and any such changes must be approved by St Vincent’s HREC.
3. You are required to submit an annual report to the Human Research Ethics Committee at the end of each year, or at the conclusion of the project if it continues for less than this time. Requests for annual reports will be sent out via Themis.

Yours sincerely

Ms Kate Murphy  
Executive Officer, Human Research Ethics  
Phone: 93442973, Email: k.murphy@unimelb.edu.au

cc: Head, Optometry and Vision Sciences  
    Andrea Phillipou
ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 196/10

Project Title: Establishment of the 'Cognitive and genetic explanations of schizophrenia and bipolar disorder' databank at the Monash-Alfred Psychiatry research centre

Principal Researcher: Professor Susan Rossell

Project Proposal version: 3 dated: 6-Aug-2010

Participant Information and Consent Form version 6 dated: 29-Sep-2010

Was considered by the Ethics Committee on 22-Jul-2010 and APPROVED on 29-Sep-2010

It is the principal researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via a Progress Report of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project (forms to be provided);

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED: [Signature]

Chair, Ethics Committee (or delegate)

R. FREW
SECRETAARY
ETHICS COMMITTEE

Please quote Project No and Title in all correspondence
Appendix C
Clinical Demographic Record

Please answer the following questions as accurately as possible.

1. General Information

First name........................................ Summary......................................................

Address ..........................................................................................................................

.................................................................................................................................

Telephone....................................................

Date of birth ....../....../...... Gender  □ Male □ Female

Marital Status........................................ Occupation................................................

First/primary language............................. Other Languages....................................

In the case that an abnormality is detected in your brain you will be contacted by Swinburne's radiologist. Or if you prefer to be contacted by your health practitioner, please give their details below:

Name........................................ Organisation................................................ Telephone...........

2. Educational and Employment History

Please tick your highest formal educational standard attained.

□ Secondary  □ TAFE/Diploma  □ Trade qualifications

□ Tertiary  □ Other:  □ Currently studying

Please tick your current employment status.

□ Employed  □ Unemployed  □ Home duties

□ Student  □ Retired  □ Other: ..................................................

Please tick your highest level of employment attained.

□ Full-time  □ Part-time/casual  □ Never been employed
3. Medical History

Have you ever suffered from a head injury accompanied by a loss of consciousness?
- Yes
- No
- Don’t know

Do you have any known neurological disorder?
- Yes
- No
- Don’t know

Do you have any known ocular (eye) pathology?
- Yes
- No
- Don’t know

Have you ever been formally diagnosed with an eating disorder?
- Yes
- No
- Don’t know

If you answered yes to the previous question please indicate which of the following eating disorder(s) you have been diagnosed with.
- Anorexia Nervosa
- Bulimia Nervosa
- Binge-Eating Disorder
- Eating Disorder Not Otherwise Specified
- Don’t know

Please list any medications you are currently taking:

<table>
<thead>
<tr>
<th>Medication name</th>
<th>Dosage (per day)</th>
<th>Medication purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Do you or anyone in your family have a mental illness? If so, please specify relationship, as well as type and duration of illness.

4. Body areas of concern

a) Are you disturbed about the appearance of some part of your body that you consider especially unattractive?

☐ Yes ☐ No ☐ Don’t know

If you responded ‘No’ to Question 4a, please proceed to Question 5.

If you responded ‘Yes’ to Question 4a, please proceed to parts b and c.

b) Please indicate the appropriate body part(s) that are your main area(s) of concern (tick as many as applicable).

☐ Arms ☐ Back ☐ Body hair
☐ Buttocks/hips/thighs ☐ Cheeks/cheekbones ☐ Chest/breasts
☐ Chin ☐ Ears ☐ Eyes
☐ Face (in general) ☐ Facial hair ☐ Feet
☐ Forehead ☐ Genitals ☐ Hair
☐ Hands/fingers ☐ Jaw ☐ Legs
☐ Mouth/lips/teeth ☐ Nose ☐ Muscle tone (in general)
☐ Shoulders ☐ Skin (eg. complexion, pore size)
☐ Waist/stomach ☐ Other(s):

5. Additional Medical History (Anorexia Nervosa patients ONLY)

Duration of treatment

Duration of condition
For official use only:

<table>
<thead>
<tr>
<th>Snellen visual acuity</th>
<th>Ishihara colour blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (weight(kg)/height(m^2))</td>
<td></td>
</tr>
</tbody>
</table>
Edinburgh Handedness Inventory

Surname............................................. Given Names...........................................

Date of Birth........................................... Sex...........................................

Have you ever had any tendency to left-handedness

Yes  No

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never use try to use the other hand unless absolutely forced to, put ++. If in any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Writing</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Drawing</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Throwing</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Scissors</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Comb</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Toothbrush</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Knife (without fork)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Spoon</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Hammer</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Screwdriver</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Tennis racket</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Knife (with fork)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Cricket bat (lower hand)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Golf club (lower hand)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Broom (upper hand)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Rake (upper hand)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Striking Match (match)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Opening box (lid)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Dealing cards (card being dealt)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Threading needle (needle or thread according to which is moved)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Which foot do you prefer to kick with</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Which eye do you use when using only one eye</td>
<td></td>
</tr>
</tbody>
</table>
**WTAR Word List**

Say, I will show you some words that I will ask you to pronounce. Place the WTAR Word Card in front of the examinee. As you point to the card, say, "Beginning with the first word on the list, pronounce each word aloud. Start with this word (point to item 1), and go down this column, one right after the other, without skipping any. When you finish this column, go to the next column (point to the second column). Pronounce each word even if you are unsure. Do you understand? When you are sure that the examinee understands the task, say, "Ready? Begin.""
MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

University of South Florida - Tampa

Hôpital de la Salpêtrière - Paris

© Copyright 1992-2006 Sheehan DV & Lecrubier Y

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by any means, electronic or mechanical, including photocopying, or by any information storage or
retrieval system, without permission in writing from Dr. Sheehan or Dr. Lecrubier. Researchers
and clinicians working in nonprofit or publicly owned settings (including universities, nonprofit
hospitals, and government institutions) may make copies of a M.I.N.I. instrument for their own
dinical and research use.

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on
any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified
licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of
symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)
<table>
<thead>
<tr>
<th>Modules</th>
<th>Time Frame</th>
<th>Meets Criteria</th>
<th>DSM-IV</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAJOR DEPRESSIVE EPISODE</td>
<td>Current (2 weeks)</td>
<td>☐</td>
<td>296.30-296.26 Single</td>
<td>F32.x</td>
</tr>
<tr>
<td>MDE WITH MELANCHOLIC FEATURES</td>
<td>Current (2 weeks)</td>
<td>☐</td>
<td>296.30-296.36 Recurrent</td>
<td>F33.x</td>
</tr>
<tr>
<td>B DYSTHYMIA</td>
<td>Current (Past 2 years)</td>
<td>☐</td>
<td>308.4</td>
<td>F34.1</td>
</tr>
<tr>
<td>C SUICIDALITY</td>
<td>Current (Past Month)</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D MANIC EPISODE</td>
<td>Current</td>
<td>☐</td>
<td>295.00-295.06</td>
<td>F30.x-F31.9</td>
</tr>
<tr>
<td>E PANIC DISORDER</td>
<td>Current (Past Month)</td>
<td>☐</td>
<td>300.01/300.21</td>
<td>F01.01-F41.0</td>
</tr>
<tr>
<td>F AGORAPHOBIA</td>
<td>Current</td>
<td>☐</td>
<td>300.22</td>
<td>F40.00</td>
</tr>
<tr>
<td>G SOCIAL PHOBIA (Social Anxiety Disorder)</td>
<td>Current (Past Month)</td>
<td>☐</td>
<td>300.23</td>
<td>F40.1</td>
</tr>
<tr>
<td>H OBSESSIVE-COMPULSIVE DISORDER</td>
<td>Current (Past Month)</td>
<td>☐</td>
<td>300.3</td>
<td>F42.8</td>
</tr>
<tr>
<td>I POSTTRAUMATIC STRESS DISORDER</td>
<td>Current (Past Month)</td>
<td>☐</td>
<td>308.81</td>
<td>F43.1</td>
</tr>
<tr>
<td>J ALCOHOL DEPENDENCE</td>
<td>Past 12 Months</td>
<td>☐</td>
<td>305.00</td>
<td>F10.4x</td>
</tr>
<tr>
<td>K SUBSTANCE DEPENDENCE (Non-alcohol)</td>
<td>Past 12 Months</td>
<td>☐</td>
<td>304.00-305.20-90</td>
<td>F11.1-F19.1</td>
</tr>
<tr>
<td>L PSYCHOTIC DISORDERS</td>
<td>Lifetime</td>
<td>☐</td>
<td>295.10-295.90/297.1/203.82/293.90/293.80</td>
<td>F20.20-F29</td>
</tr>
<tr>
<td>M ANOREXIA NERVOSA</td>
<td>Current (Past 3 Months)</td>
<td>☐</td>
<td>307.1</td>
<td>F50.0</td>
</tr>
<tr>
<td>N BULIMIA NERVOSA</td>
<td>Current (Past 3 Months)</td>
<td>☐</td>
<td>307.51</td>
<td>F50.2</td>
</tr>
<tr>
<td>ANOREXIA NERVOSA, Binge Eating Purging Type</td>
<td>Current</td>
<td>☐</td>
<td>307.1</td>
<td>F50.0</td>
</tr>
</tbody>
</table>

M.I.N.I. 5.0.0 (July 1, 2006)
<table>
<thead>
<tr>
<th>Code</th>
<th>Condition</th>
<th>Period</th>
<th>Score</th>
<th>DSM-5 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>GENERALIZED ANXIETY DISORDER</td>
<td>Current (Past 6 Months)</td>
<td>□ 300.02</td>
<td>F41.1</td>
</tr>
<tr>
<td>P</td>
<td>ANTISOCIAL PERSONALITY DISORDER</td>
<td>Lifetime</td>
<td>□ 301.7</td>
<td>F60.2</td>
</tr>
</tbody>
</table>

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).
GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category.

• At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box.

• At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in "normal font" should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in "CAPITALS" should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithm.

Sentences written in "bold" indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (↑) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle "NO" in all the diagnostic boxes and move to the next module.

When terms are separated by a slash (/), the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives). Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact:

David V. Sheehan, M.D., M.B.A.
University of South Florida College of Medicine
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E-mail: herguel@est.jussieu.fr

M.I.N.I. 5.0.0 (July 1, 2006)
### A. MAJOR DEPRESSIVE EPISODE

(⇒ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IS A1 OR A2 CODED YES?</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### A3 Over the past two weeks, when you felt depressed or uninterested:

- a. Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±6 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)?
  - **IF YES TO EITHER, CODE YES.**

- b. Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning waking or sleeping excessively)?

- c. Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?

- d. Did you feel tired or without energy almost every day?

- e. Did you feel worthless or guilty almost every day?

- f. Did you have difficulty concentrating or making decisions almost every day?

- g. Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?

**ARE 5 OR MORE ANSWERS (A1-A3) CODED YES?**

**IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:**

#### A4 During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?

- a. During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?  
  - **NO** ✔ **YES**

- b. In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?

**MAJOR DEPRESSIVE EPISODE, RECURRENT**

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).
### MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(⇒ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

**IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3 = YES), EXPLORE THE FOLLOWING:**

<table>
<thead>
<tr>
<th>A5</th>
<th>Question</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IF NO: When something good happens does it fail to make you feel better, even temporarily?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IS EITHER A5a OR A5b CODED YES?

<table>
<thead>
<tr>
<th>A6</th>
<th>Question</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Did you feel regularly worse in the morning, almost every day?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td><strong>Is A3c coded YES (Psychomotor Retardation or Agitation)?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td><strong>Is A3a coded YES for Anorexia or Weight Loss?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Did you feel excessive guilt or guilt out of proportion to the reality of the situation?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARE 3 OR MORE A6 ANSWERS CODED YES?

**Major Depressive Episode with Melancholic Features Current**
### B. DYSTHYMIA

(⇒ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

If patient's symptoms currently meet criteria for major depressive episode, do not explore this module.

<table>
<thead>
<tr>
<th>B1</th>
<th>Have you felt sad, low or depressed most of the time for the last two years?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td>Was this period interrupted by your feeling OK for two months or more?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>B3</td>
<td><strong>During this period of feeling depressed most of the time:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Did your appetite change significantly?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>b</td>
<td>Did you have trouble sleeping or sleep excessively?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>c</td>
<td>Did you feel tired or without energy?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>d</td>
<td>Did you lose your self-confidence?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>e</td>
<td>Did you have trouble concentrating or making decisions?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>f</td>
<td>Did you feel hopeless?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**Are 2 or more B3 answers coded YES?**

<table>
<thead>
<tr>
<th>B4</th>
<th>Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?</th>
</tr>
</thead>
</table>
C. SUICIDALITY

In the past month did you:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Suffer any accident?</td>
<td>NO</td>
</tr>
<tr>
<td>C1a</td>
<td>Plan or intend to hurt yourself in that accident either passively or actively?</td>
<td>NO</td>
</tr>
<tr>
<td>C1b</td>
<td>Did you intend to die as a result of this accident?</td>
<td>NO</td>
</tr>
<tr>
<td>C2</td>
<td>Think that you would be better off dead or wish you were dead?</td>
<td>NO</td>
</tr>
<tr>
<td>C3</td>
<td>Want to harm yourself or to hurt or to injure yourself?</td>
<td>NO</td>
</tr>
<tr>
<td>C4</td>
<td>Think about suicide?</td>
<td>NO</td>
</tr>
</tbody>
</table>

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Intensity</th>
<th>Can you control these impulses and state that you will not act on them while in this program?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasionally</td>
<td>Mild</td>
<td>□</td>
</tr>
<tr>
<td>Often</td>
<td>Moderate</td>
<td>□</td>
</tr>
<tr>
<td>Very often</td>
<td>Severe</td>
<td>□</td>
</tr>
</tbody>
</table>

C5 | Have a suicide plan? | NO | YES | 8 |
C6 | Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die? | NO | YES | 9 |
C7 | Deliberately injure yourself without intending to kill yourself? | NO | YES | 4 |
C8 | Attempt suicide? | NO | YES | 10 |
  | Hoped to be rescued / survive | □ |
  | Expected / intended to die | □ |

In your lifetime:

C9 | Did you ever make a suicide attempt? | NO | YES | 4 |

IS AT LEAST 1 OF THE ABOVE (EXCEPT C1) CODED YES?

If yes, add the total number of points for the answers (C1-C9) checked 'YES' and specify the level of suicide risk as indicated in the diagnostic box:

- 1-3 points Low
- 4-6 points Moderate
- ≥ 7 points High

Make any additional comments about your assessment of this patient's current and near future suicide risk in the space below:

M.I.N.I. 5.0.0 (July 1, 2006)
D. (HYPO) MANIC EPISODE

(“” MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

<table>
<thead>
<tr>
<th>D1a</th>
<th>Have you ever had a period of time when you were feeling ‘up’ or ‘high’ or ‘hyper’ or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IF PATIENT’S PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY ‘UP’ OR ‘HIGH’ OR ‘HYPER’, CLARIFY AS FOLLOWS: By ‘up’ or ‘high’ or ‘hyper’ I mean: having elated mood, increased energy, needing less sleep, having rapid thoughts, being full of ideas, having an increase in productivity, motivation, creativity, or impulsive behavior.</td>
</tr>
<tr>
<td></td>
<td>IF NO, CODE NO TO D1b. IF YES ASK:</td>
</tr>
<tr>
<td>b</td>
<td>Are you currently feeling ‘up’ or ‘high’ or ‘hyper’ or full of energy?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D2a</th>
<th>Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared to other people, even in situations that you felt were justified?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IF NO, CODE NO TO D2b. IF YES ASK:</td>
</tr>
<tr>
<td>b</td>
<td>Are you currently feeling persistently irritable?</td>
</tr>
<tr>
<td></td>
<td>IS D1a OR D2a CODED YES?</td>
</tr>
</tbody>
</table>

| D3   | IF D1b OR D2b = YES: EXPLORE THE CURRENT AND THE MOST SYMPTOMATIC PAST EPISODE, OTHERWISE IF D1b AND D2b = NO: EXPLORE ONLY THE MOST SYMPTOMATIC PAST EPISODE |

During the times when you felt high, full of energy, or irritable did you:

<table>
<thead>
<tr>
<th>Current Episode</th>
<th>Past Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Feel that you could do things others couldn’t do, or that you were an especially important person?</td>
<td></td>
</tr>
<tr>
<td>IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH ADELUSIONAL IDEA.</td>
<td>No</td>
</tr>
<tr>
<td>b. Need less sleep (for example, felt rested after only a few hours sleep)?</td>
<td></td>
</tr>
<tr>
<td>c. Talk too much without stopping, or so fast that people had difficulty understanding?</td>
<td></td>
</tr>
<tr>
<td>d. Have racing thoughts?</td>
<td></td>
</tr>
<tr>
<td>e. Become easily distracted so that any little interruption could distract you?</td>
<td></td>
</tr>
<tr>
<td>f. Become so active or physically restless that others were worried about you?</td>
<td></td>
</tr>
<tr>
<td>g. Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?</td>
<td></td>
</tr>
</tbody>
</table>

M.I.N.I. 5.0.0 (July 1, 2006)
D3 (SUMMARY): ARE 3 OR MORE D3 ANSWERS CODED YES
(OR 4 OR MORE IF D1a IS NO IN RATING PAST EPISODE) AND D1b IS NO IN RATING CURRENT EPISODE
RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE
IRRITABLE MOOD ALONE REQUIRES 4 OF THE D3 SYMPTOMS
VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

D4 Did these symptoms last at least a week and cause significant problems at home, at work, socially, or at school, or were you hospitalized for these problems?

THE EPISODE EXPLORED WAS A:

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOMANIC EPISODE</td>
<td>MANIC EPISODE</td>
</tr>
</tbody>
</table>

IS D4 CODED NO?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT</td>
<td>PAST</td>
</tr>
</tbody>
</table>

IS D4 CODED YES?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT</td>
<td>PAST</td>
</tr>
</tbody>
</table>
E. PANIC DISORDER

(⇒ MEANS: CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

| E1 | a Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way? | NO | YES |
| E1 | b Did the spells surge to a peak within 10 minutes of starting? | NO | YES |

| E2 | At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner? | NO | YES |

| E3 | Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?) | NO | YES |

| E4 | During the worst spell that you can remember: |
| E4 | a Did you have skipping, racing or pounding of your heart? | NO | YES |
| E4 | b Did you have sweating or clammy hands? | NO | YES |
| E4 | c Were you trembling or shaking? | NO | YES |
| E4 | d Did you have shortness of breath or difficulty breathing? | NO | YES |
| E4 | e Did you have a choking sensation or a lump in your throat? | NO | YES |
| E4 | f Did you have chest pain, pressure or discomfort? | NO | YES |
| E4 | g Did you have nausea, stomach problems or sudden diarrhea? | NO | YES |
| E4 | h Did you feel dizzy, unsteady, lightheaded or faint? | NO | YES |
| E4 | i Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body? | NO | YES |
| E4 | j Did you fear that you were losing control or going crazy? | NO | YES |
| E4 | k Did you fear that you were dying? | NO | YES |
| E4 | l Did you have tingling or numbness in parts of your body? | NO | YES |
| E4 | m Did you have hot flushes or chills? | NO | YES |

| E5 | ARE BOTH E3, AND 4 OR MORE E4 ANSWERS, CODED YES? | NO | YES

⇒ IF YES TO E5, SKIP TO E7.

| E6 | IF E5 = NO, ARE ANY E4 ANSWERS CODED YES? | NO | YES

⇒ THEN SKIP TO F1.

| E7 | In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack? | NO | YES

MLNI 5.0.0 (July 1, 2006)
F. AGORAPHOBIA

F1  Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?  

  NO  YES

IF F1 = NO, CIRCLE NO IN F2.

F2  Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?  

  NO  YES

IS F2 (CURRENT AGORAPHOBIA) CODED NO

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO  YES  

PANIC DISORDER without Agoraphobia CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E7 (CURRENT PANIC DISORDER) CODED YES?

NO  YES  

PANIC DISORDER with Agoraphobia CURRENT

IS F2 (CURRENT AGORAPHOBIA) CODED YES

and

IS E5 (PANIC DISORDER LIFETIME) CODED NO

NO  YES  

AGORAPHOBIA, CURRENT without history of Panic Disorder
G. SOCIAL PHOBIA (Social Anxiety Disorder)

(⇒ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

31. In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.

32. Is this social fear excessive or unreasonable?

33. Do you fear these social situations so much that you avoid them or suffer through them?

34. Do these social fears disrupt your normal work or social functioning or cause you significant distress?

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES  Generalized social phobia (social anxiety disorder)

If NO   Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT’S FEARS ARE RESTRICTED TO NON-GENERALIZED (“ONLY 1 OR SEVERAL”) SOCIAL SITUATIONS OR EXTEND TO GENERALIZED (“MOST”) SOCIAL SITUATIONS. “MOST” SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONS TYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.
### H. OBSESSIVE-COMPULSIVE DISORDER

( SYMBOL: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

| H1 | In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn't want to, or fearing you would act on some impulse, or fear of superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hearing, collecting, or religious obsessions.)  NO | YES | SKIP TO H4 |

| H2 | Did they keep coming back into your mind even when you tried to ignore or get rid of them?  NO | YES |

| H3 | Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?  NO | YES |

| H4 | In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?  NO | YES |

| IS H3 OR H4 CODED YES? |  NO | YES |

| H5 | Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?  NO | YES |

| H6 | Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?  NO | YES | O.C.D. CURRENT |

**MINI 5.0.0 (July 1, 2006)**
### I. POSTTRAUMATIC STRESS DISORDER (optional)

**MEAN:** GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else?</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Did you respond with intense fear, helplessness or horror?</td>
<td>NO</td>
</tr>
<tr>
<td>13</td>
<td>During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?</td>
<td>NO</td>
</tr>
</tbody>
</table>

### In the past month:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Have you avoided thinking about or talking about the event?</td>
<td>NO</td>
</tr>
<tr>
<td>b</td>
<td>Have you avoided activities, places or people that remind you of the event?</td>
<td>NO</td>
</tr>
<tr>
<td>c</td>
<td>Have you had trouble recalling some important part of what happened?</td>
<td>NO</td>
</tr>
<tr>
<td>d</td>
<td>Have you become much less interested in hobbies or social activities?</td>
<td>NO</td>
</tr>
<tr>
<td>e</td>
<td>Have you felt detached or estranged from others?</td>
<td>NO</td>
</tr>
<tr>
<td>f</td>
<td>Have you noticed that your feelings are numbed?</td>
<td>NO</td>
</tr>
<tr>
<td>g</td>
<td>Have you felt that your life will be shortened or that you will die sooner than other people?</td>
<td>NO</td>
</tr>
</tbody>
</table>

**ARE 3 OR MORE 14 ANSWERS CODED YES?**

### In the past month:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Have you had difficulty sleeping?</td>
<td>NO</td>
</tr>
<tr>
<td>b</td>
<td>Were you especially irritable or did you have outbursts of anger?</td>
<td>NO</td>
</tr>
<tr>
<td>c</td>
<td>Have you had difficulty concentrating?</td>
<td>NO</td>
</tr>
<tr>
<td>d</td>
<td>Were you nervous or constantly on your guard?</td>
<td>NO</td>
</tr>
<tr>
<td>e</td>
<td>Were you easily startled?</td>
<td>NO</td>
</tr>
</tbody>
</table>

**ARE 2 OR MORE 15 ANSWERS CODED YES?**

### During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?

---

M.I.N.I. 5.0.0 (July 1, 2006)
### J. ALCOHOL ABUSE AND DEPENDENCE

(➔ MEAN: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

<table>
<thead>
<tr>
<th>J1</th>
<th>In the past 12 months, have you had 3 or more alcoholic drinks within a 3-hour period on 3 or more occasions?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2</td>
<td><strong>In the past 12 months:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Did you need to drink more in order to get the same effect that you got when you first started drinking?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>b</td>
<td>When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, &quot;the shakes&quot;, sweating or agitation? IF YES TO EITHER, CODE YES.</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>c</td>
<td>During the times when you drank alcohol, did you end up drinking more than you planned when you started?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>d</td>
<td>Have you tried to reduce or stop drinking alcohol but failed?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>e</td>
<td>On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>f</td>
<td>Did you spend less time working, enjoying hobbies, or being with others because of your drinking?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>g</td>
<td>Have you continued to drink even though you knew that the drinking caused you health or mental problems?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**ARE 3 OR MORE J2 ANSWERS CODED YES?**

* IF YES, SKIP J3 QUESTIONS, CIRCLE NA IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

### J3

<table>
<thead>
<tr>
<th>J3</th>
<th>In the past 12 months:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Have you been intoxicated, high, or hung over more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THE CAUSED PROBLEMS.)</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>b</td>
<td>Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>c</td>
<td>Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>d</td>
<td>Did you continue to drink even though your drinking caused problems with your family or other people?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**ARE 1 OR MORE J3 ANSWERS CODED YES?**
K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(⇒ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you/read to you a list of street drugs or medicines.

<table>
<thead>
<tr>
<th>K1</th>
<th>a</th>
<th>In the past 12 months, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

CIRCLE EACH RISK TAKEN


Cocaine: maring, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("Special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Secobar ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Metha, GHB, Roofingl, "Roofers".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): ____________________________________________

ONLY ONE DRUG/DRUG CLASS HAS BEEN USED

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED.

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED)

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXAMINED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:

K2 Considering your use of (NAME THE DRUG/DRUG CLASS SELECTED) in the past 12 months:

a Have you found that you needed to use more (NAME OF DRUG/DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it? NO YES

b When you reduced or stopped using (NAME OF DRUG/DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shakiness, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?

IF YES TO EITHER, CODE YES.

c Have you often found that when you used (NAME OF DRUG/DRUG CLASS SELECTED), you ended up taking more than you thought you would? NO YES

d Have you tried to reduce or stop taking (NAME OF DRUG/DRUG CLASS SELECTED) but failed? NO YES

e On the days that you used (NAME OF DRUG/DRUG CLASS SELECTED) but failed, did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug? NO YES

M.I.N.I. 5.0.0 (July 1, 2006) 17
f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use?  

NO  YES

g Have you continued to use (NAME OF DRUG/DRUG CLASS SELECTED), even though it caused you health or mental problems?

NO  YES

ARE 3 OR MORE K2 ANSWERS CODED YES?

SPECIFY DRUG(S): ____________________________

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3

a Have you been intoxicated, high, or hungover from (NAME OF DRUG/DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem?

NO  YES

(CODE YES ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG/DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motobike, using machinery, boating, etc. )?

NO  YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct?

NO  YES

d Did you continue to use (NAME OF DRUG/DRUG CLASS SELECTED), even though it caused problems with your family or other people?

NO  YES

ARE 1 OR MORE K3 ANSWERS CODED YES?

SPECIFY DRUG(S): ____________________________

NO  N/A  YES

SUBSTANCE ABUSE CURRENT
L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

Now I am going to ask you about unusual experiences that some people have.

L1 a Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you?

   NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.

   IF YES OR YES BIZARRE: do you currently believe these things?

L2 a Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?

   IF YES OR YES BIZARRE: do you currently believe these things?

L3 a Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed?

   CLINICIAN: ASK FOR EXAMPLES AND DISCLOSE ANY THAT ARE NOT PSYCHOTIC.

   IF YES OR YES BIZARRE: do you currently believe these things?

L4 a Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?

   IF YES OR YES BIZARRE: do you currently believe these things?

L5 a Have your relatives or friends ever considered any of your beliefs strange or unusual?

   INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE YES IF THE EXAMPLES ARE CLEARLY DELUSIONAL IDEAS NOT EXPLORATED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSE, GUILT, GUILT, GUILT, OR DESTINATION, ETC.

   IF YES OR YES BIZARRE: do they currently consider your beliefs strange?

L6 a Have you ever heard things other people couldn't hear, such as voices?

   HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:

   IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?

   IF YES OR YES BIZARRE TO L6a: have you heard these things in the past month?

   HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?
Have you ever had visions when you were awake or have you ever seen things other people couldn’t see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b  **IF YES:** have you seen these things in the past month?

**CLINICIAN’S JUDGMENT**

b  **IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?**

b  **IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?**

b  **ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?**

b  **ARE 1 OR MORE <a> QUESTIONS FROM L1a TO L7a CODED YES OR YES BIZARRE AND IS EITHER:**

  - **MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)**
  - **OR MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES?**

  **IF NO TO L11 a, CIRCLE NO IN BOTH “MOOD DISORDER WITH PSYCHOTIC FEATURES” DIAGNOSTIC BOXES AND MOVE TO L13.**

b  You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM L1a TO L7a) restricted exclusively to times when you were feeling depressed/high/irritable?

**IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, Code NO TO THIS DISORDER.**

**IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13**

**M.I.N.I. 5.0.0 (July 1, 2006)**
### L13

**Are 1 or more «b» questions from L1b to L6b, coded **YES BIZARRE**?**

**OR**

Are 2 or more «b» questions from L1b to L10b, coded **YES (rather than YES BIZARRE)**?

And did at least two of the psychotic symptoms occur during the same 1 month period?

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PsycHOTIC DISORDER CURRENT</strong></td>
<td></td>
</tr>
</tbody>
</table>

### L14

**Is L13 coded **YES**?**

**OR**

Are 1 or more «a» questions from L1a to L6a, coded **YES BIZARRE**?

**OR**

Are 2 or more «a» questions from L1a to L7a, coded **YES (rather than YES BIZARRE)**

And did at least two of the psychotic symptoms occur during the same 1 month period?

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PsycHOTIC DISORDER LIFETIME</strong></td>
<td></td>
</tr>
</tbody>
</table>
### M. ANOREXIA NERVOSA

**MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE**

<table>
<thead>
<tr>
<th>M1</th>
<th>How tall are you?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ft</td>
</tr>
<tr>
<td></td>
<td>cm.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M1</th>
<th>What was your lowest weight in the past 3 months?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lbs.</td>
</tr>
<tr>
<td></td>
<td>kgs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M1</th>
<th>IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

**In the past 3 months:**

<table>
<thead>
<tr>
<th>M2</th>
<th>In spite of this low weight, have you tried not to gain weight?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M3</th>
<th>Have you intensely feared gaining weight or becoming fat, even though you were underweight?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M4</th>
<th>Have you considered yourself too big / fat or that part of your body was too big / fat?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M4</th>
<th>Has your body weight or shape greatly influenced how you felt about yourself?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M5</th>
<th>ARE 1 OR MORE ITEMS FROM M4 CODED YES?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M6</th>
<th>FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

**FOR WOMEN:** ARE M5 AND M6 CODED YES?  
**FOR MEN:** IS M5 CODED YES?

**ANOREXIA NERVOSA CURRENT**

### HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 kg/m²

<table>
<thead>
<tr>
<th>Height/Weight</th>
<th>ft/in.</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>49</td>
<td>145</td>
</tr>
<tr>
<td>lbs.</td>
<td>81</td>
<td>37</td>
</tr>
<tr>
<td>lbs.</td>
<td>84</td>
<td>38</td>
</tr>
<tr>
<td>lbs.</td>
<td>87</td>
<td>147</td>
</tr>
<tr>
<td>lbs.</td>
<td>89</td>
<td>150</td>
</tr>
<tr>
<td>lbs.</td>
<td>92</td>
<td>152</td>
</tr>
<tr>
<td>lbs.</td>
<td>96</td>
<td>155</td>
</tr>
<tr>
<td>lbs.</td>
<td>99</td>
<td>158</td>
</tr>
<tr>
<td>lbs.</td>
<td>102</td>
<td>160</td>
</tr>
<tr>
<td>lbs.</td>
<td>105</td>
<td>165</td>
</tr>
<tr>
<td>lbs.</td>
<td>108</td>
<td>168</td>
</tr>
<tr>
<td>lbs.</td>
<td>112</td>
<td>170</td>
</tr>
<tr>
<td>lbs.</td>
<td>115</td>
<td>173</td>
</tr>
<tr>
<td>lbs.</td>
<td>118</td>
<td>175</td>
</tr>
<tr>
<td>lbs.</td>
<td>122</td>
<td>178</td>
</tr>
<tr>
<td>kgs.</td>
<td>37</td>
<td>145</td>
</tr>
<tr>
<td>kgs.</td>
<td>38</td>
<td>147</td>
</tr>
<tr>
<td>kgs.</td>
<td>39</td>
<td>150</td>
</tr>
<tr>
<td>kgs.</td>
<td>41</td>
<td>152</td>
</tr>
<tr>
<td>kgs.</td>
<td>42</td>
<td>155</td>
</tr>
<tr>
<td>kgs.</td>
<td>43</td>
<td>158</td>
</tr>
<tr>
<td>kgs.</td>
<td>45</td>
<td>160</td>
</tr>
<tr>
<td>kgs.</td>
<td>46</td>
<td>165</td>
</tr>
<tr>
<td>kgs.</td>
<td>48</td>
<td>168</td>
</tr>
<tr>
<td>kgs.</td>
<td>49</td>
<td>170</td>
</tr>
<tr>
<td>kgs.</td>
<td>51</td>
<td>173</td>
</tr>
<tr>
<td>kgs.</td>
<td>52</td>
<td>175</td>
</tr>
<tr>
<td>kgs.</td>
<td>54</td>
<td>178</td>
</tr>
<tr>
<td>kgs.</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height/Weight</th>
<th>ft/in.</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td>51</td>
<td>180</td>
</tr>
<tr>
<td>lbs.</td>
<td>125</td>
<td>183</td>
</tr>
<tr>
<td>lbs.</td>
<td>129</td>
<td>185</td>
</tr>
<tr>
<td>lbs.</td>
<td>132</td>
<td>188</td>
</tr>
<tr>
<td>lbs.</td>
<td>136</td>
<td>191</td>
</tr>
<tr>
<td>lbs.</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>kgs.</td>
<td>57</td>
<td>180</td>
</tr>
<tr>
<td>kgs.</td>
<td>59</td>
<td>183</td>
</tr>
<tr>
<td>kgs.</td>
<td>60</td>
<td>185</td>
</tr>
<tr>
<td>kgs.</td>
<td>62</td>
<td>188</td>
</tr>
<tr>
<td>kgs.</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m² for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.
# N. BULIMIA NERVOsa

(⇒ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N2</td>
<td>In the last 3 months, did you have eating binges as often as twice a week?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N3</td>
<td>During these binges, did you feel that your eating was out of control?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N4</td>
<td>Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N5</td>
<td>Does your body weight or shape greatly influence how you feel about yourself?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N6</td>
<td>DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOsa?</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>Skip to N8</td>
</tr>
<tr>
<td>N7</td>
<td>Do these binges occur only when you are under ( ____ lbs/ ____ kg)?</td>
</tr>
<tr>
<td>Interviewer: Write in the above patient's the threshold weight for the patient's height from the height/weight table in the Anorexia Nervosa module</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>N8</td>
<td>IS N5 CODED YES AND IS EITHER N6 OR N7 CODED NO?</td>
</tr>
<tr>
<td></td>
<td>BULIMIA NERVOsa CURRENT</td>
</tr>
<tr>
<td>IS N7 CODED YES?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>ANOREXIA NERVOsa Binge Eating/Purging Type CURRENT</td>
</tr>
</tbody>
</table>
## O. GENERALIZED ANXIETY DISORDER

(● MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

<table>
<thead>
<tr>
<th>O1</th>
<th>a. Have you worried excessively or been anxious about several things over the past 6 months?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. Are these worries present most days?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

| O2  | Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing? | NO | YES |

| O3  | FOR THE FOLLOWING, CODE NO IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT. |    |     |

**When you were anxious over the past 6 months, did you, most of the time:**

<table>
<thead>
<tr>
<th>a</th>
<th>Feel restless, keyed up or on edge?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>Feel tense?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>c</td>
<td>Feel tired, weak or exhausted easily?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>d</td>
<td>Have difficulty concentrating or find your mind going blank?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>e</td>
<td>Feel irritable?</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>f</td>
<td>Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**ARE 3 OR MORE O3 ANSWERS CODED YES?**

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
</table>

**GENERALIZED ANXIETY DISORDER CURRENT**
P. ANTISOCIAL PERSONALITY DISORDER (optional)

(● MEANS: GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1  Before you were 15 years old, did you:

a. repeatedly skip school or run away from home overnight?  NO   YES
b. repeatedly lie, cheat, "con" others, or steal?  NO   YES
c. start fights or bully, threaten, or intimidate others?  NO   YES
d. deliberately destroy things or start fires?  NO   YES
e. deliberately hurt animals or people?  NO   YES
f. force someone to have sex with you?  NO  ● YES

ARE 2 OR MORE P1 ANSWERS CODED YES?  NO   YES

DO NOT CODE YES TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2  Since you were 15 years old, have you:

a. repeatedly been treated in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?  NO   YES
b. done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?  NO   YES
c. been in physical fights repeatedly (including physical fights with your spouse or children)?  NO   YES
d. often lied or "conned" other people to get money or pleasure, or lied just for fun?  NO   YES
e. exposed others to danger without caring?  NO   YES
f. felt no guilt after hurting, mistreating,lying to, or stealing from others, or after damaging property?  NO   YES

ARE 3 OR MORE P2 QUESTIONS CODED YES?  NO   YES

ANTISOCIAL PERSONALITY DISORDER LIFETIME

THIS CONCLUDES THE INTERVIEW

M.I.N.I. 5.0.0 (July 1, 2006)  25
# EATING QUESTIONNAIRE

Instructions: The following questions are concerned with the past four weeks (28 days) only. Please read each question carefully. Please answer all the questions. Thank you.

Questions 1 to 12: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days) only.

<table>
<thead>
<tr>
<th>Question</th>
<th>No days</th>
<th>1-5 days</th>
<th>6-12 days</th>
<th>13-15 days</th>
<th>16-22 days</th>
<th>23-27 days</th>
<th>Every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you been deliberately trying to limit the amount of food you eat to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2. Have you gone for long periods of time (8 waking hours or more) without eating anything at all in order to influence your shape or weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>3. Have you tried to exclude from your diet any foods that you like in order to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>4. Have you tried to follow definite rules regarding your eating (for example, a calorie limit) in order to influence your shape or weight (whether or not you have succeeded)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5. Have you had a definite desire to have an empty stomach with the aim of influencing your shape or weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6. Have you had a definite desire to have a totally flat stomach?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7. Has thinking about food, eating or calories made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>8. Has thinking about shape or weight made it very difficult to concentrate on things you are interested in (for example, working, following a conversation, or reading)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>9. Have you had a definite fear of losing control over eating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10. Have you had a definite fear that you might gain weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>11. Have you felt fat?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>12. Have you had a strong desire to lose weight?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Questions 13-18: Please fill in the appropriate number in the boxes on the right. Remember that the questions only refer to the past four weeks (28 days).

**Over the past four weeks (28 days) ......**

<table>
<thead>
<tr>
<th>Question</th>
<th>No days</th>
<th>1-5 days</th>
<th>6-12 days</th>
<th>13-15 days</th>
<th>16-22 days</th>
<th>23-27 days</th>
<th>Every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 Over the past 28 days, how many times have you eaten what other people would regard as an unusually large amount of food (given the circumstances)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 ...... On how many of these times did you have a sense of having lost control over your eating (at the time that you were eating)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Over the past 28 days, on how many DAYS have such episodes of overeating occurred (i.e., you have eaten an unusually large amount of food and have had a sense of loss of control at the time)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Over the past 28 days, how many times have you made yourself sick (vomit) as a means of controlling your shape or weight?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 Over the past 28 days, how many times have you taken laxatives as a means of controlling your shape or weight?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Over the past 28 days, how many times have you exercised in a “driven” or “compulsive” way as a means of controlling your weight, shape or amount of fat, or to burn off calories?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questions 19 to 21: Please circle the appropriate number. Please note that for these questions the term “binge eating” means eating what others would regard as an unusually large amount of food for the circumstances, accompanied by a sense of having lost control over eating.

<table>
<thead>
<tr>
<th>Question</th>
<th>None of the times</th>
<th>A few of the times</th>
<th>Less than half of the times</th>
<th>Half of the times</th>
<th>More than half of the times</th>
<th>Most of the time</th>
<th>Every time</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Over the past 28 days, on how many days have you eaten in secret (ie, furtively)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>...... Do not count episodes of binge eating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 On what proportion of the times that you have eaten have you felt guilty (felt that you've done wrong) because of its effect on your shape or weight?</td>
<td>None of the times</td>
<td>A few of the times</td>
<td>Less than half of the times</td>
<td>Half of the times</td>
<td>More than half of the times</td>
<td>Most of the time</td>
<td>Every time</td>
</tr>
<tr>
<td>...... Do not count episodes of binge eating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>21 Over the past 28 days, how concerned have you been about other people seeing you eat?</td>
<td>Not at all</td>
<td>Slightly</td>
<td>Moderately</td>
<td>Markedly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...... Do not count episodes of binge eating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Questions 22 to 28: Please circle the appropriate number on the right. Remember that the questions only refer to the past four weeks (28 days).

<table>
<thead>
<tr>
<th>Over the past 28 days ....</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Markedly</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Has your <strong>weight</strong> influenced how you think about (judge) yourself as a person?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>23 Has your <strong>shape</strong> influenced how you think about (judge) yourself as a person?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>24 How much would it have upset you if you had been asked to weigh yourself once a week (no more, or less, often) for the next four weeks?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>25 How dissatisfied have you been with your <strong>weight</strong>?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>26 How dissatisfied have you been with your <strong>shape</strong>?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>27 How uncomfortable have you felt seeing your body (for example, seeing your shape in the mirror, in a shop window reflection, while undressing or taking a bath or shower)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>28 How uncomfortable have you felt about others seeing your shape or figure (for example, in communal changing rooms, when swimming, or wearing tight clothes)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

What is your weight at present? (Please give your best estimate) ...........................................

What is your height? (Please give your best estimate) ..................................................

If female: Over the past three-to-four months have you missed any menstrual periods? ...........

If so, how many? ..........................................

Have you been taking the “pill”? ..........................................

THANK YOU
Please respond to the following questions by circling the appropriate figure number:

1. Please choose your *ideal* figure
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

2. Please choose the figure that reflects how you *think* you look
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

3. Please choose the figure that reflect how you *feel* most of the time
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

4. Please choose the figure that you think is most preferred by men
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

5. Please choose the figure that you think is most preferred by women
   
   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
Montgomery Asberg Depression Rating Scale

- Use the script as a guide, and probe as necessary to determine severity of symptoms.
- Ask ALL questions, even if patient reports no symptoms upon initial questioning. The script was designed to capture all potential symptoms of an item.
- Ask all questions in a clear time frame, usually the past week.
- Distinguish between apparent sadness (item 1) and reported sadness (item 2). Note that apparent sadness is recorded by observation at time of interview only, while reported sadness encompasses the entire week.
- Do not rate improvement from assessment to assessment. Use anchor points to rate CURRENT SEVERITY, no matter level of improvement.

Introduction: "I’d like to ask you some questions about the past week. How have you been feeling since last (day of the week)? Have you been working? Why not? I will now be asking you questions to rate symptoms you may have had during the past week.

<table>
<thead>
<tr>
<th>1. Apparent Sadness</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on OBSERVATION from interview.</td>
<td>None.</td>
<td>Looks dispirited but brightens up.</td>
<td>Sad and unhappy most of the time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representing despondency, gloom and despair (more than just transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Reported Sadness</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>How’s your mood been the past week? Have you been feeling down or depressed?</td>
<td>Occasional sadness in keeping with the circumstances</td>
<td>Sad or low but brightens up without difficulty.</td>
<td></td>
<td>Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the last week, how often have you felt (own equivalent)? Every day? All day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel better when pleasant things happen? (often, occasionally, never)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can a good joke brighten your mood?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there anything that can make you feel better, even briefly?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Inner Tension</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you been feeling especially nervous or tense this past week?</td>
<td>Placid. Only feeling inner tension.</td>
<td>Occasional feelings of edginess and ill-defined discomfort.</td>
<td></td>
<td>Continuous feelings of inner tension or intermittent panic, which patient can master only with some difficulty.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much has this made you uncomfortable?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel tension and edginess only some of the time?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you been able to handle this tension?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Script by Gary S. Sachs, M.D. and Noreen Reilly Harrington, Ph.D.
### Montgomery Asberg Depression Rating Scale

**Subject ID:___________**  
**Date: ______/_____/______**

#### 4. Reduced Sleep

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Sleeps as usual.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sleep reduced or broken by at least 2 hours.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Less than 2 or 3 hours of sleep.</td>
<td></td>
</tr>
</tbody>
</table>

#### 5. Reduced Appetite

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal or increased appetite</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Slightly reduced appetite</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No appetite</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Needs persuasion to eat at all</td>
<td></td>
</tr>
</tbody>
</table>

#### 6. Concentration Difficulties

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No difficulties concentrating.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Occasional difficulties in collecting one's thoughts.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Difficulties in concentrating and sustaining thought which reduces the ability to read or hold a conversation.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Unable to read or converse without great difficulty.</td>
<td></td>
</tr>
</tbody>
</table>

#### 7. Lassitude

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Hardly any difficulty getting started. No sluggishness.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Difficulties starting activities.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Difficulties in starting simple routines which are carried out with effort.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Complete lassitude. Unable to do anything without help.</td>
<td></td>
</tr>
</tbody>
</table>

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**8. Inability to Feel**

How have you been spending your time this week (when not at work)?

- 0 Normal interest in the surroundings and other people.
- 1 Reduced ability to enjoy usual interests.
- 2 Loss of interest in surroundings. Loss of feelings for friends/acquaintances.
- 3 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

Have you felt interested in doing (those things) or do you feel you have to push yourself to do them?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Have you stopped doing anything you used to do? *IF YES,* why?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Was there anything you were able to enjoy, even a little?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Have you lost interest in friends or acquaintances? 

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

*IF YES:* Were there times you could connect with them emotionally, even a little?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

---

**9. Pessimistic Thoughts**

During the past week, have you been pessimistic about the future?

- 0 No pessimistic thoughts
- 1 Fluctuating ideas of failure, self-reproach or self-deprecation.
- 2 Persistent self-accusations, or definite but still rational ideas of guilt or sin, increasingly pessimistic about the future.
- 3 Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd or unshakable.

How often do you feel this way?

- 0
- 1
- 2
- 3
- 4
- 5

Have there been times this week that you’ve felt you let others down, or have done things wrong?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Have you been unusually hard on yourself this past week?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

---

**10. Suicidal Thoughts**

This past week, have you had any thoughts that life is not worth living, or that you’d be better off dead?

- 0 Enjoys life or takes it as it comes.
- 1 Weary of life. Only fleeting suicidal thoughts.
- 2 Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.
- 3 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

How often do you think about suicide?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Did you make any plans to commit suicide in the past week?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

Do you plan to commit suicide?

- Yes
  - 0
  - 1
  - 2
  - 3
  - 4
  - 5

---

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Script by Gary S. Sachs, M.D. and Noreen Reilly Harrington, Ph.D.
# DASS

**Name:**

**Date:**

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:*

<table>
<thead>
<tr>
<th>Number</th>
<th>Statement</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Did not apply to me at all</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Applied to me to some degree, or some of the time</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Applied to me to a considerable degree, or a good part of time</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Applied to me very much, or most of the time</td>
<td></td>
</tr>
</tbody>
</table>

1. I found myself getting upset by quite trivial things
2. I was aware of dryness of my mouth
3. I couldn't seem to experience any positive feeling at all
4. I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)
5. I just couldn't seem to get going
6. I tended to over-react to situations
7. I had a feeling of shakiness (eg, legs going to give way)
8. I found it difficult to relax
9. I found myself in situations that made me so anxious I was most relieved when they ended
10. I felt that I had nothing to look forward to
11. I found myself getting upset rather easily
12. I felt that I was using a lot of nervous energy
13. I felt sad and depressed
14. I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)
15. I had a feeling of faintness
16. I felt that I had lost interest in just about everything
17. I felt I wasn't worth much as a person
18. I felt that I was rather touchy
19. I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion
20. I felt scared without any good reason
21. I felt that life wasn't worthwhile

*Please turn the page →*
<table>
<thead>
<tr>
<th>Question</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>I found it hard to wind down</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I had difficulty in swallowing</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I couldn't seem to get any enjoyment out of the things I did</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I felt down-hearted and blue</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I found that I was very irritable</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I felt I was close to panic</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I found it hard to calm down after something upset me</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I feared that I would be &quot;thrown&quot; by some trivial but unfamiliar task</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I was unable to become enthusiastic about anything</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I found it difficult to tolerate interruptions to what I was doing</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I was in a state of nervous tension</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I felt I was pretty worthless</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I was intolerant of anything that kept me from getting on with what I was doing</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I felt terrified</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I could see nothing in the future to be hopeful about</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I felt that life was meaningless</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I found myself getting agitated</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I was worried about situations in which I might panic and make a fool of myself</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I experienced trembling (e.g., in the hands)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>I found it difficult to work up the initiative to do things</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>
PDQ-4
Personality Questionnaire

Instructions

The purpose of this questionnaire is for you to describe the kind of person you are. When answering the questions, think about how you have tended to feel, think, and act over the past several years. To remind you of this, on the top of each page you will find the statement: “Over the past several years…”

Please answer either True or False to each item.

Where:
T (True) means that the statement is generally true for you.
F (False) means that the statement is generally false for you.

Even if you are not entirely sure about the answer, indicate “T” or “F” for every question.

For example, for the question:

X. I tend to be stubborn.

T  F

If in fact you have been stubborn over the past several years, you would answer True by circling T.

If this was not true at all for you, you would answer False by circling F.

There are no correct answers.

You make take as much time as you wish.
Over the past several years...

1. I avoid working with others who may criticise me. T F
2. I can't make decisions without the advice, or reassurance, of others. T F
3. I often get lost in details and lose sight of the "big picture". T F
4. I need to be the centre of attention. T F
5. I have accomplished far more than others give me credit for. T F
6. I'll go to extremes to prevent those who I love from ever leaving me. T F

Over the past several years...

7. Others have complained that I do not keep up with my work or commitments. T F
8. I've been in trouble with the law several times (or would have been if I had been caught). T F
9. Spending time with family or friends just doesn't interest me. T F
10. I get special messages from things happening around me. T F
11. I know that people will take advantage of me, or try to cheat me, if I let them. T F
12. Sometimes I get upset. T F
Over the past several years...

13. I make friends with people only when I am sure they like me. T F

14. I am usually depressed T F

15. I prefer that other people assume responsibility for me. T F

16. I waste time trying to make things too perfect. T F

17. I am "sexier" than most people. T F

18. I often find myself thinking about how great a person I am, or will be. T F

19. I either love someone or hate them, with nothing in between. T F

20. I get into a lot of physical fights. T F

21. I feel that others don't understand or appreciate me. T F

22. I would rather do things by myself than with other people. T F

23. I have the ability to know that some things will happen before they actually do. T F

24. I often wonder whether the people I know can really be trusted. T F
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Occasionally I talk about people behind their backs.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>I am inhibited in my intimate relationships because I am afraid of being ridiculed.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>I fear losing the support of others if I disagree with them.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>I have many shortcomings.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>I put my work ahead of being with my family or friends or having fun.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>I show my emotions easily.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Only certain special people can really appreciate and understand me.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>I often wonder who I really am.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>I have difficulty paying bills because I don't stay at any one job for very long.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Sex just doesn't interest me.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Others consider me moody and 'hot tempered'.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>I can often sense, or feel things, that others can't.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Over the past several years...

37. Others will use what I tell them against me.  T  F

38. There are some people I don't like.  T  F

39. I am more sensitive to criticism or rejection than most people.  T  F

40. I find it difficult to start something if I have to do it by myself.  T  F

41. I have a higher sense of morality than other people.  T  F

42. I am my own worst critic.  T  F

Over the past several years...

43. I use my "looks" to get the attention that I need.  T  F

44. I very much need other people to take notice of me or compliment me.  T  F

45. I have tried to hurt or kill myself.  T  F

46. I do a lot of things without considering the consequences.  T  F

47. There are few activities that I have any interest in.  T  F

48. People often have difficulty understanding what I say.  T  F
Over the past several years...

49. I object to supervisors telling me how I should do my job  T  F

50. I keep alert to figure out the real meaning of what people are saying.  T  F

51. I have never told a lie  T  F

52. I am afraid to meet new people because I feel inadequate.  T  F

53. I want people to like me so much that I volunteer to do things that I’d rather not do.  T  F

54. I have accumulated lots of things that I don’t need but I can’t bear to throw out.  T  F

55. Even though I talk a lot, people say that I have trouble getting to the point.  T  F

56. I worry a lot.  T  F

57. I expect other people to do favours for me even though I do not usually do favours for them.  T  F

58. I am a very moody person.  T  F

59. Lying comes easily to me and I often do it.  T  F

60. I am not interested in having close friends.  T  F
### Over the past several years...

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>61.</td>
<td>I am often on guard against being taken advantage of.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62.</td>
<td>I never forget, or forgive, those who do me wrong.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63.</td>
<td>I resent those who have more &quot;luck&quot; than I.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.</td>
<td>A nuclear war may not be such a bad idea.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.</td>
<td>When alone, I feel helpless and unable to care for myself.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.</td>
<td>If others can't do things correctly, I would prefer to do them myself.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Over the past several years...

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>67.</td>
<td>I have a flair for the dramatic.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.</td>
<td>Some people think that I take advantage of others.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69.</td>
<td>I feel that my life is dull and meaningless.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70.</td>
<td>I am critical of others.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.</td>
<td>I don't care what others have to say about me.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.</td>
<td>I have difficulties relating in a one-to-one situation.</td>
<td>T</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Over the past several years...

73. People have often complained that I did not realise that they were upset. T F

74. By looking at me, people might think that I'm pretty odd, eccentric or weird. T F

75. I enjoy doing risky things. T F

76. I have lied a lot on this questionnaire. T F

77. I complain a lot about my hardships. T F

78. I have difficulty controlling my anger, or temper. T F

79. Some people are jealous of me. T F

80. I am easily influenced by others T F

81. I see myself as thrifty but others see me as being cheap. T F

82. When a close relationship ends, I need to get involved with someone else immediately. T F

83. I suffer from low self-esteem. T F

84. I am a pessimist. T F
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Over the past several years...</strong></td>
<td><strong>Over the past several years...</strong></td>
<td></td>
</tr>
<tr>
<td>85. I waste no time in getting back at people who insult me.</td>
<td>91. I can be nasty with someone one minute, then find myself apologising to them the next minute.</td>
<td></td>
</tr>
<tr>
<td>86. Being around other people makes me nervous.</td>
<td>92. Others consider me to be stuck up.</td>
<td></td>
</tr>
<tr>
<td>87. In new situations, I fear being embarrassed.</td>
<td>93. When stressed, things happen. Like I get paranoid or just “black out”.</td>
<td></td>
</tr>
<tr>
<td>88. I am terrified of being left to care for myself.</td>
<td>94. I don’t care if others get hurt so long as I get what I want.</td>
<td></td>
</tr>
<tr>
<td>89. People complain that I’m “stubborn as a mule”.</td>
<td>95. I keep my distance from others.</td>
<td></td>
</tr>
<tr>
<td>90. I take relationships more seriously than do those who I’m involved with.</td>
<td>96. I often wonder whether my (husband, girlfriend, or boyfriend) has been unfaithful to me.</td>
<td></td>
</tr>
</tbody>
</table>

-17-
Over the past several years...

97. I often feel guilty. T F

98. I have done things on impulse (such as those below) that could have gotten me into trouble.

If you answered True, please check all that apply to you:

a. Spending more money than I have
b. Having sex with people I hardly know
c. Drinking too much
d. Taking drugs
e. Going on eating binges
g. Reckless driving

99. When I was a kid (before age 15), I was somewhat of a juvenile delinquent, doing some of the things below. T F

If you answered True, please check all that apply to you:

(1) I was considered a bully.
(2) I used to start fights with other kids.
(3) I used a weapon in fights that I had.
(4) I robbed or mugged other people.
(5) I was physically cruel to other people.
(6) I was physically cruel to animals.
(7) I forced someone to have sex with me.
(8) I lied a lot.
(9) I stayed out at night without my parents' permission.
(10) I stole things from others.
(11) I set fires.
(12) I broke windows or destroyed property.
(13) I ran away from home overnight more than once.
(14) I began skipping school a lot before age 13.
(15) I broke into someone's house, building or car.

Thank you for your time.
**T A S – 20**

Using the scale provided as a guide, indicate how much you agree or disagree with each of the following statements by circling the corresponding number. Give only one answer for each statement.

Circle 1 if you STRONGLY DISAGREE
Circle 2 if you MODERATELY DISAGREE
Circle 3 if you NEITHER DISAGREE NOR AGREE
Circle 4 if you MODERATELY AGREE
Circle 5 if you STRONGLY AGREE

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Moderately Disagree</th>
<th>Neither Disagree Nor Agree</th>
<th>Moderately Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am often confused about what emotion I am feeling.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. It is difficult for me to find the right words for my feelings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I have physical sensations that even doctors don’t understand.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I am able to describe my feelings easily.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. I prefer to analyze problems rather than just describe them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. When I am upset, I don’t know if I am sad, frightened, or angry.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. I am often puzzled by sensations in my body.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. I prefer to just let things happen rather than to understand why they turned out that way.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. I have feelings that I can’t quite identify.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Being in touch with emotions is essential.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td>Moderately Disagree</td>
<td>Neither Disagree Nor Agree</td>
<td>Moderately Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>---</td>
<td>------------------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td>------------------</td>
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</tr>
<tr>
<td>11. I find it hard to describe how I feel about people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. People tell me to describe my feelings more.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. I don't know what's going on inside me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. I often don't know why I am angry.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. I prefer talking to people about their daily activities rather than their feelings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. I prefer to watch &quot;light&quot; entertainment shows rather than psychological dramas</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. It is difficult for me to reveal my innermost feelings, even to close friends.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. I can feel close to someone, even in moments of silence.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. I find examination of my feelings useful in solving personal problems.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. Looking for hidden meanings in movies or plays distracts from their enjoyment.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Rarely/Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Almost Always/Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  I plan tasks carefully.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2  I do things without thinking.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3  I make-up my mind quickly.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4  I am happy-go-lucky.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5  I don’t “pay attention.”</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6  I have “racing” thoughts.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7  I plan trips well ahead of time.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8  I am self controlled.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9  I concentrate easily.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10 I save regularly</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11 I “squirm” at plays or lectures.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12 I am a careful thinker.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13 I plan for job security.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14 I say things without thinking.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15 I like to think about complex problems.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16 I change jobs.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17 I act “on impulse.”</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18 I get easily bored when solving thought problems.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19 I act on the spur of the moment.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20 I am a steady thinker.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21 I change residences.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22 I buy things on impulse.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23 I can only think about one thing at a time.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24 I change hobbies.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25 I spend or charge more than I earn.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26 I often have extraneous thoughts when thinking.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27 I am more interested in the present than the future.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28 I am restless at the theater or lectures.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>29 I like puzzles.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>30 I am future oriented.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

# Administrator's Form

**MCCB**  
MATRICS Consensus Cognitive Battery

<table>
<thead>
<tr>
<th>Score Box</th>
<th>Test</th>
<th>Raw Score</th>
<th>T-Score*</th>
<th>%ile*</th>
</tr>
</thead>
<tbody>
<tr>
<td>487</td>
<td>TMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BACS SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVLT-A</td>
<td>T-3</td>
<td>T-2</td>
<td>T-3</td>
<td>Sum</td>
</tr>
<tr>
<td>WMS-III SS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAB Mazes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVMT-R</td>
<td>T-1</td>
<td>T-2</td>
<td>T-3</td>
<td>Sum</td>
</tr>
<tr>
<td>Fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSCET™ ME</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT-IP</td>
<td>2-D</td>
<td>3-D</td>
<td>4-D</td>
<td>Mean</td>
</tr>
</tbody>
</table>

## Cognitive Domain Score Box

<table>
<thead>
<tr>
<th>Domain</th>
<th>T Score*</th>
<th>%ile*</th>
</tr>
</thead>
</table>
| Speed of Processing  
(composite of T-scores/ %iles for (1) TMT (2) BACS SC, and (3) Fluency) |          |       |
| Attention/Vigilance  
(CPT-IP scores) |          |       |
| Working Memory  
(composite of T-scores/ %iles for (1) WMS-III SS and (2) LNS) |          |       |
| Verbal Learning  
(HVLT-R scores) |          |       |
| Visual Learning  
(SVMT-R scores) |          |       |
| Reasoning and Problem Solving  
(NAB Mazes scores) |          |       |
| Social Cognition  
(MSCET™ ME scores) |          |       |

**OVERALL COMPOSITE SCORE**

*See Appendix C in the manual for the tables that convert raw scores to T-scores and percentiles.  See the back of this form for guidelines on completing the front page.

487
NOTE: Before you begin administering the first test, read the MCCB Manual. Chapters 5 and 6 deal with Administration and Scoring, respectively.

The respondent should be told that the battery involves measures of attention, learning, memory, and problem solving and that the group of measures may take up to about an hour and a half to finish. The test administrator should let the respondent know that the measures will be of various levels of difficulty and that it will be most helpful if he or she tries to do each task as well as possible.

Text that the administrator reads to the respondent is printed in boldface type.

**Trail Making Test (TMT):**

**Part A**

Administration of Sample

When you are ready to begin the test, place the Respondent's booklet turned to *Trail Making Test: Part A, Sample,* flat on the table directly in front of the respondent, with the bottom of the booklet approximately six inches from the respondent's edge of the table. Give the respondent a pencil and say: **On this page** [point] **are some numbers. Begin at number one [point to "1"] and draw a line from one to two [point to "2"],** two to three [point to "3"], **three to four [point to "4"], and so on, in order until you reach the end [point to the circle marked "END"]; Draw the lines as fast as you can. Do not lift the pencil from the paper. Ready? Begin!**

If the respondent makes a mistake on the sample, point it out and explain it. The following explanations of mistakes are acceptable:

1. You started with the wrong circle. This is where you start [point to "1"].

2. You skipped this circle [point to the one omitted]. You should go from number one [point to two [point], two to three [point], and so on, until you reach the circle marked "END" [point].

3. Please keep the pencil on the paper and continue right on to the next circle.

After the mistake has been explained, the administrator marks out the wrong part and says: **Go on from here** [point to the last circle completed correctly in the sequence].

If the respondent still cannot complete Sample A, take the respondent's hand and guide the pencil (eraser end down) through the trail. Then say: **Now you try it. Put your pencil point down. Remember, begin at number one [point] and draw a line from one to two [point to "2"], two to three [point to "3"], three to four [point to "4"], and so on, in order until you reach the circle marked "END" [point]. Do not skip around but go from one number to the next in the proper order. If you make a mistake, mark it out. Remember, work as fast as you can. Ready? Begin!**

If the respondent succeeds this time, go on to Part A of the test. If not, repeat the procedure until the respondent does succeed or it becomes evident that he or she cannot do it.
If the respondent completes the sample item correctly and in a manner that shows he or she understands what to do, say: Good! Let's try the next one. Turn to the test page.

Administration of Test

Say: On this page are numbers from 1 to 25. Do this the same way. Begin at number one [point], and draw a line from one to two [point to "2"], two to three [point to "3"], three to four [point "4"], and so on, in order until you reach the end [point]. Remember, work as fast as you can. Ready? Begin!

Start timing. If the respondent makes an error, call it to his or her attention immediately, and have the respondent proceed from the point the mistake occurred. Do not stop timing.

If the respondent completes Part A without error, remove the test sheet. Record the time in seconds. Errors count only in the increased time of performance.

Scoring

Record the total time for completion in seconds in the score space to the right.

Discontinue the test after 300 seconds, regardless of whether the subject is finished or not.

Brief Assessment of Cognition in Schizophrenia:
Symbol Coding (BACS SC)

Administration of Test

Turn to the correct page in the MCCB Respondent's Booklet. Read the following to the respondent:

Look at the boxes at the top of this page. Notice that each mark is unique and that each has a different number beneath it. Now look at these boxes down here (point). There are marks in the top part, but the bottom box is empty. Your task is to fill in the corresponding number beneath each mark. For example, here is the first mark (point to the first example). When I look up at the key, I see that this mark has a 1 beneath it, so I fill in a 1 down here (write a 1 for the first example). The next mark has a 5 beneath it, so down here I fill in a 5 (write in a 5 for the second example). Next is this mark; on the key here is a 2 beneath it (write in the 2). Now you do the rest of these examples up to this heavy line. The respondent should use a pencil without an eraser or a pen. Correct the respondent if any mistakes are made. Good! Do you have any questions? Answer any questions. If you make a mistake you cannot erase, but you can write over the number that you wrote. OK, working as quickly as you can, fill in the numbers that match the marks. Work across the rows from left to right (point), without skipping any. Ready? Make certain that the respondent is on task and prepared to start with pencil in hand before go is said. Go. Start the stopwatch immediately after saying go.

Stop the respondent after 90 seconds.

3
Scoring

Place the BACS SC scoring template (provided in the kit) over the page of the Respondent's Booklet on which the Symbol Coding responses are written. Circle any responses that are not correct. Subtract the number of incorrect responses from the total number of items completed in 90 seconds. Then count the number of correct responses and record this number in the space here.

**Hopkins Verbal Learning Test—Revised™ (HVLT-R™)**

**Administration of Test**

Use the HVLT-R Test Booklet. You will be administering only the three Learning Trials, not the Delayed Recall Trial. After this test has been administered, attach the completed HVLT-R Form to the MCCB Administrator's Form. Write the Form number in the Test 3 box on this page.

**Scoring**

Tally the number of correctly reported words. Correct minor errors in pronunciation (e.g., “cinnamon” for “cinnamon”) or pluralization (e.g., “rubies” for “ruby”) as they occur, but count these responses as correct. Self-corrections are also considered correct. Unambiguous paraphasias (e.g., “cabbage” for “lettuce” and “motel” for “hotel”) are considered errors and not counted in the trial score.

The number of words correctly recalled by the respondent is recorded and entered into the spaces provided.

**Wechsler Memory Scale-III (WMS-III): Spatial Span**

You will be using the WMS Spatial Span Board.

**Rules**

**Discontinue Rule**

After scores of 0 on both trials of any item for both Spatial Span Forward and Spatial Span Backward. For both Spatial Span Forward and Spatial Span Backward, administer both trials of each item even if Trial 1 is passed.

**Recording Rule**

Write the number of each cube in the order the respondent taps it.

**Scoring Rule**

0–1 pt. for each trial
Administration of "Forward" Section

Place the Spatial Span Board on the table with the cube numbers facing you and with the board centered at the respondent's midline so that he or she can easily reach the cubes. Say: Now I want you to do exactly what I do. Touch the blocks I touch, in the same order.

Tap out the sequence for Trial 1 of Spatial Span Forward item 1 (see below) at a rate of one cube per second.

Continue administering the items for Spatial Span Forward, using the sequences below. Record the responses. If the criterion for discontinuing is met, or if all Spatial Span Forward items have been administered, proceed with Spatial Span Backward.

<table>
<thead>
<tr>
<th>Item/Trial</th>
<th>Response</th>
<th>Score 0 or 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial 1</td>
<td>3 - 10</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>7 - 4</td>
<td></td>
</tr>
<tr>
<td>2. Trial 1</td>
<td>1 - 9 - 3</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>8 - 2 - 7</td>
<td></td>
</tr>
<tr>
<td>3. Trial 1</td>
<td>4 - 9 - 1 - 6</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>10 - 6 - 2 - 7</td>
<td></td>
</tr>
<tr>
<td>4. Trial 1</td>
<td>6 - 5 - 1 - 4 - 8</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>5 - 7 - 9 - 8 - 2</td>
<td></td>
</tr>
<tr>
<td>5. Trial 1</td>
<td>4 - 1 - 9 - 3 - 8 - 10</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>5 - 2 - 6 - 7 - 3 - 5</td>
<td></td>
</tr>
<tr>
<td>6. Trial 1</td>
<td>10 - 1 - 6 - 4 - 8 - 5 - 7</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>2 - 6 - 3 - 8 - 2 - 10 - 1</td>
<td></td>
</tr>
<tr>
<td>7. Trial 1</td>
<td>7 - 3 - 10 - 5 - 7 - 8 - 4 - 9</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>6 - 9 - 3 - 2 - 1 - 7 - 10 - 5</td>
<td></td>
</tr>
<tr>
<td>8. Trial 1</td>
<td>5 - 8 - 4 - 10 - 7 - 3 - 1 - 9 - 6</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>8 - 2 - 6 - 1 - 10 - 3 - 7 - 4 - 9</td>
<td></td>
</tr>
</tbody>
</table>

**FORWARD** Total Score: [ ]
Range = 0 to 16

Administration of "Backward" Section

Say: Now I am going to touch some more blocks. This time when I stop, I want you to touch the blocks backward, in the reverse order of mine. For example, if I touch this block (Cube 3), then this one (Cube 5), what would you do?

If a correct response is made, say: That's right. Here's the next one. Remember to touch them in the reverse order.

Then proceed with Item 1 (on the next page).
If an incorrect response is made on the 3-5 example sequence, point appropriately as you say: No, I touched this one, then this one, so, to do it in reverse, you would touch this one, then this one. Now let's try another one. If I touch this one (Cube 9), then this one (Cube 1), what would you do?

Whether the respondent succeeds or fails on the second example, proceed to Item 1.

Continue administering the items for Spatial Span Backward (using the sequences below) until the criterion for discontinuing is met or until all items are administered. Record the responses.

<table>
<thead>
<tr>
<th>Item/Trial</th>
<th>Correct Response/Response</th>
<th>Score 0 or 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial 1</td>
<td>7 - 4</td>
<td>(4 - 7)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>3 - 10</td>
<td>(10 - 3)</td>
</tr>
<tr>
<td>2. Trial 1</td>
<td>8 - 2 - 7</td>
<td>(7 - 2 - 8)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>1 - 9 - 3</td>
<td>(3 - 9 - 1)</td>
</tr>
<tr>
<td>3. Trial 1</td>
<td>10 - 6 - 2 - 7</td>
<td>(7 - 2 - 6 - 10)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>4 - 9 - 1 - 6</td>
<td>(6 - 1 - 9 - 4)</td>
</tr>
<tr>
<td>4. Trial 1</td>
<td>5 - 7 - 9 - 8 - 2</td>
<td>(2 - 8 - 9 - 7 - 5)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>6 - 5 - 1 - 4 - 8</td>
<td>(8 - 4 - 1 - 5 - 6)</td>
</tr>
<tr>
<td>5. Trial 1</td>
<td>9 - 2 - 6 - 7 - 3 - 5</td>
<td>(5 - 3 - 7 - 6 - 2 - 9)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>4 - 1 - 9 - 3 - 8 - 10</td>
<td>(10 - 8 - 3 - 9 - 1 - 4)</td>
</tr>
<tr>
<td>6. Trial 1</td>
<td>2 - 6 - 3 - 8 - 2 - 10 - 1</td>
<td>(1 - 10 - 2 - 8 - 3 - 6 - 2)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>10 - 1 - 6 - 4 - 8 - 5 - 7</td>
<td>(7 - 5 - 8 - 4 - 6 - 1 - 10)</td>
</tr>
<tr>
<td>7. Trial 1</td>
<td>6 - 9 - 3 - 2 - 1 - 7 - 10 - 5</td>
<td>(5 - 10 - 7 - 1 - 2 - 3 - 9 - 6)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>7 - 3 - 10 - 5 - 7 - 8 - 4 - 9</td>
<td>(9 - 4 - 8 - 7 - 5 - 10 - 3 - 7)</td>
</tr>
<tr>
<td>8. Trial 1</td>
<td>8 - 2 - 6 - 1 - 10 - 3 - 7 - 4 - 9</td>
<td>(9 - 4 - 7 - 3 - 10 - 1 - 6 - 2 - 8)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>5 - 8 - 4 - 10 - 7 - 3 - 1 - 9 - 6</td>
<td>(6 - 9 - 1 - 3 - 7 - 10 - 4 - 8 - 5)</td>
</tr>
</tbody>
</table>

BACKWARD Total Score: 
Range = 0 to 16

Scoring
For each trial, score 1 point if the exact sequence is tapped. Score 0 points if the respondent does not tap all of the specified cubes or makes an error in the tapping sequence.

WMS-III Spatial Span Total Score: 
Range = 0 to 32
(Sum of Forward Total Score & Backward Total Score)

6 20 – 25 mins since HVLT-R finished? DO DELAYED HVLT-R
I am going to read a list of numbers to you. Listen carefully, and repeat the numbers back to me in the same order.

<table>
<thead>
<tr>
<th>Item/Trial</th>
<th>Response</th>
<th>Score 0 or 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial 1</td>
<td>3-9</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>7-4</td>
<td></td>
</tr>
<tr>
<td>2. Trial 1</td>
<td>1-9-3</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>8-2-7</td>
<td></td>
</tr>
<tr>
<td>3. Trial 1</td>
<td>4-9-1-6</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>6-6-2-7</td>
<td></td>
</tr>
<tr>
<td>4. Trial 1</td>
<td>6-5-1-4-8</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>5-7-9-8-2</td>
<td></td>
</tr>
<tr>
<td>5. Trial 1</td>
<td>4-1-9-3-9-7</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>3-2-6-7-3-5</td>
<td></td>
</tr>
<tr>
<td>6. Trial 1</td>
<td>3-1-6-4-8-5-7</td>
<td></td>
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<tr>
<td>Trial 2</td>
<td>2-6-3-8-2-4-1</td>
<td></td>
</tr>
<tr>
<td>7. Trial 1</td>
<td>7-3-6-5-7-8-4-9</td>
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<tr>
<td>Trial 2</td>
<td>6-9-3-2-1-7-8-5</td>
<td></td>
</tr>
<tr>
<td>8. Trial 1</td>
<td>5-8-4-2-7-3-1-9-6</td>
<td></td>
</tr>
<tr>
<td>Trial 2</td>
<td>8-2-6-3-5-3-7-4-9</td>
<td></td>
</tr>
</tbody>
</table>

FORWARD TOTAL SCORE

Range = 0 to 16
**BACKWARD**

I am going to read another list of numbers to you. This time when I stop, I want you to repeat the numbers back to me in the reverse order. For example, if I say 3 -5, what would you say?

<table>
<thead>
<tr>
<th>Item/Trial</th>
<th>(Correct Response)/Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial 1</td>
<td>7 - 4</td>
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<tr>
<td></td>
<td>(4 - 7)</td>
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<tr>
<td>Trial 2</td>
<td>3 - 9</td>
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<td>(9 - 3)</td>
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<td>8 - 2 - 7</td>
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<td></td>
<td>(7 - 2 - 8)</td>
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<tr>
<td>Trial 2</td>
<td>1 - 9 - 3</td>
</tr>
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<td></td>
<td>(3 - 9 - 1)</td>
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<tr>
<td>3. Trial 1</td>
<td>8 - 4 - 2 - 7</td>
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<td></td>
<td>(7 - 2 - 6 - 8)</td>
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<tr>
<td>Trial 2</td>
<td>4 - 9 - 1 - 6</td>
</tr>
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<td></td>
<td>(6 - 1 - 9 - 4)</td>
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<tr>
<td>4. Trial 1</td>
<td>5 - 7 - 3 - 8 - 2</td>
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<td>Trial 2</td>
<td>6 - 5 - 1 - 4 - 8</td>
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<td>(8 - 4 - 1 - 5 - 6)</td>
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<tr>
<td>5. Trial 1</td>
<td>9 - 2 - 6 - 7 - 3 - 5</td>
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<tr>
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<td>(5 - 3 - 7 - 6 - 2 - 5)</td>
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<tr>
<td>Trial 2</td>
<td>4 - 1 - 9 - 3 - 8 - 7</td>
</tr>
<tr>
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<td>(7 - 2 - 3 - 9 - 1 - 4)</td>
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<td>2 - 6 - 3 - 8 - 2 - 4 - 1</td>
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<td>(7 - 5 - 8 - 4 - 6 - 1 - 3)</td>
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<tr>
<td>Trial 2</td>
<td>7 - 3 - 6 - 5 - 7 - 8 - 4 - 9</td>
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<td>8. Trial 1</td>
<td>8 - 2 - 6 - 1 - 5 - 3 - 7 - 4 - 9</td>
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<td>(9 - 4 - 7 - 3 - 5 - 1 - 6 - 2 - 8)</td>
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<tr>
<td>Trial 2</td>
<td>5 - 8 - 4 - 2 - 7 - 3 - 1 - 9 - 6</td>
</tr>
<tr>
<td></td>
<td>(8 - 9 - 1 - 3 - 7 - 2 - 4 - 8 - 5)</td>
</tr>
</tbody>
</table>

**BACKWARD TOTAL SCORE**

Range = 0 to 16

**Digit Span Total Score**

Range = 0 to 32

(Sum of Forward Total Score and Backward Total Score)

20 - 25 mins since HVLT-R finished? **DO DELAYED HVLT-R**
Letter-Number Span (LNS)

Instructions
Make sure that the respondent can repeat the alphabet correctly. Then, state to the respondent: I am going to say a list of numbers and letters. When I am through, I want you to first tell me the numbers in order from smallest to biggest. Then I want you to tell me the letters in alphabetical order. So, for example, if I say A4, the answer is 4A. The number goes first, then the letter. If I say 8B2, you answer 28B, numbers first in order, then letters.

Practice Administration
If the respondent makes an error on any practice item, correct him/her and repeat the instructions as necessary. Even if the respondent fails all practice items, continue with the test.

Try these: B9, 7C, 2P9, Z9A, 8MC.

Continue practice until the respondent can do a three-symbol sequence. If unable to do so after four additional trials (L9U, 8P4, WNS, R47), begin test.

Rules

Recording
Record the respondent’s response for each trial verbatim.

Discontinue
Discontinue after scores of 0 on all four trials of an item section.

Administration of Test
Administer all four items at each level until all items are failed at a level. Items should be read to the respondent at a rate of one letter or number per second.

Instructions may be repeated in the beginning during the 2-symbol sequence when respondents are especially likely to misinterpret the instructions.

Read the following to the respondent:
I am going to say a list of numbers and letters. When I am through, I want you to first tell me the numbers in order from smallest to biggest. Then I want you to tell me the letters in alphabetical order.

So, for example, if I say A4, the answer is 4A. The number goes first, then the letter. If I say 8B2, you answer 28B, numbers first in order, then letters.

Try these:

<table>
<thead>
<tr>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-9</td>
<td>(9-B)</td>
</tr>
<tr>
<td>7-C</td>
<td>(7-C)</td>
</tr>
<tr>
<td>2-P-9</td>
<td>(2-P-9)</td>
</tr>
<tr>
<td>7-9-A</td>
<td>(9-A-Z)</td>
</tr>
<tr>
<td>8-M-C</td>
<td>(8-C-M)</td>
</tr>
</tbody>
</table>
Try these (if needed): L-9-U (9-L-U)  
S-P-4 (4-S-P)  
W-N-S (5-N-W)  
R-4-7 (4-7-R)  

<table>
<thead>
<tr>
<th>Section</th>
<th>Item</th>
<th>Correct</th>
<th>Respondent(s)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>D-6</td>
<td>6-D</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4-L</td>
<td>4-L</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>M-2</td>
<td>2-M</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-B</td>
<td>3-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.</td>
<td>A-1-C</td>
<td>1-A-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>W-7-T</td>
<td>7-T-W</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5-R-8</td>
<td>5-R-8</td>
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<td></td>
<td>9-X-3</td>
<td>3-9-X</td>
<td></td>
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<tr>
<td>III.</td>
<td>Y-8-G-2</td>
<td>2-8-G-Y</td>
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<td></td>
<td>J-3-N-1</td>
<td>1-3-J-N</td>
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<tr>
<td></td>
<td>2-Z-5-H</td>
<td>2-5-I-Z</td>
<td></td>
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<tr>
<td></td>
<td>4-F-5-S</td>
<td>4-5-F-S</td>
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<tr>
<td>IV.</td>
<td>4-L-5-C-8</td>
<td>4-5-8-C-L</td>
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<td>B-1-J-7-W</td>
<td>1-7-B-J-W</td>
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<tr>
<td></td>
<td>9-K-3-B-2</td>
<td>2-3-9-B-K</td>
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<tr>
<td></td>
<td>N-6-R-2-U</td>
<td>2-6-N-R-U</td>
<td></td>
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<tr>
<td>V.</td>
<td>D-7-G-4-S-2</td>
<td>2-4-7-D-G-S</td>
<td></td>
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<tr>
<td></td>
<td>P-6-L-3-C-1</td>
<td>1-3-6-C-L-P</td>
<td></td>
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<tr>
<td></td>
<td>4-J-5-T-7-X</td>
<td>4-5-7-J-T-X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI.</td>
<td>C-7-G-4-Q-1-S</td>
<td>1-4-7-C-G-Q-S</td>
<td></td>
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<td></td>
<td>B-R-6-M-3-F-2</td>
<td>2-3-6-R-M-P-R</td>
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<tr>
<td></td>
<td>A-2-E-6-F-9-T</td>
<td>2-6-9-A-E-F-T</td>
<td></td>
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<tr>
<td></td>
<td>3-T-4-P-7-M-9</td>
<td>3-4-7-9-M-P-T</td>
<td></td>
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</tbody>
</table>

**Scoring**

Record the response to each trial *verbatim*, the item score, and the total test raw score (maximum score = 24).

For each trial of an item, score 1 point for each correct response, 0 points for each incorrect response. A response is incorrect if a number or letter is omitted or if the numbers or letters are not said in the specified sequence. Sum the item scores to obtain the total score. If the respondent orders the letters first and then the numbers, score these answers as incorrect.
Administration of Test

Use the Mazes Test Record Form and Executive Functions Module Response Booklet.

After administering this test, attach the completed NAB Mazes Record Form to the MCCB Administrator’s Form.

Scoring

Refer to the text and figures in chapter 6 of the MCCB Manual.

Brief Visuospatial Memory Test—Revised (BVMT-R™)

You will be using the BVMT-R Recall Stimulus Booklet.

Administration of Test

Learning Trial 1: Open the MCCB Respondent’s Booklet to the page marked T-1. Say, I will show you a sheet that has six figures on it. I want you to study the figures so that you can remember as many of them as possible. You will have just 10 seconds to study the entire display. I will present the figures right here (place hand at eye level approximately 16 inches in front of the respondent). After I take the display away, try to draw each figure exactly as it appeared and in its correct location on the page.

Repeat the instructions and clarify them as often as necessary. Open the BVMT-R Recall Stimulus Booklet to the appropriate form (i.e., Form 1, 3, 4, 5, or 6) and place it face down in front of the respondent. Write the BVMT-R Form number in the Test 7 box on the next page of this form. When the respondent is ready, expose the stimulus from a distance of approximately 16 inches. The Recall Stimulus Booklet may be presented by holding the booklet at eye level or by resting the bottom edge of the Recall Stimulus Booklet on the table top and holding it in an upright position. It is imperative that the stimulus display is exposed for a full 10 seconds. Do not begin timing until the respondent is scanning the stimulus.

After the 10-second period, remove the Recall Stimulus Booklet and say, Now draw as many of the figures as you can in their correct location on the page.

The respondent is permitted as much time as necessary for the task and is encouraged to draw the designs as precisely as possible (use of an eraser is permitted). The administrator may encourage the respondent to guess if he or she is uncertain about a response. After the respondent indicates that he or she is finished drawing, ask the respondent to put the pencil down. Turn the MCCB Respondent’s Booklet page to the response sheet for Trial 2, labeled T-2, removing the response sheet for Trial 1 from the respondent’s view.

Comments:

______________________________________________________________

______________________________________________________________

______________________________________________________________

______________________________________________________________

______________________________________________________________

______________________________________________________________

______________________________________________________________
Learning Trials 2 and 3: Say, That was fine. Now I would like to see whether you can remember more of the figures if you have another chance. I will present the display again for 10 seconds. Try to remember as many of the figures as you can this time, including the ones you remembered on your last attempt. Try to draw each figure precisely and in its correct location.

Pause to answer any questions the respondent may have, make any notes or comments on the Administrator's Form, and then again expose the stimulus as described above for exactly 10 seconds. After 10 seconds, remove the Recall Stimulus Booklet and have the respondent draw his or her responses on the response sheet for Trial 2. After the respondent indicates that he or she is finished drawing, immediately turn the page to the response sheet for Trial 3, labeled T-3, removing the response sheet for Trial 2 from the respondent's view.

After the respondent indicates that he or she is finished drawing, immediately remove the Respondent's Booklet.

Scoring
Refer to chapter 6 and Appendix A in the MCC8 Manual.

Category Fluency: Animal Naming
(Fluency)

Administration of Test
Say to the respondent:
Now tell me the names of as many animals as you can. Name them as quickly as possible. Any animals will do; they can be from the farm, the jungle, the ocean, or house pets. For instance, you could begin with DOG. Ready? Begin.

Start timing immediately. Allow 60 seconds. If the respondent discontinues before the end of the period, encourage him or her to produce more names. Repeat the basic instructions if there is a pause of 15 seconds of more, but continue timing.

<table>
<thead>
<tr>
<th>1.</th>
<th>13.</th>
<th>25.</th>
<th>37.</th>
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<tbody>
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<td>3.</td>
<td>15.</td>
<td>27.</td>
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<td>4.</td>
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<td>11.</td>
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<tr>
<td>12.</td>
<td>24.</td>
<td>36.</td>
<td>48.</td>
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</tbody>
</table>
Scoring

Award 1 point for each different animal. If the respondent generates animal names that are superordinates and subordinates (e.g., "dog, cocker spaniel, black lab, golden retriever"), the respondent gets credit for each item.

No credit will be given to fantastical animals (e.g., unicorn, dragons).

Extinct animals are valid (e.g., dinosaurs, wooly mammoth).

Credit will be given for any answers listing mankind (e.g., "humans" or "man" or "Neanderthal man").

Mayer-Salovey-Caruso Emotional Intelligence Test
(MSCEIT™): Managing Emotions

Instructions

Read the following to the respondent:
The MSCEIT™ is an ability test, so some answers get higher scores than others; for some answers, partial credit is given. It is in your best interest to answer all the questions. You do not lose points for incorrect answers.

Now I will read each item to you as you follow along on the form. After I read the item to you, decide which answer you think is best. Tell me the answer that you think is best.

Sometimes respondents will ask specifically how to respond to, or how to understand, certain items. These inquiries will sometimes require clarification of the instructions and will be straightforward to answer. Other questions may be more complicated, and care must be taken to respond in a way that will not bias responses. Often, it will be sufficient to say: That's fine but, for now, please respond as best you can, and we can discuss that after you have finished. If a respondent cannot decide between two response choices or is unsure how to answer, say something like: I know that for some questions, it is difficult to know how to respond, but please try as best you can and choose one of the responses. The respondent should answer every question.

Administration of Section D

Say: Please select an answer for every action.

Read each item aloud, and circle the respondent's answer. (The small numbers in the left margin correspond to the item numbers in the MSCEIT computer scoring program.)

1. Mara woke up feeling pretty well. She had slept well, felt well rested, and had no particular cares or concerns. How well would each action help her preserve her mood?
   Action 1: She got up and enjoyed the rest of the day.

Don't read MSCEIT to participants, let them fill it out themselves.
Action 2: Mara enjoyed the feeling, and decided to think about and appreciate all the things that were going well for her.


Action 3: She decided that it was best to ignore the feeling since it wouldn’t last anyway.


Action 4: She used the positive feeling to call her mother, who had been depressed, and tried to cheer her up.


2. Andrew works as hard, if not harder, than one of his colleagues. In fact, his ideas are usually better at getting positive results for the company. His colleague does a mediocre job but engages in office politics so as to get ahead. So, when Andrew’s boss announces that the annual merit award is being given to this colleague, Andrew is very angry. How effective would each action be in helping Andrew feel better?

Action 1: Andrew sat down and thought about all of the good things in his life and his work.


Action 2: Andrew made a list of the positive and negative traits of his colleague.


Action 3: Andrew felt terrible that he felt that way, and he told himself that it wasn’t right to be so upset over an event not under his control.


Action 4: Andrew decided to tell people just what a poor job his colleague had done, and that he did not deserve the merit award. Andrew gathered memos and notes to prove his point, so it wasn’t just his word.


3. Jane did not know when her bills were due, how many more bills would be arriving soon, or if she could pay them. Then her car began making strange noises and her mechanic said it would cost so much to fix that it might not be worth it. Jane can’t fall asleep easily, she wakes up several times at night, and she finds herself worrying all the time. How effective would each of the following actions be in reducing her worry?

Action 1: Jane tried to work out what she owed, how much was due, and when it was due.


Action 2: Jane learned deep-relaxation techniques to calm herself down.

Action 3: Jane got the name of a financial planner to help her figure out how to manage her finances properly.

11 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 4: She decided to look for a job that paid more money.

12 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

4. Nothing seems to be going right for Ed. There just isn’t much in Ed’s life that he enjoys or that brings him much pleasure. Over the next year, how effective would each of the following actions be at making Ed feel better?

Action 1: Ed started to call friends he hadn’t spoken to in awhile and made plans to see a few people.

13 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 2: He started to eat better, to get to bed earlier, and to exercise more.

14 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 3: Ed felt that he was bringing people down and decided to stay by himself more until he could work out what was bothering him. He felt he needed time alone.

15 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 4: Ed found that relaxing in front of the TV at night, with a beer or two, really helped him to feel better.

16 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

5. As Robert drove home from work, a tractor-trailer truck cut him off. He didn’t even have time to honk his horn. Robert quickly swerved to the right to avoid getting hit. He was furious. How effective would each of the following actions be in dealing with his anger?

Action 1: Robert taught the truck driver a lesson by cutting him off a few miles down the highway.

17 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 2: Robert just accepted that these things happen and drove home.

18 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 3: He yelled as loud as he could, and cursed and swore at the trucker.

19 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 4: He vowed never to drive on that highway again.

20 a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective
Administration of Section H

Say: Please select an answer for every response.

Read each item aloud, and circle the respondent’s answer.

1. John developed a close friend at work over the last year. Today, that friend completely surprised him by saying he had taken a job at another company and would be moving out of the area. He had not mentioned he was looking for other jobs. How effective would John be in maintaining a good relationship, if he chose to respond in each of the following ways?

Response 1: John felt good for him and told his friend that he was glad he got the new job. Over the next few weeks, John made arrangements to ensure they stayed in touch.


Response 2: John felt sad that his friend was leaving, but he considered what happened as an indication that the friend did not much care for him. After all, the friend said nothing about his job search. Given that his friend was leaving anyway, John did not mention it, but instead went looking for other friends at work.


Response 3: John was very angry that his friend hadn’t said anything. John showed his disapproval by deciding to ignore his friend until the friend said something about what he had done. John thought that if his friend didn’t say anything, it would confirm John’s opinion that the friend was not worth talking to.


2. Roy’s teacher has just called Roy’s parents to say that Roy is doing poorly in school. The teacher tells Roy’s parents that their son isn’t paying attention, is being disruptive, and can’t sit still. This particular teacher doesn’t do well with active boys, and Roy’s parents wonder what’s really going on. Then, the teacher says that their son will be left back unless he improves. The parents feel very angry. How helpful to their son is each of these reactions?

Response 1: The parents told the teacher that this was a big shock to them since this was the first time they had ever heard there was a problem. They asked to meet with the teacher and also requested if the principal could attend the meeting.


Response 2: The parents told the teacher that if she continued to threaten to have their son repeat the grade, they would take it up with the principal. They said “if our son is left back, we will hold you personally responsible. You are the teacher and your job is to teach, not to blame the student.”


Response 3: Roy’s parents hung up on the teacher and called the principal. They complained about the teacher’s threats and asked that their son be moved to a different classroom.

3. Everything is going well for Liz. While others have been complaining about work, Liz has just gotten a promotion and a decent raise. Her children are very happy and doing well in school, her marriage is stable and very happy. Liz is starting to feel very self-important and finds herself tempted to brag about her life to her friends. How effective would each of the following responses be for maintaining her relationships?

Response 1: Since everything is so good, it's okay to feel proud of it. But Liz also realized that some people see it as bragging, or may be jealous of her and so she only talked to close friends about her feelings.


Response 2: Liz started to think of all the things that could possibly go wrong in the future so she could gain perspective on her life. She saw that good feelings don't always last.


Response 3: Liz shared her feelings with her husband that night. Then, she decided that the family should spend time together on the weekend and get involved in several family events just to be together.


Scoring

Use the MSCEIT™ Branch 4 scoring software (included in the MCCB kit) to score the test. See chapter 6 in the MCCB Manual for directions.

Continuous Performance Test—Identical Pairs (CPT-IP)

You will be using the CPT-IP, MATRICS Version, software disk.

See chapter 5 in the MCCB Manual for directions on administration of the CPT-IP.

Scoring

For directions on scoring, see chapter 6 of the MCCB Manual. When finished, attach the computer-generated score report to the MCCB Administrator's Form.
Learning Trial Instructions

Trial 1
Say the following:

I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?

- Repeat or paraphrase the instructions if necessary.
- Read the words at the rate of approximately one word every 2 seconds.
- If the individual does not spontaneously begin reporting words after the last word is read, say the following:

   OK. Now tell me as many of those words as you can remember.

Record the responses verbatim (including repetitions and intrusions) in the Trial 1 column. When the individual indicates no more words can be recalled, proceed to Trial 2.

Trial 2
Say the following:

Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including all the words you told me the first time.

Use the same procedure as in Trial 1 to record the responses in the column for Trial 2. Then proceed to Trial 3.

Trial 3
Say the following:

I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.

Record the responses in the column for Trial 3 using the same procedure as in the previous trials.

NOTE: Do not tell the respondent that recall of the words will be tested later.

Delayed Recall Trial Instructions

After the 20-25 minute delay, say the following:

Do you remember that list of words you tried to learn before?

If the response is "No," remind the individual that you read the list three times and that he or she was asked to recall the words each time. Say the following:

Tell me as many of those words as you can remember.
Form 1

Semantic Categories: Four-Legged Animals, Precious Stones, Human Dwellings

Name ___________________________   Sex ___________________ Age _____ years _____ months

Examiner ___________________________   Date __/__/____

<table>
<thead>
<tr>
<th>Word List</th>
</tr>
</thead>
<tbody>
<tr>
<td>LION</td>
</tr>
<tr>
<td>EMERALD</td>
</tr>
<tr>
<td>HORSE</td>
</tr>
<tr>
<td>TENT</td>
</tr>
<tr>
<td>SAPPHIRE</td>
</tr>
<tr>
<td>HOTEL</td>
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<tr>
<td>CAVE</td>
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<tr>
<td>OPAL</td>
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<tr>
<td>TIGER</td>
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<tr>
<td>PEARL</td>
</tr>
<tr>
<td>COW</td>
</tr>
<tr>
<td>HUT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Learning Trials</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
<td>Trial 2</td>
<td>Trial 3</td>
<td>Trial 4</td>
</tr>
</tbody>
</table>

Total correct responses = ____________

<p>| | |</p>
<table>
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<tbody>
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</tbody>
</table>

Completion Time ____________   Start Time ____________

Trial 3 ____________   Trial 4 ____________
Delayed Recognition Trial Instructions

The Delayed Recognition (Forced Choice) trial is administered immediately after the Delayed Recall trial. Say the following:

Now I am going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list, or "No" if it was not.

Read the words of the Delayed Recognition trial list in numerical order. Allow the individual as much time as needed to respond. You may use the prompt, "Was horse on the list? Yes or no?" The individual must give you a response for every word. If the individual is not sure, ask for a guess.

| 1. HORSE | Y N | 7. house | Y N | 13. HUT | Y N | 19. TENT | Y N |
| 2. ruby | Y N | 8. OPAL | Y N | 14. EMERALD | Y N | 20. mountain | Y N |
| 3. CAVE | Y N | 9. TIGER | Y N | 15. SAPPHIRE | Y N | 21. cat | Y N |
| 4. balloon | Y N | 10. boat | Y N | 16. dog | Y N | 22. HOTEL | Y N |
| 5. soot | Y N | 11. star | Y N | 17. apartment | Y N | 23. COW | Y N |
| 6. LION | Y N | 12. PEARL | Y N | 18. penny | Y N | 24. diamond | Y N |

Total number of true-positive responses ("hits"): ——/12 (no shading)

Semantically-related false-positive errors: ——/6 (light shading)

Semantically-unrelated false-positive errors: ——/6 (darker shading)

Total number of false-positive errors: ——/12

<table>
<thead>
<tr>
<th>Total Recall (sum of total correct responses for Trials 1, 2, &amp; 2)</th>
<th>Raw score</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed Recall (Trial 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retention (%) ([(Trial 4 + Higher score of Trials 2 and 3) x 100])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition Discrimination Index (Total no. of true-positives) - (Total no. of false-positives)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normative table (Appendix A):
# Mazes Test Record Form

Form 1

Robert A. Stern, PhD
Travis White, PhD

<table>
<thead>
<tr>
<th>Name</th>
<th>ID#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Birth</td>
<td>Age</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Handedness</td>
</tr>
<tr>
<td>Date of Examination</td>
<td>Examiner</td>
</tr>
</tbody>
</table>

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**Note:** This form is intended for use with the Neuropsychological Assessment Battery® and is protected by copyright. Reproduction is not permitted without written permission from PAR, Inc.
1. Mazes

Recording
Place a check mark (✓) to indicate whether or not the maze was completed within time limit. Record completion time in seconds.

Scoring
Award 0 points if examinee does not complete the maze within the time limit. If examinee successfully completes the maze within the time limit, circle the appropriate score that corresponds to the completion time for that maze.

Discontinuation
Discontinue after three consecutive scores of 0 points.

Administration Instructions
Say, I am going to give you some mazes to complete. Open the Executive Functions Response Booklet to Maze A and say, I want you to work as quickly as you can to complete this maze. Try your best not to make any errors or stray marks. Here is the “start” (point) where you will begin and here is the “end” (point) where you will finish. You may not cut corners or cross over any lines to reach the end. Also, I do not want you to lift your pen once you have started the maze. Hand pen to examinee. Ready? BEGIN: Begin timing. Allow examinee to complete Maze A. If examinee makes several mistakes, demonstrate correct completion using a different colored pen. For Mazes B through G, say, Here is another maze. Start here (point) and end here (point). Remember not to lift your pen once you have made a mark. Ready? BEGIN: Begin timing.

If examinee begins any place other than “Start,” stop and redirect immediately. If examinee asks whether he/she can self-correct, say, Yes, you can cross back over your own lines, but do not lift your pen.

If examinee stops at a dead end, say, Keep trying and see if you can work your way out. If he/she refuses, record time and award a score of 0. An error is defined as crossing over any line by more than ¼ inch. If an error occurs on a straight line, stop examinee and mark the error by making a slash through the line; then direct him/her to the point of the error and instruct him/her to continue from that point. On a corner, an error is defined as cutting that corner so that the corner is now rounded and the cut is greater than ¼ inch away from the vertex. Again, stop examinee and mark the error by making a slash through the line; then direct him/her to the point of the error and instruct him/her to continue from that point. Do not allow the examinee to rotate the maze.

<table>
<thead>
<tr>
<th>EXAMINEE</th>
<th>Maze Item</th>
<th>Time Limit</th>
<th>Completed</th>
<th>Completion Time (in seconds)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maze A</td>
<td>30 sec.</td>
<td>□ No</td>
<td>2 1</td>
<td>1-3 sec. 2-30 sec.</td>
<td>0</td>
</tr>
<tr>
<td>Maze B</td>
<td>30 sec.</td>
<td>□ Yes</td>
<td>2 1</td>
<td>1-11 sec. 12-30 sec.</td>
<td>0</td>
</tr>
<tr>
<td>Maze C</td>
<td>30 sec.</td>
<td>□ No</td>
<td>2 1</td>
<td>1-15 sec. 16-30 sec.</td>
<td>0</td>
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</table>

EXAMINER
<table>
<thead>
<tr>
<th>EXAMINEE</th>
<th>Maze Item</th>
<th>Time Limit</th>
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<th>Completion Time (in seconds)</th>
<th>Score</th>
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<tbody>
<tr>
<td>Maze D</td>
<td>120 sec.</td>
<td>No</td>
<td>5 4 3 2 1</td>
<td>1-32 33-45 46-59 60-79 80-119 sec. sec. sec. sec.</td>
<td>0</td>
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<tr>
<td>Maze E</td>
<td>240 sec.</td>
<td>No</td>
<td>5 4 3 2 1</td>
<td>1-73 74-100 101-126 127-144 145-240 sec. sec. sec. sec. sec.</td>
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<tr>
<td>Maze F</td>
<td>240 sec.</td>
<td>No</td>
<td>5 4 3 2 1</td>
<td>1-87 88-119 120-146 147-184 185-240 sec. sec. sec. sec. sec.</td>
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</tr>
<tr>
<td>Maze G</td>
<td>240 sec.</td>
<td>No</td>
<td>5 4 3 2 1</td>
<td>1-95 100-129 130-168 169-201 202-240 sec. sec. sec. sec. sec.</td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>EXAMINER</th>
<th>Mazes (MAZ) Raw Score</th>
</tr>
</thead>
</table>

Qualitative Features (✓ if present)

- Long latency before beginning mazes
- Impulsive/quick start
- Haphazard approach
- Crossing line errors

Comments/Notes:
Recall Stimulus Booklet
Forms 1 through 6
Ralph H. B. Benedict, PhD
Respondent's Booklet

Name (or ID #):
TRAIL MAKING TEST

Part A

SAMPLE

End

8

Begin

1

7

2

3

4

5

6
Trail Making Test Part B – SAMPLE

Begin

End

1

2

3

4

A

B

C

D
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<th>2</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<td>C</td>
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</tbody>
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# Executive Functions Module Response Booklet

## Form 1

Robert A. Stern, PhD  
Travis White, PhD

<table>
<thead>
<tr>
<th>Name</th>
<th>ID#</th>
<th>Date of Birth</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Handedness</th>
<th>Education</th>
<th>Date of Examination</th>
<th>Examiner</th>
</tr>
</thead>
</table>
1. Mara woke up feeling pretty well. She had slept well, felt well rested, and had no particular cares or concerns. How well would each action help her preserve her mood?

Action 1: She got up and enjoyed the rest of the day.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 2: Mara enjoyed the feeling, and decided to think about and appreciate all the things that were going well for her.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 3: She decided that it was best to ignore the feeling since it wouldn’t last anyway.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 4: She used the positive feeling to call her mother, who had been depressed, and tried to cheer her up.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

2. Andrew works as hard, if not harder, than one of his colleagues. In fact, his ideas are usually better at getting positive results for the company. His colleague does a mediocre job but engages in office politics so as to get ahead. So, when Andrew’s boss announces that the annual merit award is being given to this colleague, Andrew is very angry. How effective would each action be in helping Andrew feel better?

Action 1: Andrew sat down and thought about all of the good things in his life and his work.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 2: Andrew made a list of the positive and negative traits of his colleague.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 3: Andrew felt terrible that he felt that way, and he told himself that it wasn’t right to be so upset over an event not under his control.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective

Action 4: Andrew decided to tell people just what a poor job his colleague had done, and that he did not deserve the merit award. Andrew gathered memos and notes to prove his point, so it wasn’t just his word.

a. Very ineffective  
b. Somewhat ineffective  
c. Neutral  
d. Somewhat effective  
e. Very effective
3. Jane did not know when her bills were due, how many more bills would be arriving soon, or if she could pay them. Then her car began making strange noises and her mechanic said it would cost so much to fix that it might not be worth it. Jane can’t fall asleep easily, she wakes up several times at night, and she finds herself worrying all the time. How effective would each of the following actions be in reducing her worry?

Action 1: Jane tried to work out what she owed, how much was due, and when it was due.

Action 2: Jane learned deep-relaxation techniques to calm herself down.

Action 3: Jane got the name of a financial planner to help her figure out how to manage her finances properly.

Action 4: She decided to look for a job that paid more money.

4. Nothing seems to be going right for Ed. There just isn’t much in Ed’s life that he enjoys or that brings him much pleasure. Over the next year, how effective would each of the following actions be at making Ed feel better?

Action 1: Ed started to call friends he hadn’t spoken to in awhile and made plans to see a few people.

Action 2: He started to eat better, to get to bed earlier, and to exercise more.

Action 3: Ed felt that he was bringing people down and decided to stay by himself more until he could work out what was bothering him. He felt he needed time alone.

Action 4: Ed found that relaxing in front of the TV at night, with a beer or two, really helped him to feel better.
5. As Robert drove home from work, a tractor-trailer truck cut him off. He didn't even have time to honk his horn. Robert quickly swerved to the right to avoid getting hit. He was furious. How effective would each of the following actions be in dealing with his anger?

Action 1: Robert taught the truck driver a lesson by cutting him off a few miles down the highway.

Action 2: Robert just accepted that these things happen and drove home.

Action 3: He yelled as loud as he could, and cursed and swore at the trucker.

Action 4: He vowed never to drive on that highway again.

1. John developed a close friend at work over the last year. Today, that friend completely surprised him by saying he had taken a job at another company and would be moving out of the area. He had not mentioned he was looking for other jobs. How effective would John be in maintaining a good relationship, if he chose to respond in each of the following ways?

Response 1: John felt good for him and told his friend that he was glad he got the new job. Over the next few weeks, John made arrangements to ensure they stayed in touch.

Response 2: John felt sad that his friend was leaving, but he considered what happened as an indication that the friend did not much care for him. After all, the friend said nothing about his job search. Given that his friend was leaving anyway, John did not mention it, but instead went looking for other friends at work.

Response 3: John was very angry that his friend hadn't said anything. John showed his disapproval by deciding to ignore his friend until the friend said something about what he had done. John thought that if his friend didn't say anything, it would confirm John's opinion that the friend was not worth talking to.
2. Roy's teacher has just called Roy's parents to say that Roy is doing poorly in school. The teacher tells Roy's parents that their son isn't paying attention, is being disruptive, and can't sit still. This particular teacher doesn't do well with active boys, and Roy's parents wonder what's really going on. Then, the teacher says that their son will be left back unless he improves. The parents feel very angry. How helpful to their son is each of these reactions?

Response 1: The parents told the teacher that this was a big shock to them since this was the first time they had ever heard there was a problem. They asked to meet with the teacher and also requested if the principal could attend the meeting.


Response 2: The parents told the teacher that if she continued to threaten to have their son repeat the grade, they would take it up with the principal. They said "if our son is left back, we will hold you personally responsible. You are the teacher and your job is to teach, not to blame the student."


Response 3: Roy's parents hung up on the teacher and called the principal. They complained about the teacher's threats and asked that their son be moved to a different classroom.


3. Everything is going well for Liz. While others have been complaining about work, Liz has just gotten a promotion and a decent raise. Her children are very happy and doing well in school, her marriage is stable and very happy. Liz is starting to feel very self-important and finds herself tempted to brag about her life to her friends. How effective would each of the following responses be for maintaining her relationships?

Response 1: Since everything is so good, it's okay to feel proud of it. But Liz also realized that some people see it as bragging, or may be jealous of her and so she only talked to close friends about her feelings.


Response 2: Liz started to think of all the things that could possibly go wrong in the future so she could gain perspective on her life. She saw that good feelings don't always last.


Response 3: Liz shared her feelings with her husband that night. Then, she decided that the family should spend time together on the weekend and get involved in several family events just to be together.

Appendix D
Information sheet for persons participating in research projects

**Participant Information and Consent Form, Anorexia Nervosa group**
The University of Melbourne, St Vincent’s Hospital

**Full Project Title:** Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: A/Prof Larry Abel, The University of Melbourne

- Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPrc)
- Prof David Castle, St Vincent’s Hospital and The University of Melbourne
- A/Prof Richard Newton, Austin Health
- Dr William Woods, Swinburne University of Technology
- Dr Charlotte Keating, Swinburne University of Technology
- Dr Chia Huang, The Melbourne Clinic

Student Researcher: Andrea Phillipou, The University of Melbourne

Site of Research: The University of Melbourne, St Vincent’s Hospital, The Austin Hospital, The Melbourne Clinic, Swinburne University of Technology

1. **Introduction**

You are invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to complete certain tasks. This is because you have either been referred through the Body Image Eating Disorders Treatment & Recovery Service (BETRS) or you’ve responded to an advertisement.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.
2. **What is the purpose of this research project?**

The reason this study is being undertaken is that although there are high rates of Anorexia Nervosa in today’s society, the psychological and neurological processes involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BETRS, the Melbourne Clinic or via advertisement in support groups, whereas healthy control participants will be recruited from the general public through advertisements.

The results of this research will be used by the researcher Andrea Phillipou to obtain a PhD degree.

This research has been funded in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation and the Dick & Pip Smith Foundation.

3. **What does participation in this research project involve?**

If you agree to participate in this study, you will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, gender, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking 2 different types of brain scans, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning. fMRI uses a strong magnetic field to produce images of the brain and measures brain activity by detecting changes in blood flow, whereas MEG is a technique for mapping electrical activity of the brain. During these scans participants will perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your face photographed, and having your photograph included amongst the existing task stimuli. Participation in this additional task is entirely voluntary, and if you don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- **The MEG session**

Before the MEG session begins, you will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. You will be asked to sit in a quiet room and sit in a chair where your head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, you will be able to speak to the researchers via an intercom at all times. Prior to entering the room you will be asked to remove any metal from your clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone, metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- **The MRI session**
After the MEG session we will ask you to have an MRI scan. Before the MRI session begins, you will be asked to complete a Swinburne MRI safety questionnaire administered by our staff radiographer that largely entails questions regarding any metal you have on or in your body, such as that from any surgery involving metal plates and pace makers, though other questions are asked. A copy of the safety questionnaire is attached to this document. Due to the nature of MRI, that involves strong magnetic fields, no metal can be taken into the room. It is very important that you fill in this questionnaire correctly, as some conditions, i.e. having a pacemaker, can be dangerous. The scanner is also quite noisy so you will be provided with some headphones to reduce this noise.

All three sessions will take place at the Brain and Psychological Sciences Research Centre (BPSyC) at Swinburne University of Technology. The time commitment for the first session is approximately 3 hours and approximately 1.5-2.5 hours each for the second and third sessions, with breaks as required.

You will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive taxi vouchers for the three sessions.

4. What are the possible benefits?

There will be no clear immediate benefits to you from your participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. What are the possible risks?

In general, foreseeable risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

During the clinical interview if the researcher has concerns over your current presentation they will discuss these concerns with you and contact your clinician, with your permission.

If you become upset or distressed as a result of your participation in this research project, the researcher is able to arrange for counselling or some other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if you suffer from claustrophobia, we recommend that you do not participate. It also makes a loud hammering sound. You will wear headphones to lessen the scanner noise. You may also occasionally feel warmth. Foam cushioning and velcro straps are used to keep your head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with you during the scanning. If you are becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. You can also request that the scanning be stopped at any time by pushing on a button.
After your scan session, a radiologist will examine your brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, whichever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your brain which might, or might not, affect you later in life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you don’t wish to take part, you don’t have to do so. If you decide to take part and later change your mind, you are free to withdraw from this study at a later stage.

If you decide to withdraw, please notify a member of the research team before you withdraw.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you don’t want them to do this, you must tell them before you withdraw from the study.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team, if any.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

8. What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and only be used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.
In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

9. Can I access research information kept about me?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document, if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about you after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by Human Research Ethics Committee at St Vincent’s Hospital.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project (for example, feelings of distress), you can contact one of the principal researchers, Prof Susan Rossell on (03) 9214 8173 or any of the following people:

Name: Dr Larry Abel
Role: Principal Researcher
Telephone: (03) 8344 7007

Name: Ms Andrea Philippou
Role: Student Researcher
Telephone: 0401 675 741
For complaints:

If you have any complaints about any aspect of the study or the way in which it is being conducted, you may contact the Patient Liaison Officer at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3108. You will need to tell the Patient Liaison Officer the name of the person who is noted above as principal investigator.

Research Participant Rights If you have any questions about your rights as a research participant, then you may contact the Executive Officer Research at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3930.

12. Consent

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Please tick if you are agreeable to the optional task component, which involves taking your photograph, and including it a task that includes viewing faces.

Participant’s name (printed):

Signature: ___________________ Date: ___________________

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.

Name of witness to participant’s signature (printed):

Signature: ___________________ Date: ___________________

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Researcher’s name (printed):

Signature: ___________________ Date: ___________________
Participant Information and Consent Form, Control group
The University of Melbourne, St Vincent’s Hospital

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: A/Prof Larry Abel, The University of Melbourne

Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPrc)

Prof David Castle, St Vincent’s Hospital and The University of Melbourne

A/Prof Richard Newton, Austin Health

Dr William Woods, Swinburne University of Technology

Dr Charlotte Keating, Swinburne University of Technology

Dr Chia Huang, The Melbourne Clinic

Student Researcher: AndreaPhillipou, The University of Melbourne

Site of Research: The University of Melbourne, St Vincent’s Hospital, The Austin Hospital, The Melbourne Clinic, Swinburne University of Technology

1. Introduction

You are invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to complete certain tasks. This is because you have responded to an advertisement to participate as a control participant.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.
2. What is the purpose of this research project?

The reason this study is being undertaken is that although there are high rates of Anorexia Nervosa in today’s society, the psychological and neurological processes involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BETRS, the Melbourne Clinic or via advertisement in support groups, whereas healthy control participants will be recruited from the general public through advertisements.

The results of this research will be used by the researcher Andrea Phillipou to obtain a PhD degree.

This research has been funded in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation and the Dick & Pip Smith Foundation.

3. What does participation in this research project involve?

If you agree to participate in this study, you will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, gender, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking 2 different types of brain scans, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning. fMRI uses a strong magnetic field to produce images of the brain and measures brain activity by detecting changes in blood flow, whereas MEG is a technique for mapping electrical activity of the brain. During these scans participants will perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your face photographed, and having your photograph included amongst the existing task stimuli. Participation in this additional task is entirely voluntary, and if you don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- The MEG session

Before the MEG session begins, you will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. You will be asked to sit in a quiet room and sit in a chair where your head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, you will be able to speak to the researchers via an intercom at all times. Prior to entering the room you will be asked to remove any metal from your clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone, metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- The MRI session
After the MEG session we will ask you to have an MRI scan. Before the MRI session begins, you will be asked to complete a Swinburne MRI safety questionnaire administered by our staff radiographer that largely entails questions regarding any metal you have on or in your body, such as that from any surgery involving metal plates and pace makers, though other questions are asked. A copy of the safety questionnaire is attached to this document. Due to the nature of MRI, that involves strong magnetic fields, no metal can be taken into the room. It is very important that you fill in this questionnaire correctly, as some conditions, i.e. having a pacemaker, can be dangerous. The scanner is also quite noisy so you will be provided with some headphones to reduce this noise.

All three sessions will take place at the Brain and Psychological Sciences Research Centre (BPsyC) at Swinburne University of Technology. The time commitment for the first session is approximately 3 hours and 1.5-2.5 hours each for the second and third sessions, with breaks as required.

You will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive taxi vouchers for the three sessions.

4. What are the possible benefits?

There will be no clear immediate benefits to you from your participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. What are the possible risks?

In general, foreseeable risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will have the option to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

During the clinical screen if the investigator uncovers a suspected psychiatric diagnosis the research team will arrange for you to see a medical professional who is not part of the research team.

If you become upset or distressed as a result of your participation in this research project, the researcher is able to arrange for counselling or some other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if you suffer from claustrophobia, we recommend that you do not participate. It also makes a loud hammering sound. You will wear headphones to lessen the scanner noise. You may also occasionally feel warmth. Foam cushioning and head straps are used to keep your head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with you during the scanning. If you are becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and, if desired, continue at another time. You can also request that the scanning be stopped at any time by pushing on a button.
After your scan session, a radiologist will examine your brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, whichever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your brain which might, or might not, affect you later in life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you don’t wish to take part, you don’t have to do so. If you decide to take part and later change your mind, you are free to withdraw from this study at a later stage.

If you decide to withdraw, please notify a member of the research team before you withdraw.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you don’t want them to do this, you must tell them before you withdraw from the study.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team, if any.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

8. What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and only be used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.
In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

9. Can I access research information kept about me?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document, if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about you after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by Human Research Ethics Committee at St Vincent’s Hospital.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project (for example, feelings of distress), you can contact one of the principal researchers, Prof Susan Rossell on (03) 9214 8173 or any of the following people:

Name: Dr Larry Abel
Role: Principal Researcher
Telephone: (03) 8344 7007

Name: Ms Andrea Phillipou
Role: Student Researcher
Telephone: 0401 675 741
For complaints:
If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the Patient Liaison Officer at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3108. You will need to tell the Patient Liaison Officer the name of the person who is noted above as principal investigator.

Research Participant Rights If you have any questions about your rights as a research participant, then you may contact the Executive Officer Research at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3930.

12. Consent

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

☐ Please tick if you are agreeable to the optional task component, which involves taking your photograph, and including it a task that includes viewing faces.

Participant’s name (printed):
Signature: __________________________ Date: __________________________

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.

Name of witness to participant’s signature (printed):
Signature: __________________________ Date: __________________________

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Researcher’s name (printed):
Signature: __________________________ Date: __________________________
057/12. HREC-A 057/12.
Information sheet for persons participating in research projects

Parent Information and Consent Form, Anorexia Nervosa group
The University of Melbourne, St Vincent’s Hospital

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: A/Prof Larry Abel, The University of Melbourne

- Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPrc)
- Prof David Castle, St Vincent’s Hospital and The University of Melbourne
- A/Prof Richard Newton, Austin Health
- Dr William Woods, Swinburne University of Technology
- Dr Charlotte Keating, Swinburne University of Technology
- Dr Chia Huang, The Melbourne Clinic

Student Researcher: Andrea Phillipou, The University of Melbourne

Site of Research: The University of Melbourne, St Vincent’s Hospital, The Austin Hospital, The Melbourne Clinic, Swinburne University of Technology

1. Introduction

Your child is invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to undertake certain tasks. This is because your child has either been referred through the Body Image Eating Disorders Treatment & Recovery Service (BETRS) or you’ve responded to an advertisement.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want your child to take part.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don’t wish for your child to take part, they don’t have to.

If you decide you want your child to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent for your child to take part in the research project;
- consent for your child to be involved in the procedures described;
- consent to the use of your child’s personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.
2. **What is the purpose of this research project?**

The reason this study is being undertaken is that although Anorexia Nervosa is an increasingly prevalent condition in today’s society, the psychological and neurological mechanisms involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BETRS, the Melbourne Clinic or via advertisement in support groups, whereas healthy control participants will be recruited from the general public through advertisements.

The results of this research will be used by the researcher Andrea Philippou to obtain a PhD degree.

This research has been funded by in part by a setup grant provided to Prof Rossell at Swinburne University, by the Jack Brockhoff Foundation, and the Dick & Pip Smith Foundation.

3. **What does participation in this research project involve?**

If you agree for your child to participate in this study, they will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, gender, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking 2 different types of brain scans, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning. fMRI uses a strong magnetic field to produce images of the brain and measures brain activity by detecting changes in blood flow, whereas MEG is a technique for mapping electrical activity of the brain. During these scans participants will perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your child’s face photographed, and having their photograph included amongst the existing task stimuli. Participation in this additional task is entirely voluntary, and if you or your child don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- **The MEG session**

Before the MEG session begins, your child will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. Your child will be asked to sit in a quiet room and sit in a chair where their head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, they will be able to speak to the researchers via an intercom at all times. Prior to entering the room your child will be asked to remove any metal from their clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone, metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- **The MRI session**
After the MEG session we will ask your child to have an MRI scan that will be used to help analyse the MEG data. Before the MRI session begins, your child will be asked to complete a Swinburne MRI safety questionnaire administered by our staff radiographer that largely entails questions regarding any metal you have on or in your body, such as that from any surgery involving metal plates and pace makers, though other questions are asked. A copy of the safety questionnaire is attached to this document. Due to the nature of MRI, that involves strong magnetic fields, no metal can be taken into the room. It is very important that you fill in this questionnaire correctly, as some conditions, i.e. having a pacemaker, can be dangerous. The scanner is also quite noisy so your child will be provided with some headphones to reduce this noise.

All three sessions will take place at the Brain and Psychological Sciences Research Centre (BPsc) at Swinburne University of Technology. The time commitment for the first session is approximately 3 hours and approximately 1.5-2.5 hours each for the second and third sessions, with breaks as required.

Your child will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive taxi vouchers for the three sessions.

4. What are the possible benefits?

There will be no clear immediate benefits to you from your child’s participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. What are the possible risks?

In general, foreseeable risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they feel too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

During the clinical interview if the researcher has concerns over your child’s current presentation they will discuss these concerns with you and your child and contact your clinician, with your permission.

If your child becomes upset or distressed as a result of their participation in this research project, the researcher is able to arrange for counselling or some other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if your child suffers from claustrophobia, we recommend that they do not participate. It also makes a loud hammering sound. Your child will wear headphones to lessen the scanner noise. They may also occasionally feel warmth. Foam cushioning and velcro straps are used to keep your child’s head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with your child during the scanning. If your child is becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. Your child can also request that the scanning be stopped at any time by pushing on a button.
After your child’s scan session, a radiologist will examine their brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your child’s brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, whom ever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your child’s brain which might, or might not, affect your child later in life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

6. **Do I have to take part in this research project?**

Participation in any research project is voluntary. If you don’t wish for your child to take part, they don’t have to do so. If your child decides to take part and you or your child later change your mind, your child is free to withdraw from this study at a later stage.

If you or your child decide to withdraw, please notify a member of the research team before you withdraw.

If you or your child decide to leave the project, the researchers would like to keep the personal and health information about your child that has been collected. This is to help them make sure that the results of the research can be measured properly. If you don’t want them to do this, you must tell them before you withdraw from the study.

Your decision for your child to take part or not, or to take part and then withdraw, will not affect you or your child’s relationship with the researchers or members of your treating team, if any.

7. **How will I be informed of the final results of this research project?**

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

8. **What will happen to information about me?**

Any information obtained in connection with this research project that can identify your child will remain confidential and only be used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the
research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.

In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your child’s data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

9. Can I access research information kept about me?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about your child. Please contact one of the researchers named at the end of this document, if you would like to access your child’s information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about your child after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by Human Research Ethics Committee at St Vincent’s Hospital.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project (for example, feelings of distress), you can contact one of the principal researchers, Prof Susan Rossell on (03) 9214 8173 or any of the following people:

Name: Dr Larry Abel
Role: Principal Researcher
Telephone: (03) 8344 7007

Name: Ms Andrea Phillipou
Role: Student Researcher
Telephone: 0401 675 741

For complaints:

HREC-A057/12 Parent Information & Consent Form, Anorexia Nervosa group, Version 3.4, Date: 03/02/2014
If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the Patient Liaison Officer at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3108. You will need to tell the Patient Liaison Officer the name of the person who is noted above as principal investigator.

Research Participant Rights If you have any questions about your rights as a research participant, then you may contact the Executive Officer Research at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3930.

12. Consent

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree for my child to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

☐ Please tick if you are agreeable to the optional task component, which involves taking your child’s photograph, and including it a task that includes viewing faces.

Child’s name (printed):

Parent/Guardian’s name (printed):

Signature: ____________________ Date: ____________________

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.

_________________________________________________________

Name of witness to parent’s signature (printed):

Signature: ____________________ Date: ____________________

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Researcher’s name (printed):

Signature: ____________________ Date: ____________________
Parent Information and Consent Form, Control group
The University of Melbourne, St Vincent’s Hospital

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: A/Prof Larry Abel, The University of Melbourne
Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPRC)
Prof David Castle, St Vincent’s Hospital and The University of Melbourne
A/Prof Richard Newton, Austin Health
Dr William Woods, Swinburne University of Technology
Dr Charlotte Keating, Swinburne University of Technology
Dr Chia Huang, The Melbourne Clinic

Student Researcher: Andrea Phillipou, The University of Melbourne

Site of Research: The University of Melbourne, St Vincent’s Hospital, The Austin Hospital, The Melbourne Clinic, Swinburne University of Technology

1. Introduction

Your child is invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to undertake certain tasks. This is because you’ve responded to an advertisement for your child to participate as a control participant.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want your child to take part.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don’t wish for your child to take part, they don’t have to.

If you decide you want your child to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent for your child to take part in the research project;
- consent for your child to be involved in the procedures described;
- consent to the use of your child’s personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The reason this study is being undertaken is that although Anorexia Nervosa is an increasingly prevalent condition in today’s society, the psychological and neurological
mechanisms involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BEATRS, the Melbourne Clinic or via advertisement in support groups, whereas healthy control participants will be recruited from the general public through advertisements.

The results of this research will be used by the researcher Andrea Phillipou to obtain a PhD degree.

This research has been funded by in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation, and the Dick and Pip Smith Foundation.

3. What does participation in this research project involve?

If you agree for your child to participate in this study, they will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, gender, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking 2 different types of brain scans, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning. fMRI uses a strong magnetic field to produce images of the brain and measures brain activity by detecting changes in blood flow, whereas MEG is a technique for mapping electrical activity of the brain. During these scans participants will perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your child’s face photographed, and having their photograph included amongst the existing task stimuli. Participation in this additional task is entirely voluntary, and if you or your child don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- The MEG session

Before the MEG session begins, your child will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. Your child will be asked to sit in a quiet room and sit in a chair where their head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, they will be able to speak to the researchers via an intercom at all times. Prior to entering the room your child will be asked to remove any metal from their clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone, metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- The MRI session

After the MEG session we will ask your child to have an MRI scan that will be used to help analyse the MEG data. Before the MRI session begins, your child will be asked to complete a Swinburne MRI safety questionnaire administered by our staff radiographer.
that largely entails questions regarding any metal you have on or in your body, such as that from any surgery involving metal plates and pace makers, though other questions are asked. A copy of the safety questionnaire is attached to this document. Due to the nature of MRI, that involves strong magnetic fields, no metal can be taken into the room. It is very important that you fill in this questionnaire correctly, as some conditions, i.e. having a pacemaker, can be dangerous. The scanner is also quite noisy so your child will be provided with some headphones to reduce this noise.

All three sessions will take place at the Brain and Psychological Sciences Research Centre (BPsyC) at Swinburne University of Technology. The time commitment for the first session is approximately 3 hours and approximately 1.5-2.5 hours each for the second and third sessions, with breaks as required.

Your child will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive taxi vouchers for the three sessions.

4. **What are the possible benefits?**

There will be no clear immediate benefits to you from your child’s participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. **What are the possible risks?**

In general, foreseeable risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

During the clinical screen if the investigator uncovers a suspected psychiatric diagnosis the research team will arrange for your child to see a medical professional who is not part of the research team.

If your child becomes upset or distressed as a result of their participation in this research project, the researcher is able to arrange for counselling or some other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if your child suffers from claustrophobia, we recommend that they do not participate. It also makes a loud hammering sound. Your child will wear headphones to lessen the scanner noise. They may also occasionally feel warmth. Foam cushioning and velcro straps are used to keep your child’s head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with your child during the scanning. If your child is becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. Your child can also request that the scanning be stopped at any time by pushing on a button.

After your child’s scan session, a radiologist will examine their brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific
research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your child’s brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, which ever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your child’s brain which might, or might not, affect your child later in life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you don’t wish for your child to take part, they don’t have to do so. If your child decides to take part and you or your child later change your mind, your child is free to withdraw from this study at a later stage.

If you or your child decide to withdraw, please notify a member of the research team before you withdraw.

If you or your child decide to leave the project, the researchers would like to keep the personal and health information about your child that has been collected. This is to help them make sure that the results of the research can be measured properly. If you don’t want them to do this, you must tell them before you withdraw from the study.

Your decision for your child to take part or not, or to take part and then withdraw, will not affect you or your child’s relationship with the researchers or members of your treating team, if any.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

8. What will happen to information about me?

Any information obtained in connection with this research project that can identify your child will remain confidential and only be used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.
In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your child’s data to be stored for this, the collected data will be destroyed under the direction of the principal researcher after seven years.

9. Can I access research information kept about me?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about your child. Please contact one of the researchers named at the end of this document, if you would like to access your child’s information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about your child after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by Human Research Ethics Committee at St Vincent’s Hospital.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project (for example, feelings of distress), you can contact one of the principal researchers, Prof Susan Rossell on (03) 9214 8173 or any of the following people:

Name: Dr Larry Abel
Role: Principal Researcher
Telephone: (03) 8344 7007

Name: Ms Andrea Phillipou
Role: Student Researcher
Telephone: 0401 675 741

For complaints:
If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the Patient Liaison Officer at St Vincent’s Hospital (Melbourne) on Telephone: (03) 9288 3108. You will need to tell the Patient Liaison Officer the name of the person who is noted above as principal investigator.

Research Participant Rights If you have any questions about your rights as a research participant, then you may contact the Executive Officer Research at St Vincent’s Hospital (Melbourne) on Telephone: (02) 9288 3930.

12. Consent

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree for my child to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

☐ Please tick if you are agreeable to the optional task component, which involves taking your child’s photograph, and including it a task that includes viewing faces.

Child’s name (printed):

Parent/Guardian’s name (printed):

Signature: __________________________ Date: __________________________

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.

__________________________________________________________________________

Name of witness to parent’s signature (printed):

Signature: __________________________ Date: __________________________

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Researcher’s name (printed):

Signature: __________________________ Date: __________________________
Participant Information and Consent Form

Version 3.3, Dated 06/01/2014

Project No. H2012/04646

Participant Information and Consent Form

Body Image Eating Disorders Treatment and Recovery Service (BETRS), Austin Hospital

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researcher: A/Prof Larry Abel, The University of Melbourne

    Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPRC)
    Prof David Castle, St Vincent’s Hospital and The University of Melbourne
    A/Prof Richard Newton, Austin Health
    Dr William Woods, Swinburne University of Technology
    Dr Charlotte Keating, Swinburne University of Technology
    Dr Chia Huang, The Melbourne Clinic

Student Researcher: Ms Andrea Phillipou, The University of Melbourne

1. Introduction

You are invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to complete certain tasks. This is because you have either been referred through the Body Image Eating Disorders Treatment & Recovery Service (BETRS), you’ve responded to an advertisement or because you have been invited to participate as a control participant.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
2. What is the purpose of this research project?

The reason this study is being undertaken is that although there are high rates of Anorexia Nervosa in today’s society, the psychological and neurological processes involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BETRS, the Melbourne Clinic or via advertisement in support groups. The aim is to recruit approximately 10-15 individuals with Anorexia Nervosa from the inpatient service of the BETRS at the Austin, and 10-15 individuals with Anorexia Nervosa from the outpatient service of the BETRS at St Vincent’s site, and 5-10 individuals from the Melbourne Clinic. Healthy control participants will be recruited from the general public through advertisements.

Participants will be required to meet the following selection criteria: female; right handed; minimum of 16 years of age; are not pregnant; have no metallic pins or implants; English speaking; have no history of neurological condition or brain injury; no significant ocular pathology; no colour vision deficiency; normal visual acuity (correction with contact lenses is acceptable, but glasses cannot be worn); no psychotic conditions; and control participants will be required to have no history of an eating disorder or psychiatric condition.

The research involves the collaboration of researchers from The University of Melbourne, Swinburne University of Technology, Austin Health and St Vincent’s Health.

The results of this research will be used by the researcher Andrea Philippou to obtain a PhD degree.

This research has been funded in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation and the Dick & Pip Smith Foundation.

This research is being conducted by The University of Melbourne.

3. What does participation in this research project involve?

No interpreter will be used in the consent or data collection process; only individuals who are able to speak and understand English fluently will be invited to take part in this research project. If you agree to participate in this study, you will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, occupation, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning while participants perform a number of different tasks, which will require you to respond to different stimuli, including dots, and
human faces and bodies, as they appear on screen. An optional task involves having your face photographed, and having your photograph included amongst the existing task stimuli. The photograph of your face will be included in amongst other face stimuli during the MRI session. You will not be presented with the photographs of other people who participate in the project, nor will they be presented with your photograph. Participation in this additional task is entirely voluntary, and if you don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- **The MEG session**

Before the MEG session begins, you will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. You will be asked to sit in a quiet room and sit in a chair where your head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, you will be able to speak to the researchers via an intercom at all times. Prior to entering the room you will be asked to remove any metal from their clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- **The MRI session**

Magnetic Resonance Imaging (MRI) is a computerised scan performed in the x-ray department that provides a 3-dimensional picture of the inside of the body using a strong magnetic field. A MRI scan is performed like a CT scan. It is performed in a large, tunnel-shaped machine but it does not use x-rays. The MRI uses radio frequency waves, like those in an AM/FM radio, and a powerful magnet. The space inside the MRI scanner is quite confined and consists of a long, open cylinder that may produce feelings of claustrophobia or unease from being in a confined space. The MRI scanner is noisy while it is operating so you will wear earplugs or earphones to minimise the noise, the examiners talk with you via an intercom throughout the procedure in case you require anything. These scans are painless and you are required to remain still during the procedure.

You must not have any metal objects on or in your body, for example, brain aneurysm clips or a pacemaker, to be able to have a MRI scan.

The first sessions will take place at either the Body Image Eating Disorders Treatment and Recovery Service (BETRS), The University of Melbourne, or at the Brain and Psychological Sciences Research Centre (BPSyC) at Swinburne University of Technology, as you prefer. In this session you will be required to complete a set of neuropsychological assessments. The second and third sessions will take place at BPSyC at Swinburne University of Technology. In these sessions you will undertake the MRI and MEG scans. The time commitment is approximately 3 hours for the first session, and approximately 1.5-2.5 hours each for the second and third sessions.

You will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive an additional $100 in taxi vouchers in total over the three sessions.
4. **What are the possible benefits?**

There will be no clear immediate benefits to you from your participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. **What are the possible risks?**

In general, potential risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if you suffer from claustrophobia, we recommend that you do not participate. It also makes a loud hammering sound. You will wear headphones to lessen the scanner noise. You may also occasionally feel warmth. Foam cushioning and velcro straps are used to keep your head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with you during the scanning. If you are becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. You can also request that the scanning be stopped at any time by pushing on a button.

The effects of MRI on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you do become pregnant whilst participating in the study, you should advise your treating doctor immediately. Your doctor will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

After your scan session, a radiologist will examine your brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, whichever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your brain which might, or might not, affect you later in life. If you do not want to know, then it is better not to participate in this study.
Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team. In addition, you may prefer to suspend or end your participation in the research if distress occurs.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Can I have other treatments during this research project?

It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researcher about any changes to these during your participation in the research.

8. Are there alternatives to participation?

Participation in this research is not your only option. You are free to decline participation in this project or withdraw at any time once it has commenced. Discuss these options with your healthcare worker before deciding whether or not to take part in this research project.

9. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don’t have to. If you decide to take part and you later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team, if any.

10. What if I withdraw from this research project?

If you decide to withdraw, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you join the research project.
11. Could this research project be stopped unexpectedly?

Termination of the research project will only occur if participants wish to withdraw or participants experience unwanted effects, for example, anxiety or claustrophobia whilst in the scanner.

12. How will I be informed of the results of this research project?

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

13. What else do I need to know?

- What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

- How can I access my information?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document, if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about you after this point will not be possible.

- What happens if I am injured as a result of participating in this research project?
If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

### 14. Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The University of Melbourne concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

☐ Please tick if you are agreeable to the optional task component, which involves taking your photograph, and including it in a task that includes viewing faces.

Participant’s name (printed) ..........................................................

Signature  
Date

Name of witness to participant’s signature (printed) ...........................................

Signature  
Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian of the participant has understood that explanation.

Researcher’s name (printed) ..........................................................

Signature  
Date
* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the consent section must date their own signature.

15. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher, Dr Larry Abel, on (03) 8344 7007 or any of the following people:

Name: Prof Rossell
Role: Principal researcher
Telephone: (03) 9076 8650

Name: Prof Newton
Role: Principal researcher
Telephone: (03) 9496 6496

For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Siama Panagiotopoulou
Position: Manager, Office for Research
Telephone: (03) 9496 5088
Parent/Guardian Information and Consent Form

Parent/Guardian Information and Consent Form

Body Image Eating Disorders Treatment and Recovery Service (BETRS), Austin Hospital

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: A/Prof. Larry Abel, The University of Melbourne

Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPrc)

Prof David Castle, St Vincent’s Hospital and The University of Melbourne

A/Prof Richard Newton, Austin Health

Dr William Woods, Swinburne University of Technology

Dr Charlotte Keating, Swinburne University of Technology

Dr Chia Huang, The Melbourne Clinic

Student Researchers: Ms Andrea Phillipou, The University of Melbourne

1. Introduction

Your child is invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to complete certain tasks. This is because your child has either been referred through the Body Image Eating Disorders Treatment & Recovery Service (BETRS), you’ve responded to an advertisement or because your child has been invited to participate as a control participant.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don’t wish for your child to take part, they don’t have to. Your child will receive the best possible care whether they take part or not.

If you decide you want your child to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
2. What is the purpose of this research project?

The reason this study is being undertaken is that although there are high rates of Anorexia Nervosa in today’s society, the psychological and neurological processes involved in the development and maintenance of the condition are still poorly understood.

A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited through BETRS, the Melbourne Clinic or via advertisement in support groups. The aim is to recruit approximately 10-15 individuals with Anorexia Nervosa from the inpatient service of the BETRS at the Austin, 10-15 individuals with Anorexia Nervosa from the outpatient service of the BETRS at the St Vincent’s site, and 5-10 individuals from the Melbourne Clinic site. Healthy control participants will be recruited from the general public through advertisements.

Participants will be required to meet the following selection criteria: female; right handed; minimum of 16 years of age; are not pregnant; have no metallic pins or implants; English speaking; have no history of neurological condition or brain injury; no significant ocular pathology; no colour vision deficiency; normal visual acuity (correction with contact lenses is acceptable, but glasses cannot be worn); no psychotic conditions; and control participants will be required to have no history of an eating disorder or psychiatric condition.

The research involves the collaboration of researchers from The University of Melbourne, Swinburne University of Technology, Austin Health and St Vincent’s Health.

The results of this research will be used by the researcher Andrea Philiopoulos to obtain a PhD degree.

This research has been funded in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation and the Dick & Pip Smith Foundation.

This research is being conducted by The University of Melbourne.

3. What does participation in this research project involve?

No interpreter will be used in the consent or data collection process; only individuals who are able to speak and understand English fluently will be invited to take part in this research project. If you agree for your child to participate in this study, they will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, occupation, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning while
participants perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your child’s face photographed, and having their photograph included amongst the existing task stimuli. The photograph of your child’s face will be included in amongst other face stimuli during the MRI session. Your child will not be presented with the photographs of other people who participate in the project, nor will they be presented with your child’s photograph. Participation in this additional task is entirely voluntary, and if you or your child don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- The MEG session

Before the MEG session begins, your child will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. Your child will be asked to sit in a quiet room and sit in a chair where your head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, your child will be able to speak to the researchers via an intercom at all times. Prior to entering the room your child will be asked to remove any metal from their clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- The MRI session

Magnetic Resonance Imaging (MRI) is a computerised scan performed in the x-ray department that provides a 3-dimensional picture of the inside of the body using a strong magnetic field. A MRI scan is performed like a CT scan. It is performed in a large, tunnel-shaped machine but it does not use x-rays. The MRI uses radio frequency waves, like those in an AM/FM radio, and a powerful magnet. The space inside the MRI scanner is quite confined and consists of a long, open cylinder that may produce feelings of claustrophobia or unease from being in a confined space. The MRI scanner is noisy while it is operating so your child will wear earplugs or earphones to minimise the noise, the examiners talk with your child via an intercom throughout the procedure in case they require anything. These scans are painless and your child is required to remain still during the procedure.

Your child must not have any metal objects on or in their body, for example, brain aneurysm clips or a pacemaker, to be able to have a MRI scan.

The first session will take place at either the Body Image Eating Disorders Treatment and Recovery Service (BETRS), The University of Melbourne, or at the Brain and Psychological Sciences Research Centre (BPsyC) at Swinburne University of Technology, as you prefer. In this session your child will be required to complete a set of neuropsychological assessments. The second and third sessions will take place at BPsyC at Swinburne University of Technology. In these sessions your child will undertake the MRI and MEG scans. The time commitment is approximately 3 hours for the first session, and approximately 1.5-2.5 hours each for the second and third sessions.

Your child will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will receive an additional $100 in taxi vouchers in total over the three sessions.
4. What are the possible benefits?

There will be no clear immediate benefits to you or your child from your child’s participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. What are the possible risks?

In general, potential risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if your child suffers from claustrophobia, we recommend that they do not participate. It also makes a loud hammering sound. Your child will wear headphones to lessen the scanner noise. Your child may also occasionally feel warmth. Foam cushioning and Velcro straps are used to keep your child’s head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with your child during the scanning. If your child is becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. Your child can also request that the scanning be stopped at any time by pushing on a button.

The effects of MRI on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. Your child must not participate in the research if they are pregnant or trying to become pregnant, or breast-feeding. If they do become pregnant whilst participating in the study, you should advise your treating doctor immediately. Your doctor will withdraw your child from the study and advise on further medical attention should this be necessary. Your child must not continue in the research if they become pregnant.

After your child’s scan session, a radiologist will examine their brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found that is significant and which should be investigated further. If such an abnormality is detected in your child’s brain, you will be contacted by Swinburne’s radiologist or your nominated health practitioner (GP, psychiatrist or neurologist, which ever you have nominated on your demographic form). It is their responsibility to follow up these findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one is detected and you are informed, then this knowledge may have consequences for you or your child. Please take the time to consider carefully what it would mean to you if you were informed of an abnormality in your child’s brain which might, or might not, affect
them later in life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne University MRI consent form (MRI-14) to ensure that there are no MRI contraindications that may cause risks in or around the scanner.

If your child becomes upset or distressed as a result of their participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team. In addition, you may prefer to suspend or end your child’s participation in the research if distress occurs.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Can I have other treatments during this research project?

It is important to tell your doctor and the research staff about any treatments or medications your child may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researcher about any changes to these during your child’s participation in the research.

8. Are there alternatives to participation?

Participation in this research is not your only option. Your child is free to decline participation in this project or withdraw at any time once it has commenced. Discuss these options with your healthcare worker before deciding whether or not to take part in this research project.

9. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for your child to take part they don’t have to. If you decide for your child to take part and you or your child later change your mind, they are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team, if any.

10. What if I withdraw from this research project?

If you decide for your child to withdraw, please notify a member of the research team before they withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide for your child to leave the project, the researchers would like to keep the personal and health information about them that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before your child joins the research project.
11. Could this research project be stopped unexpectedly?

Termination of the research project will only occur if participants or parents wish to withdraw or participants experience unwanted effects, for example, anxiety or claustrophobia whilst in the scanner.

12. How will I be informed of the results of this research project?

A summary of the general findings of this research project will be made available to all participants via post or email, if they have indicated consent to receive such further communication. These results will also be reported in a thesis, and potentially published in appropriate scientific journals and/or presented at academic conferences. Final results may be expected to be available at the end of 2014.

13. What else do I need to know?

- What will happen to information about me?

Any information obtained in connection with this research project that can identify your child will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and replaced by a code, so that participants will not be able to be individually identified. All data will be stored securely, under lock-and-key, or via password protection, at the research venue. Access to the data will only be available to the principal researchers and the supervised PhD student responsible for this study.

In any publication and/or presentation, information will be provided in such a way that your child cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your child’s data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

- How can I access my information?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about your child. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document, if you would like to access your child’s information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about your child after this point will not be possible.

- What happens if I am injured as a result of participating in this research project?
If your child suffers an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect for your child to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

14. **Consent**

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The University of Melbourne concerning my child's disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree for my child to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

☐ **Please tick if you are agreeable to the optional task component, which involves taking your child's photograph, and including it in a task that includes viewing faces.**

Parent/guardian's name (printed) ................................................

Signature  
Date

Name of witness to parent/guardian's signature (printed) ........................................

Signature  
Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian of the participant has understood that explanation.

Researcher's name (printed) ............................................................

Signature  
Date
* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the consent section must date their own signature.

15. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher, Dr Larry Abel, on (03) 8344 7007 or any of the following people:

Name: Prof Rossell
Role: Principal researcher
Telephone: (03) 9076 8650

Name: Prof Newton
Role: Principal researcher
Telephone: (03) 9496 6496

For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Sianna Panagiopoulou
Position: Manager, Office for Research
Telephone: (03) 9496 5088
Information sheet for persons participating in research projects

Participant Information and Consent Form

Full Project Title: Investigating the neurobiological and cognitive features of Anorexia Nervosa

Principal Researchers: Dr Larry Abel, The University of Melbourne
Prof Susan Rossell, Swinburne University of Technology and Monash Alfred Psychiatry Research Centre (MAPrc)
Prof David Castle, St Vincent’s Hospital and The University of Melbourne
A/Prof Richard Newton, Austin Health
Dr William Woods, Swinburne University of Technology
Dr Charlotte Keating, Swinburne University of Technology
Dr Chia Huang, The Melbourne Clinic

Student Researcher: Andrea Philippou, The University of Melbourne

1. Introduction

You are invited to take part in this research project which aims to investigate whether individuals diagnosed with Anorexia Nervosa use different strategies to complete certain tasks. This is because you have either been referred through The Melbourne Clinic or you’ve responded to an advertisement.

This Participant Information and Consent Form tells you about the research project. It explains what is involved to help you decide if you want to take part.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local health worker.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The reason this study is being undertaken is that although there are high rates of Anorexia Nervosa in today’s society, the psychological and neurological processes involved in the development and maintenance of the condition are still poorly understood.
A group of 25 individuals with Anorexia Nervosa and a control group of 25 healthy individuals will be invited to take part in this study. Individuals with Anorexia Nervosa will be recruited though The Melbourne Clinic, the Body Image Eating Disorders Treatment and Recovery Service (BETRS) or via advertisement in support groups, whereas healthy control participants will be recruited from the general public through advertisements.

The results of this research will be used by the researcher Andrea Phillipou to obtain a PhD degree.

This research has been funded in part by a setup grant provided to Prof Rossell at Swinburne University, the Jack Brockhoff Foundation, and the Dick and Pip Smith Foundation.

3. What does participation in this research project involve?

If you agree to participate in this study, you will be asked to participate in three sessions. Over the three sessions a set of neuropsychological tests will be administered to participants to assess a number of cognitive functions. Basic information about age, gender, etc., will also be collected. Body mass index (BMI) will also be measured which requires participants’ height and weight to be recorded. Participation will also involve undertaking 2 different types of brain scans, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) scanning. fMRI uses a strong magnetic field to produce images of the brain and measures brain activity by detecting changes in blood flow, whereas MEG is a technique for mapping electrical activity of the brain. During these scans participants will perform a number of different tasks, which will require them to respond to different stimuli, including dots, and human faces and bodies, as they appear on screen. An optional task involves having your face photographed, and having your photograph included amongst the existing task stimuli. Participation in this additional task is entirely voluntary, and if you don’t feel comfortable taking part, you are under no obligation to do so. While participants undertake tasks in both scanners, their eye movements will also be recorded. The eye-tracking technique, as well as the fMRI and MEG scanning techniques, are non-invasive and should cause minimal discomfort.

- The MEG session

Before the MEG session begins, you will be asked to complete a Swinburne MEG safety questionnaire. MEG is a non-invasive brain imaging technique that is safe. Tiny sensors in a helmet pick up electrical activity of the brain. You will be asked to sit in a quiet room and sit in a chair where your head will be raised into the MEG helmet. The researchers will be on the outside of this specially designed room to reduce interference. However, you will be able to speak to the researchers via an intercom at all times. Prior to entering the room you will be asked to remove any metal from your clothes, or to get changed into non-metallic clothes provided by the researchers. Although MEG presents no dangers to anyone, metal on clothes and on your person can destroy the sensors of the MEG, so no metallic objects can be taken into the special MEG room.

- The MRI session

After the MEG session we will ask you to have an MRI scan. Before the MRI session begins, you will be asked to complete a Swinburne MRI safety questionnaire administered by our staff radiographer that largely entails questions regarding any metal you have on or in your body, such as that from any surgery involving metal plates and pace makers, though other questions are asked. A copy of the safety questionnaire is
attached to this document. Due to the nature of MRI, that involves strong magnetic fields, no metal can be taken into the room. It is very important that you fill in this questionnaire correctly, as some conditions, i.e. having a pacemaker, can be dangerous. The scanner is also quite noisy so you will be provided with some headphones to reduce this noise.

All three sessions will take place at the Brain and Psychological Sciences Research Centre (BPsc) at Swinburne University of Technology. The time commitment for the first session is approximately 3 hours and approximately 1.5-2.5 hours each for the second and third sessions, with breaks as required.

You will be reimbursed with a total of $100 to cover costs you may incur as a result of participating in this research project. Anorexia Nervosa patients requiring assisted transportation will also receive taxi vouchers to and from the testing venue.

4. What are the possible benefits?

There will be no clear immediate benefits to you from your participation in this research project; however, possible future benefits may include early identification and intervention measures as well as possible advances in treatments for Anorexia Nervosa.

5. What are the possible risks?

In general, foreseeable risks and side effects to participants in this research project are minimal. Possible discomforts primarily relate to a small degree of physical fatigue that may accompany remaining in the same position as scanning is being undertaken. Participants will be free to withdraw from the scanning if they are feeling too much discomfort. Some individuals may also feel somewhat uncomfortable about viewing their own face on the computer screen. This task component has thus been made entirely voluntary, so that participants may decline involvement if they so wish.

During the clinical interview if the researcher has concerns over your current presentation they will discuss these concerns with you and contact your clinician, with your permission.

If you become upset or distressed as a result of your participation in this research project, the researcher is able to arrange for counselling or some other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

There are no known risks associated with MEG.

MRI is a little different: it is shaped like a tunnel and is a bit tight for space, so if you suffer from claustrophobia, we recommend that you do not participate. It also makes a loud hampering sound. You will wear headphones to lessen the scanner noise. You may also occasionally feel warmth. Foam cushioning and velcro straps are used to keep your head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with you during the scanning. If you are becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. You can also request that the scanning be stopped at any time by pushing on a button.

After your scan session, a radiologist will examine your brain scans (this will not be done on the day of your study). Minor changes are sometimes found in completely healthy people. You should be aware that because the scans are taken for a specific research purpose, not all abnormalities that might be detected by other Magnetic Resonance scans are necessarily seen. On extremely rare occasions, an abnormality may be found
that is significant and which should be investigated further. If such an abnormality is
detected in your brain, you will be contacted by Swinburne’s radiologist or your
nominated health practitioner (GP, psychiatrist or neurologist, which ever you have
ominated on your demographic form). It is their responsibility to follow up these
findings with you.

Although a significant abnormality is extremely unlikely, you should be aware that if one
is detected and you are informed, then this knowledge may have consequences for you.
Please take the time to consider carefully what it would mean to you if you were
informed of an abnormality in your brain which might, or might not, affect you later in
life. If you do not want to know, then it is better not to participate in this study.

Participants must take time to answer all the questions in the attached Swinburne
University MRI consent form (MRI-14) to ensure that there are no MRI contraindications
that may cause risks in or around the scanner.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you don’t wish to take part, you
don’t have to do so. If you decide to take part and later change your mind, you are free
to withdraw from this study at a later stage.

If you decide to withdraw, please notify a member of the research team before you
withdraw.

If you decide to leave the project, the researchers would like to keep the personal and
health information about you that has been collected. This is to help them make sure
that the results of the research can be measured properly. If you don’t want them to do
this, you must tell them before you withdraw from the study.

Your decision whether to take part or not, or to take part and then withdraw, will not
affect your relationship with the researchers or members of your treating team, if any.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research project will be made available to all
participants via post or email, if they have indicated consent to receive such further
communication. These results will also be reported in a thesis, and potentially published
in appropriate scientific journals and/or presented at academic conferences. Final results
may be expected to be available at the end of 2014.

8. What will happen to information about me?

Any information obtained in connection with this research project that can identify you
will remain confidential and only be used for the purpose of this study. It will only be
disclosed with your permission, except as required by law.

In the handling of data, all references to personal information will be removed and
replaced by a code, so that participants will not be able to be individually identified. All
data will be stored securely, under lock-and-key, or via password protection, at the
research venue. Access to the data will only be available to the principal researchers and
the supervised PhD student responsible for this study.

In any publication and/or presentation, information will be provided in such a way that
you cannot be identified, except with your permission. All participants will remain
anonymous, with results presented as pooled group data only.
Data derived from this study may be compared with that from a previous study conducted by the same investigators.

If you agree for your data to be stored for this project, the collected data will be destroyed under the direction of the principal researcher after seven years.

9. Can I access research information kept about me?

In accordance with the relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document, if you would like to access your information.

Further, in accordance with regulatory guidelines, the information collected in this research project will be kept for at least five years. You must be aware that the information may become de-identified at some point, and access to information about you after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by Human Research Ethics Committee at The Melbourne Clinic.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project (for example, feelings of distress), you can contact one of the principal researchers, Prof Susan Rossell on (03) 9214 8173 or any of the following people:

Name: Dr Larry Abel
Role: Principal Researcher
Telephone: (03) 8344 7007

Name: Ms Andrea Phillipou
Role: Student Researcher
Telephone: 0401 675 741

For complaints:

If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the chairmen of the Research Ethics Committee at The Melbourne Clinic on Telephone: (03) 9420 9350.
COGNITIVE AND GENETIC EXPLANATIONS OF MENTAL ILLNESSES (CAGEMIS) BIO-DATABANK

Participant Information & Consent Form

Principal Researchers: Professor Susan Rossell & Professor Jayashri Kulkami

This Participant Information Sheet contains detailed information about the project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this document carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker. Participation in this research is voluntary. If you don’t wish to take part, you don’t have to.

You will be given a copy of the Participant Information Sheet to keep as a record.

1. What is the purpose of the CAGEMIS bio-databank?

The main purpose for the data-biobank is to bring together information regarding the symptoms, cognitive functioning and genetic factors involved in schizophrenia, bipolar disorder and other mental conditions. The CAGEMIS bio-databank is proposed to be an indefinite store and source of this information. Through a clearer understanding of these aspects, methods of future research into the causes, origins and effects of both illnesses could be improved. This will then lead to potential therapeutic and life course benefits for individuals.

Who is participating?

The CAGEMIS bio-databank is collecting information from people with schizophrenia, bipolar disorders and other mental conditions, relatives of people with these illnesses, and other healthy volunteers. We hope that comparing the results of these different groups of samples will help us uncover the genetic and cognitive causes of mental illness. You are invited to participate in this research project because you fall into one of these groups, and have agreed to participate in a related cognitive/linguistic/genetic study at MAPrc.
2. What will I have to do?

Participation in this project will involve you consenting to having your personal information (including age, highest education level), medical history (if applicable) and cognitive and linguistic test data entered into the CAGEMIS bio-databank. This information would have been collected only in a previous or current related study (known as a feeder study) in which you have consented to participate and have your data made available for future research. As mentioned above, all future research conducted with data stored in CAGEMIS will be related to studies investigating cognition, symptoms and the link to genes in schizophrenia, bipolar disorder and other mental conditions.

Additionally, if you have contributed a blood sample as part of the study you are/were involved in, we are asking that you allow us to store and use the genetic information collected as part of this bio-databank. You would have already been informed of the storage conditions of your blood sample through the information sheets of the study you are participating in. This genetic information will assist us in understanding the genetic factors involved in schizophrenia, bipolar disorder and other mental conditions as specified, and any relationships between genes and other symptoms of these illnesses. Stored blood samples will be used in future projects (with ethics approval) to conduct additional genetic testing which may be relevant to later areas of investigation.

If you do not wish to donate your blood sample for storage and future analyses, but still wish to donate your other test data (which includes the results of genetic tests already completed as part of the feeder study), you will be given an opportunity to specify this on the consent form page at the end of this document.

You do not have to complete any other testing.

This whole process, including reading this information sheet and providing consent should not take more than 10 minutes. This will take place at the Monash-Alfred Psychiatry research centre (MAPrc). The MAPrc is located at:

Level 1, Old Baker Building
Alfred Hospital
Commercial Rd
Melbourne, Victoria, 3004

You will not be paid for your participation in this research project.

3. What are the possible benefits?

There will be no clear benefit to you from your participation in this research. However, future analyses on the pooled data in the bio-databank may lead to the development of new and better diagnostic and therapeutic methods in future.

4. What are the possible risks?

There are no foreseeable risks of participation in this research project.
5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part you don't have to. You are also free to request that your information stored in the databank be withdrawn at any time.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project as specified.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your participation in other studies with MAPrc or your relationship with the Alfred Hospital.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you agree to participate and then decide to withdraw, please complete and return the Revocation of Consent Form, attached at the end of this document. Alternatively, you may notify the Principal Researcher Professor Susan Rossell in writing (contact details below in Section 8). Once we receive your request, all your details and information we may have obtained will be deleted from the CAGEMIS bio-database database. If you have donated a blood sample, this will also be destroyed. A letter of confirmation will be sent to you verifying that these procedures have been followed.

6. Can I be updated on research done with information from this databank?

Results will potentially be published in appropriate scientific journals and presented at academic conferences. All data in this report will be presented as group data, thereby maintaining your confidentiality.

We would like to keep you informed of our progress and plan to send out an annual update of our research activities in the form of a one-page newsletter to CAGES-B bio-database donors. The information in the newsletter will not identify any of the donors, unless we have their permission.

Please advise us on the consent form if you do not wish to receive the newsletter.

7. Will my details be kept confidential?

Yes: Any information obtained in connection with this research project that can identify you will be treated as highly confidential and securely stored. Information that you give us will be stored in the databank and used for the future research projects as described in section 1. Identifying information, including your name, address, telephone number and email, will not be stored with your test data in the databank. These will be stored separately, and only accessible by the principal researcher. Similarly, the blood sample will be labeled with a code number and stored in a fridge on a separate site.

All information about you will NOT be disclosed, except with your permission. However, in some circumstances, we may be required to disclose information for legal reasons. If we are required to disclose information that identifies you, we will
do our best to notify you before we disclose it. To our knowledge, researchers at this institution have not been required by law to provide information.

If you give us your permission by signing the Consent Form:

* The CAGEMIS bio-databank will collect and collate **ONLY** your demographic, cognitive, linguistic and genetic (if applicable) test data from the related study that you are participating, or have participated in. This information will be stored indefinitely according to standard Alfred research policy. This information will be stored in a secure password-protected electronic databank within the offices of MAPrc, without any personally identifying information attached to them.

* Only the principal researcher will have the key to re-identify these codes if we need to contact you, with approval from the Human Research Ethics Committee.

* your blood sample (if one is donated as part of the current feeder study) will be stored in a low-temperature fridge at an approved site. No identifying information will be attached to the blood sample.

For all research uses of your test data, blood sample (for genetic analysis) and accompanying information, a code number will be assigned so that none of your personal identifying details are attached. These personal identifying details will be stored separately from the actual test data, and only accessible by the principal researcher. This is called "de-identified" information. Researchers authorised by the Human Research Ethics Committee may access only your de-identified data and information to complete their research.

In any publication, information will be provided in such a way that you cannot be identified.

In accordance with the *Freedom of Information Act 1982* (Vic), you have the right to access and to request correction of information held about you by the CAGEMIS bio-databank; and can do this by contacting the bio-databank (see contact details in Section 8).

8. **Who can I contact?**

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

**For further information:**

Professor Susan Rossell  
Monash Alfred Psychiatry research centre  
Level 1, Old Baker Building  
Alfred Hospital  
Commercial Rd  
Melbourne, Victoria, 3004

Telephone: 03 9076 6850  
Fax: 03 9207 1545  
Email: Susan.Rossell@monash.edu
For complaints:
If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Ms Rowan Frew
Position: Ethics Manager, Research & Ethics Unit
Telephone: 03 9076 3848

9. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans 2007 produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committees of The Alfred Hospital and the Baker IDI Heart and Diabetes Institute.
COGNITIVE AND GENETIC EXPLANATIONS OF MENTAL ILLNESSES (CAGEMIS) BIO-DATABANK

CONSENT FORM

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my demographic, cognitive, linguistic or genetic data to be released to the CAGEMIS bio-databank. I understand that such information will remain confidential, and only accessible to authorized personnel.

My consent to all future studies involving my demographic, cognitive, linguistic or genetic test data from the CAGEMIS bio-databank, as described in Section 2 above, is ongoing unless I choose to withdraw from the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

☐ I would like to receive the annual CAGEMIS bio-databank donors newsletter.

Participant’s name (printed) ________________________________

Signature __________________________________________ Date __________

Name of witness to participant’s signature (printed) ________________________________

Signature __________________________________________ Date __________

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher’s name (printed) ________________________________

Signature __________________________________________ Date __________

If you have donated a blood sample in a feeder study:

I freely give/do not give my permission for my blood sample to be stored and accessed by the CAGEMIS bio-databank for the purposes of future genetic testing. I understand that this will be in line with the descriptions provided to me in this document.

Participant’s name (printed) ________________________________

Signature __________________________________________ Date __________

Name of witness to participant’s signature (printed) ________________________________

Signature __________________________________________ Date __________
COGNITIVE AND GENETIC EXPLANATIONS OF MENTAL ILLNESSES (CAGEMIS) BIO-DATABANK

REVOCATION OF CONSENT FORM

Principal Researcher: Professor Susan Rossell
Monash Alfred Psychiatry research centre
Level 1, Old Baker Building
Alfred Hospital
Commercial Rd
Melbourne, Victoria, 3004

Telephone: 03 9076 6850
Fax: 03 9207 1545
Email: Susan.Rossell@monash.edu

*To withdraw from this project, please mail or fax this form to the principal researcher at the contact details above.

I hereby wish to WITHDRAW my consent to have my data stored in the CAGEMIS bio-databank for the purposes of future research.

If I have donated a blood sample in a feeder study, I wish to WITHDRAW my consent for CAGEMIS to access my stored blood sample for the purposes of future genetic testing. I understand that this blood sample will be destroyed immediately (if the genetic analysis I consented to in the feeder study is complete) or immediately after it is completed.

I understand that all my data entered into the CAGEMIS bio-databank will be removed from the CAGEMIS bio-databank permanently. I also understand that CAGEMIS will no longer have access to my stored blood sample donated in the feeder study that I participated in.

I understand that my withdrawal from participating in the CAGEMIS bio-databank WILL NOT affect my participation in other current or future research projects at MAPrc or the Alfred Hospital.

I understand that my withdrawal WILL NOT affect my treatment or any relationship with MAPrc and the Alfred Hospital.

Participant’s Name (printed):

Signature
Date

PICF Version 9, Date: 30/04/12
Page 7 of 7
M.R.I. Pre Scan Information

WHAT IS AN M.R.I.?
Magnetic Resonance Imaging (M.R.I.) is a medical imaging technique that uses a powerful magnetic field and radio-frequencies to obtain very detailed cross-sectional images inside the body.

IS THERE ANY PREPARATION?
To help us provide an efficient service, you could assist us by: wearing clothing that does not have metal fastenings; not wearing any jewellery and removing all eye make-up (as this can interfere with scans of the head). You will also be required to complete an M.R.I. safety questionnaire before your scan.

CAN ANYONE HAVE AN M.R.I. SCAN?
No. There are some preconditions which can make M.R.I. scanning hazardous. Due to the powerful M.R.I. magnetic field, any person with a pacemaker, metal clips on arteries or certain implanted devices cannot have an M.R.I. scan. Women who are pregnant or breast feeding cannot have an M.R.I. scan. It is also advisable for some people with specific medical conditions not to have a scan. These conditions will be rigorously screened for during your pre-assessment for M.R.I. scanning.

IS AN M.R.I. SCAN SAFE?
M.R.I. scanning has been in use as a medical imaging tool for many years and with proper safety controls is commonly regarded by clinicians as a safe procedure. It does not employ ionising radiation (such as x-rays) and hence does not induce an additional cancer risk. It does however entail exposure to electromagnetic fields (E.M.F.) which are much higher than levels recommended by international safety guidelines for general exposure (though still within limits of special guidelines for M.R.I. scanning). Very occasionally, these E.M.F.s may cause some tingling or heating sensations. These effects do not persist after scanning and have no known long term impact on health. Your M.R.I. exposure will be carefully controlled to avoid such effects, and you will be constantly monitored for any signs of these effects and may direct us to stop the scan at any time if you experience uncomfortable sensations. The staff on duty will answer any queries you might have on the day, or if in doubt, call our department before your appointment.

WHAT WILL HAPPEN WHEN I ARRIVE?
The M.R.I. Radiographer or another senior M.R.I. staff member will greet you at the M.R.I. unit waiting room and reception, explain the procedure and ask you questions about previous surgery you may have had regarding implanted metal in your body. You will be asked to leave your valuables (coins, keys, watch, jewellery, credit cards, mobile phones, pagers etc) in a locker. The staff member will guide you on to our M.R.I. scan table. Some equipment may be placed around the body part we will be scanning.

THE SCANNING PROCESS
When we are taking the pictures, you will hear a very loud sound, rather like a vibration, and hearing protection will be provided. When you hear this noise it is important that you keep your body very still as movement will degrade the quality of the image. Usually there are about 4 or 5 different scans, lasting for 2-8 minutes each; and for most studies you will be in the scanner for about 60 minutes. You are welcome to bring along your favourite CD or cassette to listen to, during your scan.

WHAT WILL HAPPEN AFTER THE SCAN?
You can leave immediately after your scan. The images that have been taken will be used to address the research question for the study you have agreed to take part in. In addition they will be examined by a Radiologist. On extremely rare occasions, the radiologist might find an abnormality that is significant and which should be investigated further. If the Radiologist finds such a significant abnormality in your brain, he/she will contact the researcher directly involved in the study. It is then their responsibility to follow up with you; they will speak with your GP who can recommend the most appropriate action.
MRI Pre Scan Safety Questionnaire

This questionnaire is designed to screen for various conditions in a potential MRI participant which could lead to moderate or serious injury during MRI scanning. It is VERY important that you complete it as honestly and comprehensively as possible – please ask if you have any questions. This form will be checked by MRI staff on your arrival.

NAME: ___________ DATE: ___________ ID No. _____

DATE OF BIRTH: ___________ HEIGHT: ___________ WEIGHT: ___________

STUDY/PROJECT NAME: ________________________________________________________________________________

Please circle if any of the following are relevant to you: Please circle

Do you have or have you ever had a cardia pacemaker? YES/NO
Do you have an implanted cardiac defibrillator? YES/NO
Do you have an aneurysm clip or been treated for a aneurysm in the head? YES/NO
Do you have cochlear or stapes Implant? YES/NO
Do you have a neurostimulator or spinal cord stimulator? YES/NO
Do you have any implanted electronic or magnetically activated devices? YES/NO
Have you ever had any metal enter your eyes? (Cutting metal, grinding or welding) YES/NO
If yes, was it removed by a doctor? YES/NO

If you answered “Yes” to any of the questions above, please contact MRI on 9214 5514.

Please indicate if you have any of the following:

Hip replacement or artificial joint? YES/NO Contraceptive IUD? YES/NO
Pin, plate or screw? YES/NO Inflatable breast implant? YES/NO
Prosthesis-eye, limb, penile implant? YES/NO Are you/could you be pregnant? YES/NO
Implanted coil, filter, shunt or stent? YES/NO Medication patches applied? YES/NO
Eyeliner or other facial make up? YES/NO Wire mesh implanted? YES/NO
Piercings or any jewellery? YES/NO Spine or head shunt? YES/NO
Hearing aid? YES/NO Vascular port or catheter? YES/NO
Eyelid spring or wire? YES/NO Any other implanted metal? YES/NO
Do you have any tattoos? YES/NO Any metal foreign bodies? YES/NO
Artificial heart valve? YES/NO Other concerns? YES/NO

SIGNATURE: ____________________________________________________________

MRI-15 Checklist and consent form for participants no contrast version 2  Page 2 of 3
PARTICIPANT CONSENT

Are you breast-feeding?        YES/NO
Do you suffer from claustrophobia?        YES/NO
Do you suffer from epilepsy or ever had a seizure?        YES/NO
Do you wear braces, a dental plate or false teeth?        YES/NO
Do you suffer from any heart condition that would make you susceptible to an increased risk of cardiac arrest?        YES/NO
Have you ever had a surgical operation?        YES/NO
If yes, please provide details of body area (head, arm) and medical condition

Have you had a MRI scan before?        YES/NO
If yes, where? .......................................................... Clinical purposes or research? ..........................................................
Did you experience any problems while having an MRI scan?        YES/NO
Do you have any allergies?        YES/NO
If yes, details:

---------------------------------------------------------------

MRI Pre Scan Consent

I have read the above information and am aware of the risks and benefits of undergoing an MRI examination.

I have been provided with the opportunity to have any questions answered and I therefore give my consent to an MRI scan. I confirm that the questions have been answered to the best of my knowledge.

PARTICIPANTS NAME.................................

SIGNATURE............................................ DATE..............................

MRI STAFF MEMBER NAME: ........................................

SIGNATURE............................................ DATE..............................

Please empty your pockets of all magnetic items including wallet, bank cards and coins.
You will also need to remove shoes, metal belt buckles and any jewellery you have on.
You will also need to remove your eye glasses as the radiographer will provide you with alternatives.

MRI-15 Checklist and consent form for participants no contrast version 2

Page 3 of 3
MEG Pre-Scan Information

WHAT IS MEG?
Magnetoencephalography (MEG) is a safe, non-invasive and entirely passive human brain imaging technique. The MEG scanner measures the very small magnetic fields outside the head - these arise naturally from electrical activity within the brain.

IS THERE ANY PREPARATION?
The MEG instrument is extremely sensitive to metallic objects entering the shielded room. Hence, you could assist by:

- wearing clothing that does not have metal fastenings;
- not wearing any jewellery, and
- removing all eye make-up (as this can interfere with scans of the head).

You will also be required to complete a MEG safety questionnaire before your scan.

CAN ANYONE HAVE A MEG SCAN?
No. There are some pre-conditions which can damage the MEG scanner. The MEG scanner is extremely sensitive to the presence of metallic objects, either permanently or temporarily carried in or near to your body. These conditions will be rigorously screened for during your pre-assessment for MEG scanning. Having metallic objects on your person, although not a danger to you, may cause damage to our equipment.

IS AN MEG SCAN SAFE?
MEG scanning has been in use as a medical imaging and research tool for many years and is commonly regarded by clinicians and scientists as a safe procedure. It does not employ ionising radiation (such as x-rays) and hence does not pose an additional cancer risk. The researchers on duty will answer any queries you might have on the day, or if in doubt, please call the chief investigator.

WHAT WILL HAPPEN WHEN I ARRIVE?
The researcher will greet you at the MEG unit waiting room and reception, explain the procedure and ask you questions about previous surgery you may have had regarding implanted metal in your body. You will be asked to leave your valuables (coins, keys, watch, jewellery, credit cards, mobile phones, pagers etc.) in a locker. The researcher will guide you to the magnetically shielded room housing the MEG scanner. Some equipment may be placed around you whilst scanning; this may include headphones and/or a stimulus screen.

THE SCANNING PROCESS
When we are taking the pictures, we will ask you to keep as still as possible. Usually there will be about 4 or 5 different scans, lasting for 2-8 minutes each; and for most studies you will be in the scanner for about 60 minutes. For some studies you are welcome to bring along your favourite CD or cassette to listen to, during your scan, please ask your researcher.

WHAT WILL HAPPEN AFTER THE SCAN?
You can leave immediately after your scan. The images that have been taken will be used to address the research question for the study you have agreed to take part in.
MEG Pre-Scan Safety Questionnaire

This questionnaire is designed to screen for various conditions in a potential MEG participant. It is VERY important that you complete it as honestly and comprehensively as possible – please ask if you have any questions. This form is to be completed under the supervision of a staff member PRIOR to entering the MEG room. Note that answering YES to any of the questions does not automatically disqualify a person from having an MEG scan.

Please answer YES or NO to the following:

Have you ever done or been near welding? ........................................ YES / NO
Have you ever been injured by a piece of metal that has not been removed (bullet/shrapnel)? ... YES / NO
Do you know of any metal that has been implanted into your eye, skin or body at anytime? .... YES / NO
Do you have any of the following:
  - Aneurysm clip (on a blood vessel) ........................................... YES / NO
  - Ocular / eye implant .............................................................. YES / NO
  - Cochlear / ear implant ........................................................... YES / NO
  - Hearing aid (removable) ......................................................... YES / NO
  - Cardiac pacemaker/pacing wires or implanted cardioverter defibrillator .......... YES / NO
  - Artificial heart valves ............................................................ YES / NO
  - Other implanted electronics devices (bone growth, neurostimulator) ............ YES / NO
  - Implanted infusion or drug pump ............................................ YES / NO
  - Hip replacement or artificial joint or artificial limb .................................. YES / NO
  - Pin, plate or screw attached to a bone ....................................... YES / NO
  - Implantable coil, filter, shunt or stent ........................................ YES / NO
  - IUD, diaphragm, or pessary .................................................... YES / NO
  - Non-removable piercings or jewellery ........................................ YES / NO
  - Permanent make up .................................................................. YES / NO
  - Medication patches (Nicotine, Nitroglycerine) ..................................... YES / NO
  - Dental bridge; partial plates; permanent retainer; temporary spacers .......... YES / NO
  - Crowns on teeth; posts in teeth ................................................ YES / NO
  - Dental implants ...................................................................... YES / NO

Have you ever had a surgical operation? ........................................... YES / NO
  If yes, please provide details of body area(s) (head, arm) and medical condition

Approximately how many fillings do you have? zero
Do you have any allergies? ............................................................... YES / NO
  If yes, details: ........................................................................

Consent

I have read the above information and am aware of the processes involved in an MEG examination. I have been provided with the opportunity to have any questions answered and I therefore give my consent to an MEG scan. I confirm that the questions have been answered to the best of my knowledge.

STUDY/PROJECT NAME: ........................................................................................................................................

PARTICIPANTS NAME............................................................................................................................................

SIGNATURE: .......................................................................................... DATE: .../.../...

MEG RESEARCHER NAME: ..................................................................................................................................

SIGNATURE: .......................................................................................... DATE: .../.../...
MEG Personal Preparation

Preparing for your MEG Scan

On the day of your MEG scan, we request that you take the following steps:

1) Please empty your pockets of all magnetic items including wallet, bank cards and coins. You will also need to remove any jewellery you have on.
2) Do not wear make up.
3) (If applicable) Do not wear an underwire bra (sports bras that have no underwire are fine).
4) If you wear eye glasses you will not be able to wear them in the MEG scanner. Immediately prior to entering the MEG we can provide you with MEG compatible glasses. If you bring your prescription or know your prescription this will help us to give you the best temporary glasses for your scan. Contact lenses are fine for MEG scans.
Appendix E
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<td>OCD compulsions</td>
<td>AN</td>
</tr>
<tr>
<td>MADRS raw score</td>
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<td>34</td>
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Note: AN= anorexia nervosa; BMI= body mass index; WTAR= Wechsler Test of Adult Reading; OCD= obsessive compulsive disorder; BN= bulimia nervosa; MADRS; Montgomery-Asberg Depression Rating Scale; Age, age of AN onset, illness duration and treatment duration reported in years; both participants completed only the first session which included the clinical interview, cognitive battery and a resting state scan in the magnetic resonance imaging (MRI) scanner.
Table E.2

Clinical and demographic information for healthy control participants who did not complete the entire study

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<th>Control 1</th>
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<td>WTAR</td>
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<td>Studying</td>
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<td>Cycling</td>
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<td>Medications</td>
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<td>Axis I disorders</td>
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<td>DASS</td>
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<td>Anxiety= 0</td>
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<td>Stress= 0</td>
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<td>personality disorder</td>
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<td>Restraint= 0.60</td>
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<td>Eating concern= 0.40</td>
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<td>Women prefer= 2</td>
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<td>Attention (2nd order)= 16</td>
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<td>Attention (1st order)= 10</td>
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<td>Cognitive stability (1st order)= 6</td>
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<td>Motor (2nd order)= 27</td>
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<td>Motor (1st order)= 20</td>
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Table E2 cont’d

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<td>BIS-11</td>
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<td>Perseverance (1\textsuperscript{st} order)= 7</td>
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<td>\textit{Non-planning (2\textsuperscript{nd} order)= 22}</td>
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<td>Self-control (1\textsuperscript{st} order)= 10</td>
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<td>TAS= 32</td>
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Note: BMI= body mass index; WTAR= Wechsler Test of Adult Reading; MADRS; Montgomery-Asberg Depression Rating Scale; DASS: Depressions Anxiety Stress Scale; PDQ-4= Personality Diagnostic Questionnaire; EDE-Q= Eating Disorder Examination Questionnaire; FRS= Figure Rating Scale; BIS-11= Barratt Impulsiveness Scale; 1\textsuperscript{st} order= first order factor; 2\textsuperscript{nd} order= second order factor; TAS-20= Toronto Alexithymia Scale; Age is reported in years; all three participants completed the first session which included the clinical interview, cognitive battery and a resting state scan in the magnetic resonance imaging (MRI) scanner; control 3 also completed the ‘long MRI’ session which included the battery of questionnaires, prosaccade/antisaccade/no-go saccade task and emotional faces task in the MRI, and the behavioural eyetracking tasks which include the emotional faces task, memory-guided and self-paced saccade tasks, and the implicit and explicit biological motion tasks.
Appendix F
Chapter 6 – analyses unrelated to group

For rate of emotion identification errors, a 2 (group) x 7 (emotion) mixed design ANOVA revealed a significant main effect of emotion (F(4.59,215.52)= 12.57, p < 0.001), with more errors to faces depicting anger (F(1,46)= 12.32, p= 0.001), fear (F(1,46)= 16.90, p < 0.001) and sadness (F(1,46)= 16.65, p < 0.001).

For fixation count, a 2 (group) x 7 (condition) x 2 (task) mixed design ANOVA revealed a significant main effect of condition (F(4.08,159.20)= 2.96, p= 0.021) with a greater number of fixations made to participants’ own faces (F(1,39)= 5.31, p= 0.027), and faces depicting anger (F(1,39)= 5.44, p= 0.025) and fear (F(1,39)= 10.97, p= 0.002). A significant interaction between condition and task was also found (F(3.38,131.91)= 7.61, p < 0.001) with a decreased number of fixations between implicit and explicit tasks for participants’ own faces (F(1,39)=15.92, p < 0.001) and faces depicting fear (F(1,39)= 13.50, p= 0.001).

A 2 (group) x 7 (condition) x 2 (task) mixed design ANOVA conducted on the FDI revealed a significant main effect of condition (F(2.28,81.95)= 16.37, p < 0.001) with longer fixations to salient features of own faces (F(1,36)= 5.95, p= 0.020), and faces depicting anger (F(1,36)= 12.34, p= 0.001), disgust (F(1,36)= 24.77, p < 0.001), fear (F(1,36)= 42.40, p < 0.001), happiness (F(1,36)= 30.53, p < 0.001) and sadness (F(1,36)= 29.19, p < 0.001). A significant interaction between condition and task was also found with greater attention to salient features of one’s own face during the implicit compared to explicit task (F(1,36)= 5.39, p= 0.026).

A 2 (group) x 7 (condition) x 2 (task) mixed design ANOVA conducted on the FFI revealed a significant main effect of condition with a greater number of fixations to salient features of own faces (F(1,33)= 9.61, p= 0.004), and faces depicting anger (F(1,33)= 7.38, p= 0.010), disgust (F(1,33)= 23.38, p < 0.001), fear (F(1,33)= 58.26, p < 0.001), happiness (F(1,33)= 24.32, p < 0.001), and sadness (F(1,33)= 32.66, p < 0.001). A significant interaction between condition and task was also found, with more attention to salient features of own face stimuli during implicit compared to explicit tasks (F(1,33)= 4.56, p= 0.040).
A 2 (group) x 6 (emotion) x 2 (task) mixed design ANOVA conducted on the FFI revealed a significant main effect of emotion (F(5,185)= 15.56, p < 0.001) with more fixations to salient features of faces depicting anger (F(1,37)= 9.59, p= 0.004), disgust (F(1,37)=25.45, p < 0.001), fear (F(1,37)= 68.22, p < 0.001), happiness (F(1,37)= 34.39, p < 0.001) and sadness (F(1,37)= 38.10, p < 0.001). A significant interaction between condition and task was also found with greater attention to salient features of one’s own face during the implicit compared to explicit task (F(1,36)= 5.387, p= 0.026). A significant interaction between task and emotion was also found (F(5,185)= 2.95, p= 0.014), with a trend for more attention to salient features of sad faces in the explicit task.

A 2 (group) x 6 (emotion) x 2 (task) mixed design ANOVA conducted on the FFI revealed a significant main effect of emotion with more attention to salient features of faces depicting anger (F(1,33)= 9.83, p= 0.004), disgust (F(1,33)= 30.85, p < 0.001), fear (F(1,33)= 52.88, p < 0.001), happiness (F(1,33)= 26.04, p < 0.001) and sadness (F(1,33)= 28.09, p < 0.001).
A 2 (group) x 5 (body size category) x 2 (gender) mixed design ANOVA conducted on the explicit biological motion task for the body size discrimination score revealed a significant main effect of body size category (F(1.50,70.61)= 525.10, p < 0.001) with body size estimation decreasing (underestimating) as the stimulus size increased. Participants underestimated stimuli to a greater extent between thin and thin-mid stimuli (F(1,47)= 231.47, p < 0.001), thin-mid and mid (F(1,47)= 406.59, p < 0.001), mid and mid-heavy (F(1,47)= 207.34, p < 0.001), and mid-heavy and heavy stimuli (F(1,47)= 266.67, p < 0.001). A significant interaction between body size category and gender was also found (F(2.11,99.01)= 12.94, p < 0.001), with greater underestimation of male stimuli with mid-heavy (F(1,47)= 21.09, p < 0.001) and heavy body sizes (F(1,47)= 9.35, p= 0.004).

A 2 (group) x 5 (body size category) x 2 (gender) x 2 (task) mixed design ANOVA carried out for fixation count revealed a significant body size category by task interaction, with more fixations in the explicit task for mid-heavy (F(1,46)= 10.01, p= 0.003) and heavy body sizes (F(1,46)= 11.73, p= 0.001).

A 2 (group) x 5 (body size category) x 2 (gender) x 2 (task) mixed design ANOVA carried out for fixation duration revealed a significant main effect of body size category (F(2.87,131.93)= 4.65, p= 0.005) with longer fixation durations to thin (F(1,46)= 4.92, p= 0.031) and heavy body sizes (F(1,46)= 11.92, p= 0.001).

A 2 (group) x 5 (body size category) x 2 (gender) x 2 (task) mixed design ANOVA carried out for saccade amplitude revealed a significant main effect of body size category (F(2.69,123.69)= 3.54, p= 0.020) with larger amplitudes to thin (F(1,46)= 8.00, p= 0.007) and thin-mid body sizes (F(1,46)= 12.09, p= 0.001).

A 2 (group) x 5 (body size category) x 2 (gender) x 2 (task) mixed design ANOVA undertaken for fixation count to AOIs revealed a significant main effect of body size category (F(2.75,120.80)= 26.22, p < 0.001) with increased fixations to mid (F(1,44)= 6.01, p= 0.018), mid-heavy (F(1,44)= 29.60, p < 0.001) and heavy stimuli (F(1,44)= 9.53, p= 0.003). A significant main effect of body area was also found (F(1,97,86.78)= 63.44, p < 0.001) with a greater number of fixations to the hips (F(1,44)= 65.41, p < 0.001), shoulders (F(1,44)= 5.91, p= 0.019), knees
(F(1,44)= 81.53, p < 0.001) and feet (F(1,44)= 20.88, p < 0.001), and fewer fixations to the head (F(1,44)= 134.59, p < 0.001). A significant interaction was found between task and body area (F(2.09,91.73)= 3.42, p= 0.035) with fewer fixations to the head (F(1,44)= 4.85, p= 0.033), and more fixations to the hips (F(1,44)= 7.34, p= 0.010) and feet (F(1,44)= 15.17, p < 0.001) during the implicit task. A significant interaction was also found between body size category, gender and body area (F(7.57,333.14)= 4.10, p < 0.001) with fewer fixations to the head of thin (F(1,44)= 7.93, p= 0.007) and thin-mid (F(1,44)= 17.09, p < 0.001) male stimuli.

A 2 (group) x 5 (body size category) x 6 (body area) 2 (gender) x 2 (task) mixed design ANOVA undertaken for dwell time to AOIs revealed a significant main effect of body size category (F(2.95,129.93)= 17.60, p < 0.001) with increased dwell times to mid-heavy stimuli (F(1,44)=26.76, p < 0.001). A significant main effect of body area was also found (F(2.21,97.43)= 74.78, p < 0.001) with increased dwell times to the hips (F(1,44)= 99.20, p < 0.001), shoulders (F(1,44)= 13.08, p= 0.001), knees (F(1,44)= 64.81, p < 0.001) and feet (F(1,44)= 16.50, p < 0.001), and decreased dwell times to the head (F(1,44)= 117.0, p < 0.001). A significant interaction was also found between body size category, gender and body area (F(8.67,381.48)= 3.07, p= 0.002), with increased dwell times to the head of thin female stimuli (F(1,44)= 7.74, p= 0.008), the hips of thin female stimuli (F(1,44)= 4.55, p= 0.038), the shoulders of mid-size female stimuli (F(1,44)= 9.74, p= 0.003), and the arms of mid-heavy female stimuli (F(1,44)= 4.91, p= 0.032).

A 2 (group) x 5 (body size category) x 2 (task) mixed design ANOVA conducted on the FFI revealed a significant main effect of body size with increased fixations to non-salient stimuli relative to salient stimuli of thin-mid (F(1,44)= 15.42, p < 0.001), mid (F(1,44)= 41.44, p < 0.001), and heavy stimuli (F(1,44)= 21.24, p < 0.001). A significant interaction between body size category and task was also found with increased attention to non-salient features of thin-mid stimuli during the implicit task, and mid stimuli during the explicit task (F(4,176)= 3.17, p= 0.015).

A 2 (group) x 5 (body size category) x 2 (task) mixed design ANOVA conducted on the FDI revealed a significant main effect of body size category with greater attention to non-salient features of mid (F(1,44)= 35.78, p < 0.001) and mid-heavy stimuli (F(1,44)= 28.02, p < 0.001).
Author/s: 
PHILLIPOU, ANDREA

Title: 
Investigating the neurobiological and cognitive features of anorexia nervosa

Date: 
2015

Persistent Link: 
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File Description: 
Investigating the neurobiological and cognitive features of anorexia nervosa