Neurocognitive and psychiatric markers of network disease in epilepsy

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Behavioral markers of network disease in epilepsy

Abstract

People with epilepsy frequently experience debilitating memory and mood difficulties. Autobiographic memory impairments are a vulnerability factor for developing and maintaining unipolar depression in the psychiatric population, yet despite the wealth of research examining cognition and behaviour in epilepsy, the links between them remain unclear. This thesis aimed to profile the autobiographic memory and mood function of patients with focal epilepsy relative to healthy controls, and characterise how these functions may be interlinked. Three behavioural studies were conducted to achieve these objectives.

Participants were prospectively recruited from the Comprehensive Epilepsy Programme at Austin Health, Melbourne, between 2010-2014. The cognitive and psychiatric functioning of 85 adults with chronic focal epilepsy was compared to that of 72 sociodemographically-matched controls largely recruited from the patients’ families (N=157). Gold-standard psychometric measures assessed depressive symptoms and cognitive function.

Study One was an initial qualitative exploration of the relationships between cognitive impairment and depression in a form of focal epilepsy not typically linked to memory disorder, to assess the effects of seizures and pathology on those functions. A well-characterised case series of nine patients with frontal lobe epilepsy (FLE) was contrasted to 24 matched controls. Results suggested that FLE can selectively interrupt the integrity of the autobiographic memory/cognitive control networks versus the affective network. Study Two aimed to quantitatively delineate the effects of seizure chronicity on impaired autobiographic memory in a large cohort of patients (n=85) relative to healthy controls (n=72), and the potential links between poor autobiographic recall and mood. This revealed that chronic seizures beginning in childhood dysregulate cognition-related networks important for autobiographic recall, while autobiographic memory impairments in patients with a more recent disease onset are largely linked to depressive symptoms, perhaps reflecting maladaptive psychological adjustment to the onset of epilepsy as an adult. Together, the first two studies show that autobiographic memory difficulties are only related to depression in certain epilepsy syndromes.
Finally, Study Three comprised a data-driven investigation into the existence of a cognitive phenotype of depression in epilepsy. Results showed that of the 21 (25%) patients currently meeting criteria for a formal depressive disorder, 15 (71%) had a ‘Cognitive’ phenotype of the disorder, while six (29%) presented with a ‘Somatic’ phenotype. These findings are congruent with phenotypes of depression found in other populations, and suggest that different presentations of depression in epilepsy may uniquely index dysregulation of selected brain networks. Moreover the lack of seizure-related correlates to the Cognitive phenotype discounts the widespread assumption that cognitive and affective network dysfunction in epilepsy is a side-effect of seizures.

The results of this thesis suggest that epilepsy can selectively disrupt large-scale brain networks important to cognition and affect, and that behavioural disturbances in people with epilepsy may be primary manifestations of the network disease.
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.

GENEVIEVE RAYNER
Preface

Publications to arise from this thesis

Publications in refereed journals


Manuscripts currently under review


Manuscripts currently in preparation

Rayner G, Jackson GD, Wilson SJ. Memories are made of this: Determinants of autobiographic memory impairment in focal epilepsy

Rayner G, Jackson GD, Wilson SJ. Cognitive profiling identifies subtypes of depression in epilepsy

Conference abstracts


Presentations

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Fracturing the coherent lived experience: Are autobiographic memory deficits related to mood in epilepsy? Workshop Presentation, 2011 Epilepsy Research Retreat, Lorne.

August 2012

October 2012

July 2013

July 2014

July 2014

September 2014
Publications to arise during the course of candidature

**Book Chapters**


**Publications in refereed journals**


**Invited publication for the journal of the American Epilepsy Society:**


**Manuscripts currently under review**


**Manuscripts currently in preparation**

Siveges B, Rayner G, Wilson SJ. Autobiographic memory and subjective memory complaints in epilepsy

Hupfauf E, Rayner G, Macleod L, Wilson SJ. Autobiographical memory specificity, self-identity, and mood in patients with epileptic versus psychogenic seizures


Wilson SJ, Rayner G, Lawrence JA. New methods for examining family functioning in epilepsy.
Conference abstracts


Other presentations to arise during candidature

July 2009

*Differential contributions of objective memory and mood to subjective memory complaints in refractory focal epilepsy*. Workshop Presentation, 2009 Epilepsy Research Retreat, Hepburn Springs.

October 2010

*Differential contributions of objective memory and mood to subjective memory complaints in refractory focal epilepsy*. Platform Presentation, 8th Asian Oceanic Epilepsy Congress, Melbourne, Australia.

- Awarded best oral presentation, Neuropsychology & Psychiatry session.
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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
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<tr>
<td>AED</td>
<td>anti-epileptic drug</td>
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<tr>
<td>AMI</td>
<td>Autobiographic Memory Interview</td>
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<tr>
<td>AMN</td>
<td>autobiographic memory network</td>
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<tr>
<td>AN</td>
<td>affective network</td>
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<tr>
<td>BCE</td>
<td>Before Common Era (aka B.C.)</td>
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<tr>
<td>BOLD</td>
<td>blood oxygen level dependent</td>
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<tr>
<td>CCN</td>
<td>cognitive control network</td>
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<tr>
<td>CE</td>
<td>Common Era (aka A.D.)</td>
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<tr>
<td>DDNOS</td>
<td>Depressive Disorder Not Otherwise Specified</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
</tr>
<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
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<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
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<tr>
<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>FDG-PET</td>
<td>fludeoxyglucose positron emission tomography</td>
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<tr>
<td>FLE</td>
<td>frontal lobe epilepsy</td>
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<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FSIQ</td>
<td>full scale intelligence quotient</td>
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<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<tr>
<td>GAD</td>
<td>generalised anxiety disorder</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems, 10th revision</td>
</tr>
<tr>
<td>IDD</td>
<td>interictal dysphoric disorder</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitors</td>
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<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitors</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>MDE</td>
<td>Major Depressive Episode</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>MTL</td>
<td>mesial temporal lobe</td>
</tr>
<tr>
<td>NAA</td>
<td>N-acetyl aspartate</td>
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<tr>
<td>NDDI-E</td>
<td>Neurological Disorders Depression Inventory for Epilepsy</td>
</tr>
<tr>
<td>NDRI</td>
<td>noradrenaline-dopamine reuptake inhibitor</td>
</tr>
<tr>
<td>PCC</td>
<td>posterior cingulate cortex</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
</tr>
<tr>
<td>PHQ-GAD-7</td>
<td>Patient Health Questionnaire for Generalised Anxiety Disorder, 7-item</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for DSM-IV Disorders</td>
</tr>
<tr>
<td>SNRI</td>
<td>selective noradrenaline reuptake inhibitor</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressants</td>
</tr>
<tr>
<td>TLE</td>
<td>temporal lobe epilepsy</td>
</tr>
<tr>
<td>TMS</td>
<td>transient magnetic stimulation</td>
</tr>
<tr>
<td>WMS-IV</td>
<td>Wechsler Memory Scale, 4th edition</td>
</tr>
<tr>
<td>WTAR</td>
<td>Wechsler Test of Adult Reading</td>
</tr>
</tbody>
</table>
# Table of Contents

Abstract ....................................................................................................................i  
Declaration .............................................................................................................iii  
Preface .....................................................................................................................v  
Acknowledgements ....................................................................................................xi  
Abbreviations ..........................................................................................................xiii  
Table of Contents ......................................................................................................xv  
List of Tables ............................................................................................................xxiii  
List of Figures ..........................................................................................................xxv  

Chapter 1. Overview ...............................................................................................1  

Chapter 2. The Central Role of Cognition in Depression .......................................5  

2.1. Depression throughout civilization: a brief tour ..............................................5  

2.1.1 Classical conceptions of depression ...............................................................5  

2.1.2 Depression as spiritual and moral failure .......................................................5  

2.1.3 Psychiatry in the late modern period ............................................................6  

2.1.4 The modern approach: biological treatments and distorted cognitive styles ..7  

2.1.4.1 Beck’s cognitive model of depression ......................................................8  

2.2 Symptom-based nosologies of unipolar depression .......................................10  

2.2.1 Mood disorder according to the Diagnostic and Statistical Manual of Mental Disorders ..................................................................................................................10  

2.2.2 Major Depressive Disorder ...........................................................................11  

2.2.3 Dysthymic Disorder .......................................................................................12  

2.2.4 Depressive Disorder Not Otherwise Specified ..........................................12  

2.3 The symptomatology of unipolar depression .................................................13  

2.3.1 Affective features of depression .................................................................13  

2.3.2 Somatic and vegetative features of depression ..........................................14  

2.3.3 Cognitive features of depression .................................................................15  

2.3.3.1 Depression and autobiographic memory: a distorted self-perception...15  

2.3.3.2 Depression and subjective memory complaints ......................................18  

2.3.3.3 Depression and psychometric cognitive impairments: reduced cognitive control ............................................................................................................................19  

2.4 Symptom-based subtypes of unipolar depression .........................................22
2.4.1 Phenotypes in psychiatric populations: ‘Endogenous’ versus ‘Neurotic’ depression .................................................................22
2.4.2 ‘Cognitive’ versus ‘Somatic’ subtypes of depression .........................25

Chapter 3. Cognition-related brain networks and the symptomatology of unipolar depression .................................................................................................................29
3.1 General comments on regional co-activation versus resting state networks ....31
3.2 The autobiographic memory network .......................................................32
  3.2.1 Depression’s hyperactive AMN .........................................................33
3.3 The cognitive control network .................................................................37
  3.3.1 Depression’s lacklustre CCN .............................................................37
3.4 AMN and CCN dysregulation in depression: heightened anti-correlation ....40
  3.4.1 Altered dynamics between neurocognitive networks in depression ......41
  3.4.2 The impact of neurocognitive network dysfunction on affective networks ..................................................................................42
    3.4.2.1 Decoupling of the CCN and the Affective Network ..................42
    3.4.2.2 Strengthened coupling of the AMN and the Affective Network ....43
3.5 The neurocognitive network model of depression .......................................45
3.6 Broadening the psychiatric concept of depression .......................................45
  3.6.1 The neurocognitive network model of depression: Implications for future research and clinical practice .................................................................47
    3.6.1.1 Broadening research parameters ..............................................47
    3.6.1.2 Advancing development of new treatments .........................48
  3.6.2 Facilitating patient-tailored clinical management: towards precision medicine in psychiatry .................................................................48

Chapter 4. Depression in Epilepsy ..................................................................51
4.1 Focal epilepsy: a model of network disorder ...........................................51
  4.1.1 Seizure classification ...........................................................................51
    4.1.1.1 Defining focal epilepsy ..............................................................51
    4.1.2 Epidemiology ..................................................................................53
  4.1.3 Ætiology of focal epilepsy .....................................................................53
    4.1.3.1 Electroclinical focal epilepsy syndromes ..................................53
4.1.3.2 Structural-metabolic causes of focal epilepsy ........................................54
4.1.3.3 Genetics of focal epilepsy .................................................................54
4.1.4 Focal epilepsy networks ..........................................................................55
   4.1.4.1 The relationship between focal epilepsy and neurocognitive networks .................................................................56
      4.1.4.1.1 Focal epilepsy and the AN .......................................................56
      4.1.4.1.2 Focal epilepsy and the AMN ...................................................57
      4.1.4.1.3 Focal epilepsy and the CCN ..................................................58
4.1.5 Cognitive comorbidities in epilepsy .......................................................60
   4.1.5.1 Memory deficits in focal epilepsy ....................................................61
      4.1.5.1.1 Autobiographic memory deficits in epilepsy .........................63
4.2 Depression in epilepsy ..............................................................................65
   4.2.1 Prevalence and significance .................................................................65
   4.2.2 Phenomenology of depression in epilepsy ........................................66
      4.2.2.1 Interictal dysphoric disorder .......................................................67
      4.2.2.2 Subsyndromic depression ..........................................................67
   4.2.3 Depression and epilepsy: a bidirectional relationship ..........................68
   4.2.4 Correlates of depression in epilepsy ..................................................69
      4.2.4.1 Psychosocial features of depression in epilepsy .......................69
      4.2.4.2 Epileptological features of depression in epilepsy ....................70
      4.2.4.3 Neurobiological features of depression in epilepsy ..................70
         4.2.4.3.1 Neurochemical features .......................................................70
         4.2.4.3.2 Immunological features .....................................................71
         4.2.4.3.3 Anatomical features ...........................................................72
         4.2.4.3.4 Functional features .............................................................72
      4.2.4.4 Cognitive features ........................................................................74
         4.2.4.4.1 Objective cognitive impairments ......................................74
         4.2.4.4.2 Autobiographic memory impairments .................................75
4.3 Aims & Hypotheses ................................................................................77

Chapter 5. Study One. Behavioural profiles in frontal lobe epilepsy: Autobiographic memory versus mood impairment ..................................................81
5.1 Methods ..................................................................................................82
5.1.1 Participants .................................................................82
5.1.2 Measures .............................................................................82
  5.1.2.1 Psychiatric evaluation ..........................................................83
    5.1.2.1.1 DSM-IV Axis I diagnoses of mood disorder .........................83
    5.1.2.1.2 Linear measures of mood symptomotogy ..............................83
  5.2.2.2 Neuropsychological evaluation ........................................84
    5.1.2.2.1 Autobiographic memory .....................................................84
    5.1.2.2.2 Broader memory evaluation .................................................84
5.1.3 Statistical analyses ............................................................86
5.2 Results ..................................................................................86
  5.2.1 FLE patients have worse autobiographic memory than controls ..........88
  5.2.2 High levels of clinical depression in FLE patients ..........................90
  5.2.3 Profiling FLE cases: Impaired Cognition versus Impaired Mood .........90
  5.2.4 Characterising the two profiles: Impaired Cognition vs Impaired Mood .....93
    5.2.4.1 Seizure-related factors ............................................................93
    5.2.4.2 Broader cognitive factors .........................................................93
    5.2.4.3 Mood-related factors ..............................................................93
5.3 Discussion .............................................................................94
  5.3.1 Brain networks supporting autobiographic memory may be disturbed by an
    active frontal lobe seizure focus .......................................................94
  5.3.2 Dissociation of semantic and episodic autobiographic memory ..........96
  5.3.3 Dissociation of autobiographic memory and depression ....................96
  5.3.4 Differential markers of network dysfunction: future directions ............97
  5.3.5 Study One conclusions ..........................................................98

Chapter 6. Study Two. Memories are made of this: determinants of impaired
  autobiographic memory in epilepsy ..............................................99
6.1 Methods ..............................................................................100
  6.1.1 Participants .........................................................................100
  6.1.2 Measures .............................................................................102
  6.1.3 Statistical analyses ...............................................................102
6.2 Results ..................................................................................103
  6.2.1 Focal epilepsy patients have pervasive memory impairments ............103
6.2.2 Patients have high rates of depressive disorder and symptoms ..................105
6.2.3 Neurodevelopmental context of autobiographic memory predictors ..........105
   6.2.3.1 Autobiographic impairments in early onset epilepsy are related to disease
   chronicity .............................................................................................................106
   6.2.3.2 Autobiographic impairments in late onset epilepsy are linked to
   depression .............................................................................................................107
6.3 Discussion ...........................................................................................................108
   6.3.1 Neurocognitive impact of disease chronicity in early onset epilepsy ..........108
   6.3.1.1 Key role of working memory in autobiographic retrieval .....................109
   6.3.2 The cognitive impact of adjusting to seizures in adulthood .....................110
   6.3.2.1 Is lesional focal epilepsy a cognitive vulnerability factor in late onset
   epilepsy .................................................................................................................111
   6.3.3 Implications for practice and research across neurological disorders ........111
   6.3.4 Study Two conclusions .............................................................................111

Chapter 7. Study Three. Data-driven profiling identifies a cognitive subtype of
   depression in epilepsy ..........................................................................................115
7.1 Method ...............................................................................................................116
   7.1.1 Participants .................................................................................................116
   7.1.2 Materials ...................................................................................................117
   7.1.3 Statistical analyses ....................................................................................118
7.2 Results ...............................................................................................................119
   7.2.1 Two subtypes of depression in epilepsy ....................................................119
   7.2.2 Correlates of Cognitive vs Somatic subtypes of depression in epilepsy ......120
      7.2.2.1 Cognitive features ...............................................................................120
      7.2.2.2 Psychosocial and demographic features .............................................122
7.3 Discussion ..........................................................................................................124
   7.3.1 Unique profiles of network disruption .......................................................124
      7.3.1.1 Cognitive phenotype networks .............................................................124
      7.3.1.2 Somatic phenotype networks ...............................................................125
   7.3.2 Cognitive & Somatic phenotypes of depression in other populations .......126
   7.3.3 Clinical implications ...................................................................................127
   7.3.4 Future directions .........................................................................................128
7.3.5 Study Three conclusions .................................................................129

Chapter 8. General Discussion ...........................................................................131

8.1 Extension of the neurocognitive network model of depression to focal epilepsy ........................................................................................................132

8.2 Primary effects of epilepsy on cognition and behaviour; or, "Cognitive reframing for epilepsy researchers" .................................................................133

8.3 Phenotyping in epilepsy .................................................................................135

8.4 Directions for future research .........................................................................136

8.5 Conclusions .....................................................................................................137

References ..........................................................................................................139

Appendices .........................................................................................................169
List of Tables

Table 2.1. Convergent evidence for the typical symptom profile of the ‘Cognitive’ phenotype of depression .................................................................24

Table 2.2. Convergent evidence for the typical symptom profile of the ‘Somatic’ phenotype of depression .................................................................25

Table 3.1. Summary of key functional neuroimaging studies finding altered activation in the Autobiographic Memory Network (AMN) in adults with depression relative to healthy controls ......................................................36

Table 3.2. Summary of key functional neuroimaging studies finding altered activation in the Cognitive Control Network (CCN) in adults with depression relative to healthy controls .............................................................39

Table 3.3. Example of a nosology of depression inclusive of cognitive networks .......47

Table 4.1. Classification of seizures ................................................................51

Table 4.2. Descriptors of focal seizures according to the degree of impairment during a seizure ......................................................................................52

Table 5.1. Measures of cognitive functioning employed in Study One ..................85

Table 5.2. Key demographic and epileptological features of the nine FLE cases ......87

Table 5.3. Cognitive and psychiatric scores: patients versus controls .....................88

Table 5.4. Autobiographic memory and general cognitive functioning of the nine cases ........................................................................................................91

Table 5.5. Mood profile of the nine FLE cases ........................................................92

Table 6.1. Demographic and clinical profile of the sample (N=157) ......................101

Table 6.2. Cognitive and psychiatric profile of patients versus controls .................104

Table 7.1. Demographic and clinical profile of the sample (N=156) ......................117

Table 7.2. Cluster analysis of DSM-IV symptoms reveals two profiles of current depression in epilepsy ..............................................................................120

Table 7.3. Cognitive profile of Cognitive vs Somatic subtype of depression relative to controls .........................................................................................121

Table 7.4. Demographic & psychosocial profile of Cognitive vs Somatic subtypes of depression ..................................................................................123
List of Figures

Figure 2.1. Beck’s cross-sectional cognitive model of depression and the self..................8
Figure 2.2. Developmental model of depression (Adapted from Beck, 2008)....................9
Figure 2.3. A schematic of what is assumed to occur when people are asked to retrieve an autobiographic memory in response to a cue word. Retrieval starts with elaborating the cue semantically and moving through generating generic descriptions to more specific mnemonic material. Early in generative retrieval, more verbal–abstract code is involved, whereas a more sensory–perceptual code is used later in the process. (Adapted from Williams et al., 2007)..........................................................16
Figure 2.4. Saggittal section of the human brain, showing the principal noradrenergic pathways (Source: Moret & Briley, 2011).................................20
Figure 2.5. Hierarchical model of cognitive deficits in depression.................................21
Figure 2.6. Graphical summary of the key features of cognitive versus somatic phenotypes of unipolar depression, as well as the differential health-related outcomes associated with each phenotype.................................................27
Figure 3.1 The autobiographic memory network (Source: Dang et al, 2012)................32
Figure 3.2. Engagement of the cognitive control network during a nonself focused task in healthy controls (A) and people with depression (B). (A): In healthy controls, activation of the CCN (red) downregulates the AN (green) and is anticorrelated with the AMN (blue). This allows for efficient completion of externally-focused tasks. (B): In people with depression, the introspective AMN is pathologically engaged (red), suppressing the activation of the CCN (blue) and leading to uninhibited activation of the AN (orange). In the context of maladaptive core beliefs about the self and the world, this gives rise to symptoms of depression such as rumination, dysphoria, poor concentration, diminished work performance, and self critical information processing.........................................................34
Figure 3.3 The cognitive control network (Source: Dang et al, 2012)..........................37
Figure 4.1. Incidence of all unprovoked seizures by age in Iceland from 1995 to 1999 (Source: Olafsson et al., 2005)-----------------------------------------------------53

Figure 4.2. MRI findings in patients with focal epilepsy ........................................54

Figure 4.3. In graph theory, networks range from completely orderly (left) to completely random (right). "Small world" networks lie between these two extremes (Source: Brock, 2010) ..............................................55

Figure 4.4. Summary of the altered function and connectivity seen in mood-related cognitive networks in patients with focal epilepsy ........................................60

Figure 4.5. Brain section of patient H.M., revealing circumscribed but bilateral mesial temporal lobe ablation.................................................................61

Figure 4.6. Depressive disorders in epilepsy are considered to lie on a spectrum of severity ranging from low-grade ‘sub-syndromic’ depressive episodes to severe, suicidal depression. They may not always fit dominant category based diagnostic systems such as DSM-IV-TR or ICD-10, but can show overlapping features. Interictal Dysphoric Disorder is postulated to be caused by paroxysmal, subthreshold hypersynchronous neural discharges that produce increasingly inhibitory responses in the mood network (Source: Rayner & Wilson, 2012) ...............................................................66

Figure 4.7. Neurobiological, psychiatric, and psychosocial markers of depression in medically refractory focal epilepsy. (adapted from Wrench, Matsumoto, Inuoe & Wilson, 2011).................................................................72

Figure 5.1. Mood and memory function of frontal lobe epilepsy (FLE; n=9) patients relative to healthy controls (n=24). Panel A depicts significantly poorer episodic autobiographic memory recall in FLE patients; Panel B shows higher levels of depressive symptoms in FLE patients relative to controls; Panel C plots autobiographic memory against depressive symptoms, showing the clustering of patients with lower memory scores (‘Impaired Cognition’=orange circles) versus higher depression scores (‘Impaired Mood’=blue triangles). Healthy controls largely form their own cluster of normal performance (black squares). Note that in Panel C, there is one patient in the Impaired Cognition group with an NDDI-E score >15........89
Figure 5.2. Proposed effect of an active seizure focus on cognitive [blue arrows] and affective [teal arrows] functions regulated by brain networks with nodes in the prefrontal cortex, suggesting that autobiographic memory dysfunction in frontal lobe epilepsy can stem from either primary disruption to the Autobiographic Memory Network (AMN), or via secondary disruption to the AMN caused by altered function of the Cognitive Control Network (CCN)………………………………………………………………………..97

Figure 6.1. Impaired autobiographic memory recall in patients with early onset in epilepsy is linked to indices of increased seizure chronicity and reduced working memory, while the impairment seen in patients with late onset epilepsy is largely predicted by elevated symptoms of depression………..106

Figure 7.1. Reduced neuropsychological functioning of the two depression phenotypes relative to a baseline of normal task performance provided by the control group (z score = 0). Patients with the Cognitive phenotype perform worse than those with Somatic depression across nearly all cognitive domains. Somatic patients, however, endorse elevated symptoms of anxiety……….122

Figure 7.2. Symptom profiles of the two phenotypes of depression in epilepsy, together with their psychosocial and cognitive correlates and putative underlying networks………………………………………………………………………..125

Figure 7.3. The “piriform axis”. T1-weighted image of a 37 year old man, displayed in a (a) para-sagittal and (b) oblique-axial orientation, approximately +20° relative to the anterior commissure-posterior commissure axis. This orientation allows the relationship between the piriform cortex (Pir), amygdala (Am) and hippocampus (Hip) to be seen. The arrow indicates the position of the middle cerebral artery (MCA) within the endorhinal sulcus (Source: Vaughan & Jackson, 2014)……………………………………………………………..126

Figure 8.1 Summary of the findings of the current study, showing the cognitive and affective correlates of autobiographic memory disturbance in focal epilepsy using a phenotyuping approach. ………………………………………………………………..132

Figure 8.2. Primary effects of epilepsy disease on cognition and mood versus the secondary effects of seizures on behavioural phenomenon………………..134
Chapter 1. Overview

Depression and cognitive impairment commonly accompany focal epilepsy, and are often perceived by patients as more debilitating than the primary problem of unpredictable seizures. Modern approaches to studying the brain consider mood and cognition to be the emergent property of brain networks, and epilepsy as a disease that causes seizures to propagate along these same networks (Sporns, 2011). This thesis poses the question: does seizure-related disruption to cognitive networks contribute to depression in epilepsy?

This question stems from the psychiatric literature, where profiling of unipolar depression reveals that cognitive distortions and autobiographic memory deficits are robust features of depressive disorder (Chapter 2), and functional neuroimaging captures disturbed functioning of cognition-related brain networks that support autobiographic memory and cognitive control (Chapter 3). In parallel, epilepsy researchers find that the normal organisation of cognitive networks can be altered by seizures and related to behavioural patterns of impairment, contributing to the contemporary view that cognitive or behavioural dysfunction provides a marker of the underlying epilepsy network (Chapter 4).

Extension of this work to depression in epilepsy is clear. This thesis will explore what happens to networks that subserve autobiographic memory in a disease that periodically interferes with brain function, and relate diminished cognitive function to markers of depression. This will provide new insights into how neurocognitive networks contribute to depression in epilepsy.

To achieve this aim, three behavioural studies have been undertaken, comparing the cognitive and psychiatric functioning of 85 patients with chronic focal epilepsy to that of 72 sociodemographically-matched healthy controls (N=157). Participants were administered gold-standard psychometric measures of autobiographic memory, working memory, auditory-verbal memory, visual memory, and psychiatric symptomatology, with patients assessed for diagnoses of past and current unipolar depressive disorder using DSM-IV criteria.

The first study is an in-depth case series of nine patients with frontal lobe epilepsy (FLE) examined relative to 24 matched controls, encompassing a careful qualitative exploration of relationships between cognitive impairment and depression in focal
epilepsy. Results showed that at a group level, FLE patients exhibit significantly poorer autobiographic memory than controls, and endorse higher levels of current depressive symptomatology (P < .001). Individual profiling revealed two distinct patient groups: one characterised by reduced autobiographic recollection and working memory but largely euthymic mood (n=5), and a second characterised by high rates of current and past mood disorder but preserved cognition (n=4). The study suggests that (i) reduced working memory is a key feature of autobiographic memory impairments in focal epilepsy, and (ii) frontal lobe seizures and disease can selectively interrupt the integrity of the autobiographic memory/cognitive control networks versus the affective network.

The second study quantitatively delineated the effects of seizure chronicity on impaired autobiographic memory function in a large cohort of patients with focal epilepsy, and examined whether reduced autobiographic recollection was linked to depression in subgroups of patients with differing levels of seizure chronicity. Relative to healthy controls (n=72), patients (n=85) performed significantly worse on measures of autobiographic memory and showed higher rates of current depressive symptomatology and disorder (P < .001). Taking a developmental perspective of seizure chronicity, patients were grouped according to their age at habitual seizure onset: early (childhood/adolescence; n=43) versus late (adulthood; n=42). Analyses showed that the factors that contribute to autobiographical memory impairment differed across the two groups. Poor autobiographic memory in patients with early onset epilepsy was associated with more frequent seizures, earlier age at onset, and reduced working memory. In contrast, the difficulties in later onset patients are correlated with symptoms of current depression and the presence of a lesion on MRI. This study revealed that (i) a longstanding seizure burden is associated with dysregulation of cognition-related networks, while (ii) autobiographic memory impairments in patients with less chronic seizures is linked to depressive symptoms, perhaps reflecting poor psychological adjustment to the onset of epilepsy.

The third study comprised a data-driven investigation into the existence of a cognitive phenotype of depression in epilepsy. Results demonstrated rates of current depression in the cohort of patients with chronic focal epilepsy (25%) were far in excess of the global point prevalence of depressive disorder of 4.7%. Cluster analysis showed that of the 21 patients currently meeting criteria for a formal depressive disorder, 15
(76%) had a ‘Cognitive’ phenotype of the disorder while six (24%) presented with a ‘Somatic’ phenotype. These findings are congruent with phenotypes of depression found in other medical and community populations, and suggest that distinctive presentations of depression in epilepsy index dysregulation of differential brain networks. Clinically, this information refines our recognition of depression in epilepsy and may reveal more individualised prognostic information for psychiatric disorders that co-occur with seizures.

Together, these studies provide behavioural evidence that habitual seizures interrupt the functioning of cognition-related brain networks known to be important to the pathogenesis of unipolar depression. The decrement in cognitive function commonly observed in focal epilepsy patients, however, does not directly contribute to their excessive depressive symptomatology. Instead relationships between cognitive impairment and depression in epilepsy are nuanced, with reductions in autobiographic memory linked to depressive symptoms only in certain subgroups of patients: namely, (i) those adjusting to the onset of seizures in adulthood, and (ii) patients with phenotypes of depressive disorder characterised by distorted cognitive processing. Neither of these relationships was strongly linked to seizure chronicity or severity, suggesting that the network disease giving rise to seizures may be independently disrupting cognitive and affective networks. This would make behavioural disorders a primary manifestation of epilepsy in some individuals.

Mood disorders in epilepsy are of critical clinical concern. Depression in this population is highly prevalent and yet remains largely undertreated, leading to unacceptably elevated rates of morbidity and mortality. This thesis advances our understanding of the presentation of depression in epilepsy and its neurocognitive underpinnings. In doing this, it helps to refine our clinical recognition of the disorder and provides a new framework for advancing biological research with the ultimate goal of improving how we prevent and treat depression in people with epilepsy.
Chapter 2. The Central Role of Cognition in Depression

2.1. Depression throughout civilisation: a brief tour

Depression is an undiscriminating human experience. It has afflicted individuals from across history regardless of their race, gender, intelligence, or socioeconomic status. Descriptions of disordered mood pepper writings from Antiquity onwards (Davison, 2006), with depictions of it being the wrath of supernatural beings gradually evolving into an empirical concept linking mental states to cognitive processes and dysfunction in the brain.

2.1.1 Classical conceptions of depression

*If fear (phobos) or distress (dysthymia) last for a long time, it is melancholia*

—Hippocrates, cited in Lewis (1934)

Hippocrates (460–377 BCE) is credited with the first unequivocal statement that melancholia could be a clinical condition resulting from dysfunction of the brain. He mused that this cerebral dysfunction was caused by an excess of black bile, one of the four bodily humours early physicians believed needed to be kept in equilibrium to maintain good temperament (Davison, 2006). Aretæus of Cappadocia (81–138 CE) contributed a detailed description of severe melancholia, gave criteria for differential diagnoses, and noted the recurrent character of the condition (Lewis, 1934). Roman scholars similarly subscribed to a neurobiological concept of depression, with Galen (129–c.200 CE) confident that: “if we were well acquainted with the physiology of the brain, we should assuredly find in its pathological condition both the place and nature of the remedy” (cited in Lewis, 1934). Greco-Roman concepts of melancholia persisted in both European and Islamic medicine for the next millennia (Davison, 2006).

2.1.2 Depression as spiritual and moral failure

After the decline and fall of the Roman Empire in the 4th and 5th centuries, the Church usurped physicians as the authority on mental disturbance in the Western world. Demoniacal possession, incubi and succubi, witchcraft, and lycanthropy were regarded as the pathogenesis of depression and other psychiatric illnesses during the Middle Ages.
In the sixteenth century, however, there was a gradual reversion to Græco-Roman teachings, with renewed recognition of organic causes of depressive states (Davison, 2006). Philosopher Michel Foucault contends that this shift stemmed from the overarching rational belief system of the Enlightenment (c.1650-1789 CE). In this ‘age of reason’, mental illness was conceived of as unreason and the mentally ill, previously consigned to society’s fringes, were now wholly separated and institutionalised (Foucault, 1964). Physicians became arbitrators of what constituted normal versus abnormal behaviour. These decisions were somewhat based on the physicians’ implicit moral assumptions, with segregating people with depression a way of banishing their socially unsettling behaviour (Gutting, 2013). Segregation, however, also made severely depressed individuals conveniently available to physicians, some of whom began to view mood disturbance as a natural phenomenon worthy of inquiry (Foucault, 1964).

2.1.3 Psychiatry in the late modern period

Pre-eminent amongst 19th century psychiatrists was Emil Kræpelin (1856–1926), whose careful clinical observations delineated various types of depressive states and differentiated mood disturbance from schizophrenia (Davison, 2006; Decker, 2004; Kræpelin, 1923). He formed the view that there is no pathognomonic sign of depression, and instead taught his students that it comprises a pleomorphic constellation of symptoms. Kræpelin was exceptionally influential in propagating the view that depressive states were manifestations of organic disease, with different clusters of presenting features probably reflecting different underlying causes, such as neurobiological or genetic derangement (Decker, 2004; Kræpelin, 1923).

Contemporaneous to –but entirely separate from– Kræpelin, Sigmund Freud (1856–1939) and his acolytes adopted a bio-psychological approach to the study of depression. Originally a practicing neurologist, many of the metapsychological processes proposed by Freud were conceptualised within a ‘psycho-physical parallelism’ that in many ways pre-empts the modern neuropsychiatric tradition of interrelating psychiatric
disorders with neurology (Carhart-Harris et al., 2008). His definition of depression is close to that used in clinical practice today:

*A profoundly painful sense of dejection, a cessation of interest in the outside world, loss of capacity to love, inhibition of all activity...a lowering of the self-regarding feelings to a degree that finds utterance in self-reproaches and self-revilings, and culminates in a delusional expectation of punishment*

–Freud (*Mourning and Melancholia*, 1917, p.244)

For Freud, depression was the product of personal life events from the past affecting the current life of the sufferer; that is, an inward, self-focused redirection of aggression for a lost love object. The rising inner need to suffer and punish oneself was thought to trigger guilt and lead to symptoms of depression such as anhedonia, diminished libido, self-criticism, and suicidality. Although unfashionable in current psychiatry, Freud’s formulation of depression was the first to position cognitive processes such as autobiographic memory and distorted information processing as central to the pathogenesis of affective disturbance.

### 2.1.4 The modern approach: biological treatments and distorted cognitive styles

Biological treatments for depression were originally devised by neurologists and neurosurgeons at the beginning of the 20th century, and included psychosurgery, electroplexy, hydrotherapy, and insulin shock therapy. Although harsh by current standards, these methods evidenced some efficacy in ameliorating depressive symptoms (Mashour et al., 2005). From the mid-20th century, observations of the effects of reserpine and iproniazid in simultaneously altering monoamine neurotransmitter levels and relieving depressive symptoms lead to the then-paradigm shifting hypothesis that depression was caused by a so-called ‘chemical imbalance’ in the central nervous system (West & Dally, 1959). This underpinned the development of pharmacological treatments of depressive disorder that act across diverse neurotransmitter systems. Examples include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), noradrenaline-dopamine reuptake inhibitors (NDRIs), et cetera.
2.1.4.1 Beck’s cognitive model of depression

In the latter part of the 20th century, psychologist Aaron Beck (1921 - ) gained the impression that the internalised thought processes of people with depression are characterised by a chronically self-deprecating way of thinking about themselves, their future, and the world around them (Beck, 1967). That is, their depression stems from maladaptive cognitive processes (See Figure 2.1).

![Figure 2.1. Beck’s cross-sectional cognitive model of depression and the self](image)

At the core of the depressed person’s identity lies highly charged, irrational, and dysfunctional beliefs about themselves that were formed by negative developmental experiences

Core beliefs underpin systematic biases in information processing, such as selectively attending to the negative aspects of experiences, and blocking of positive events and memories

Biased information processing gives rise to a cognitive style in which readily accessible negativity pervades the patient’s internal stream-of-consciousness, as well as the way in which he or she interprets their daily experiences

Symptoms: hopelessness, guilt, self-criticism, loss of motivation, fixating on negative events, suicidality

Beck’s cognitive model of depression germinated in his attempt to empirically validate Freud’s hypothesis that depression resulted from hostility being deflected inwards. He analysed the dream content of people with depression and found that it actually contained less hostility than the dreams of euthymic persons. Instead, the dreams of depressed individuals showed prominent themes of being rejected, deprived, or thwarted. Beck hypothesised that these themes reflected the way that patients saw themselves, and that their internal communication was jammed with intrusive and punitive thoughts about themselves.

Moreover, Beck noted that these pre-conscious, negative, automatic thoughts were distortions of reality and full of errors. One example of a depressive error is selective abstraction, where a person makes a judgment based on an isolated, magnified portion of (negative) information, but disregards other (positive) information from that same
context\(^1\). He argues that these irrational biases act as a warped prism for how people view themselves, the world around them, and their future (the so-called ‘cognitive triad’; Beck, 1976). His model of psychotherapy, known as cognitive behavioural therapy, engages patients in challenging their depressogenic thoughts with evidence and behavioural experiments. In this way, Beck firmly roots the pathogenesis of depression in abnormal cognitive styles, giving rise to a multi-layered model of the disorder: In sum, maladaptive core schema about the self that typically stem from early life experiences hijack an individual’s information processing and produce the negative cognitive biases that make some people vulnerable to depressed mood (Beck, 1987). Such maladaptive belief systems and negative schemata have been objectively identified in samples of people with depression (Hollon et al. 1986, Scott et al. 2000).

The original cognitive model has since been expanded to incorporate clinical genetic, neurophysiological, and neurochemical pathways that interact with cognitive functioning (see Figure 2.2; Beck, 2008). In a review of neurobiological investigations into depression, Beck concluded that some individuals have a genetic vulnerability to depression, which impacts on neural functioning in the amygdala and prefrontal cortices and leads to a negative appraisal of adverse life experiences. Moreover, genetic polymorphisms may be involved in the overreaction to stress and the subsequent hypercortisolemia observed in depression. Beck believes that these epigenetic effects are “probably mediated by cognitive distortions” (p.969, 2008).

\(^1\) e.g., After receiving comments about a work presentation, the depressed person focuses on the single suggestion for further improvement and ignores all positive feedback.
2.2 Symptom-based nosologies of unipolar depression

All operationalised diagnostic systems for psychiatric illness contain a category that corresponds to the concept of depression. The term ‘major depressive disorder’ was introduced in the mid-1970s as part of clinical consensus statements for diagnostic criteria, and was based on patterns of symptoms. The resultant symptom-based nosology of depression currently used in clinical practice and research is popularised by the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (DSM), as well as the World Health Organization’s *International Statistical Classification of Diseases and Related Health Problems* (ICD). Descriptive comparison of the definitions for unipolar depression given in these two diagnostic schema suggests that their symptom-based criteria are largely equivocal, with differences limited to cut-off, time, and exclusion criteria (Phillip et al., 1991). For this reason, this dissertation will employ the classification criteria most commonly applied in current Australian practice and research, i.e., the *Diagnostic and Statistical Manual of Mental Disorders fourth edition, text revised* (DSM-IV-TR; American Psychiatric Association, 2000).

2.2.1 Mood disorder according to the Diagnostic and Statistical Manual of Mental Disorders

The American Psychiatric Association incorporates the concept of unipolar depression in the broader category of Mood Disorders. This section of the manual encompasses all disorders that have a disturbance in mood as a predominant feature, including the Depressive Disorders (unipolar depression), the Bipolar Disorders, and two disorders based on ætiology i.e., Mood Disorder due to a General Medical Condition and Substance-Induced Mood Disorder. The Bipolar Disorders and the two disorders based

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2 c.f. bipolar depression, a psychiatric disorder in which bouts of depression are interspersed with periods of wildly elevated mood

3 More recently, the American Psychiatric Association released the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V; 2013), an updated version of the manual superseding DSM-IV-TR. Most notably, the Mood Disorders category has been split into two separate sections: ‘Bipolar and Related Disorders’ and ‘Depressive Disorders’. Within the latter category, major changes from DSM-IV-TR comprise:

- Removing the bereavement exclusion criterion from depressive disorders
- Dysthymia is now known as ‘Persistent Depressive Disorder’
- Addition of ‘Disruptive Mood Regulation Disorder’ for children under 18 years of age
- ‘Premenstrual Dysphoric Disorder’ instated as a disorder
- Specifiers added for mixed symptoms and for anxiety
on ætiology are underpinned by pathogenic processes that are distinctly different to those seen in unipolar depression (de Almeida & Phillips, 2013), and therefore only unipolar depression will be discussed in this thesis. The common feature of all unipolar depressive disorders is the presence of sad, empty, or anhedonic mood, accompanied by somatic and cognitive changes that significantly affect the individual’s capacity to function. Within the category of depressive disorders, however, the manual provides diagnostic criteria for different types of clinically significant unipolar depression based on phenomenology and course. These include Major Depressive Disorder, Dysthymic Disorder, and Depressive Disorders Not Otherwise Specified.

2.2.2 Major Depressive Disorder

Major Depressive Disorder (MDD) represents the archetypal condition in the group of unipolar depressive disorders (American Psychiatric Association, 2013). DSM-IV-TR (American Psychiatric Association, 2000) states that the diagnosis of MDD requires the experience of at least one current or past Major Depressive Episode (MDE). As in all unipolar mood disorders defined by DSM-IV-TR, symptoms cannot occur in the context of co-morbid manic mood or a psychotic illness with depressive features, or be better accounted for by recent bereavement, a substance, or a physiological condition.

The essence of an MDE is a period characterised by (i) depressed mood and/or (ii) the loss of interest or pleasure in nearly all activities, i.e., anhedonia. The individual must also experience at least four additional symptoms: changes in appetite or weight; changes in sleep patterns; altered psychomotor activity; anergia; feelings of worthlessness or inappropriate guilt; difficulty thinking, concentrating, or making decisions; recurrent thoughts of death or suicidality. These symptoms must be either novel or have clearly worsened relative to the premorbid state. They must persist for most of the day, nearly every day, for at least two consecutive weeks and be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2000).

Importantly, there were no changes to the diagnostic criteria of unipolar depression and the above changes do not significantly impact on the research and discussion expressed here that is based on DSM-IV-TR terminology.
2.2.3 Dysthymic Disorder

The essential feature of Dysthymic Disorder is a chronically depressed mood that endures for most of the day, more days than not, for at least two years. During this time, at least two of the following additional symptoms are present: poor appetite or overeating; insomnia or hypersomnia; anergia; low self-esteem; poor concentration or difficulty making decisions; and feelings of hopelessness. Any symptom-free interval may last no longer than two months. If the chronic depressive symptoms include a MDE during the initial two-year period of dysphoria, then the diagnosis is MDD (Chronic) or MDD (In Partial Remission). After the initial two years of Dysthymic Disorder, MDEs may be superimposed on the Dysthymic Disorder. In such cases ("double depression"), both MDD and Dysthymic Disorder are diagnosed until the patient returns to a dysthymic baseline, at which point only Dysthymic Disorder is diagnosed (American Psychiatric Association, 2000).

Dysthymic Disorder and MDD are differentiated based on severity, chronicity, and persistence. Usually MDD consists of one or more discrete MDEs that can be distinguished from the person’s usual functioning, whereas Dysthymic Disorder is characterised by less severe depressive symptoms that persist for many years (American Psychiatric Association, 2000).

2.2.4 Depressive Disorder Not Otherwise Specified

Depressive Disorder Not Otherwise Specified (DDNOS) is a diagnostic category encompassing disorders with mood symptoms that do not meet criteria for any specific Mood Disorder. Examples provided by the American Psychiatric Association include Recurrent Brief Depressive Disorder, Premenstrual Dysphoric Disorder, Post Psychotic Depressive Disorder, and Minor Depressive Disorder. Minor Depressive Disorder is commonly referred to as subthreshold depression and is defined as the presence of at least two, but less than five, symptoms of an MDE during a two-week period, representing a change from previous functioning. As in MDE, at least one of the symptoms must be either dysphoria or anhedonia (First et al., 2002).
2.3 The symptomatology of unipolar depression

Depression is a multifaceted disorder typified by internalised distress (Andrews et al., 2007). The cardinal signs and symptoms used to diagnose depression today are broadly equivalent to the phenomenology described in ancient texts: disturbed mood, self-castigation, a wish to die, physical and vegetative complaints, and delusions of having committed unforgivable sins (Davison, 2006).

Very few studies have been designed to delineate the typical clinical presentation of depression. This section is therefore largely based on Beck and Alford’s (2009) effort to describe the symptoms that occur significantly more often in depressed versus nondepressed people, an attempt based on systematic patient interviews as well as analysis of psychiatric textbooks and monographs. Three major categories of depressive symptoms emerge, each underpinned by distinct neurobiological substrates: affective symptoms, vegetative symptoms, and cognitive symptoms (Davidson et al., 2005).

2.3.1 Affective features of depression

The chief complaint in depression is frequently the affective disturbance, and thus it is often considered to form the ‘cardinal’ feature of the disorder (American Psychiatric Association, 2000). Affective features of depression refer to changes in the patient’s feelings, or changes in their overt behaviour that are directly attributable to their feelings.

Manifestations of affective change classically include (i) dejected mood (dysphoria), which may range from feeling down or sad through to feelings of intolerable misery and hopelessness, and (ii) reduced gratification (anhedonia), ranging from losing ‘pep’ for activities previously enjoyed through to complaints of nothing giving any degree of satisfaction. Other affective features of depression are loss of emotional attachments, emotional numbness, crying spells, as well as loss of a mirth response and being unable to be cheered up.

Perhaps paradoxically, however, a subjective change in mood is not endorsed by all depressed patients. Beck and Alford (2009) found that only 53% of mildly depressed individuals acknowledged feeling sad or unhappy, and a large-scale study using World

\footnote{Other minor categories defined by Beck and Alford (2009) comprise motivational and delusional manifestations of depression.}
Health Organization data reported that 11% of people meeting criteria for major depression deny affective symptoms of depression on direct questioning\(^5\) (Simon et al., 1999). Some of these patients may instead express their distress in somatic terms, such as an empty feeling in the pit of the stomach, a heavy feeling weighing on the chest, or a lump in the throat (Kirmayer, 2001). De Wester (1996) hypothesised that the unfortunate stigma sometimes associated with depression may result in unwillingness from some patients to talk about their emotional complaints. In contrast, physical symptoms seem more ‘legitimate’ and are less awkward for some people to disclose.

### 2.3.2 Somatic and vegetative features of depression

Vegetative features of depression are often considered to be evidence of an autonomic basis for depression (Bao et al., 2008). Somatic complaints commonly include loss of appetite, sleep disturbance, psychomotor agitation or retardation, decreased libido, pain, gastrointestinal problems, headache, anergia, and fatigue (Beck & Alford, 2009; American Psychiatric Association, 2013). Some physicians may consider patients to be in remission from depression when their affective symptoms have abated, but Trivedi (2004) argues that residual physical symptoms are common and increase the likelihood of relapse. Physical symptoms in depression may arise from alterations in the neurochemical resources shared by affective and somatic processing, with response to physical discomfort modulated by the same neurotransmitter systems that regulate mood: namely, serotonin and noradrenaline (Stahl, 2002).

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most consistent biological findings in unipolar depression (Nemeroff & Vale, 2005), and the resultant hypercortisolemia is linked to many of the somatic features of unipolar depression. The activated HPA axis not only regulates endocrine function such as metabolism and immunity (Pariante & Lightman, 2008), it also has profound effects on brain functions such as neuronal survival, neurogenesis, neurotransmitter systems such as noradrenaline and serotonin, circadian rhythms, the size of complex anatomical structures such as the hippocampus, the acquisition of new memories, and the emotional appraisal of events (reviewed by Herbert et al., 2006). As such, hyperactivation of the HPA axis in depression impacts on these systems and has clinical correlates consistent

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\(^5\) Cardinal affective symptoms can also be diagnosed based on informant report
with its somatic features, such as sleep disturbance (Antonijevic & Antonijevic, 2008), appetite changes and anergia (Andréasson et al., 2007), and psychomotor symptoms (Schrijvers et al., 2008).

2.3.3 Cognitive features of depression

Pseudodementia was a clinical phenomenon first noted in the 1880s, describing a phenotype of depression associated with apparent cognitive decline. Of importance, the ‘dementia’ remitted with successful treatment of the mood disturbance (Berrios, 1985), suggesting that the cognitive impairment was directly related to features of the depressed mood, such as amotivation and apathy (Hall et al., 2011). More contemporary investigation reveals that the cognitive features of depression are diverse in form, and encompass maladaptive and distorted cognitive styles of thinking about the self and the world, as well as subjective and objective impairments in cognitive capability.

2.3.3.1 Depression and autobiographic memory: a distorted self-perception

The ability to project ourselves into an imagined future or vividly re-experience personal events from our past is believed to be a uniquely human gift (Tulving, 2002). Labelled autonoetic (self-knowing) consciousness, this effortless capacity for mental time travel is an expression of the episodic autobiographic memory system. Autobiographic memory encompasses the encoding, storage, and retrieval of the events, people, and situations encountered in conscious experience (Wheeler et al., 1997). It contributes to an individual’s identity, as well as their ability to pursue goals effectively (Williams et al., 2007). It does this by allowing us to use our memories to construct fictional scenes in our mind to reflect on what might have been had we chosen another path, or to imagine what might happen in the future in light of past experiences (Hassabis & Maguire, 2007).

Conway and Pleydell-Pearce (2000) conceptualize the self-memory system as comprising (i) a store of autobiographic knowledge and (ii) current goals of the self. Executive control processes use the current goals of the self to modulate activation of the autobiographic memory network and access to the knowledge store. This triggers a hierarchical search for retrieving personal events. The autobiographical knowledge store may also influence the goals of the current self, making it a reciprocal model with both top-down and bottom-up mechanisms. Baddeley (2001) considers the essence of episodic memory to be its specificity, its ability to capture personal life events within a spatio-
temporal framework, suffused with subjective meaning. By gathering a web of neurocognitive resources, autobiographic memory integrates episodic memory, emotion, and a continuous sense of identity to produce the contextual framework of who we are: a coherent lived experience (Blinder, 2007).

The coherent lived experience is crucial to our mental health. Most strikingly, people with depression more readily recall negative memories, and exhibit a characteristically overgeneral autobiographic memory. That is, they have a tendency to recall categories of events (e.g., “birthday parties”) when asked to provide specific instances of events from their lives (e.g., “a birthday party at the zoo for my brother at around the age of 10”; Williams, 2006), especially for positive experiences (Brittlebank et al., 1993). Williams et al (2007) believe that depressed individuals begin retrieving personal events but the hierarchical search is truncated at an early stage, leading to vague, poorly localised and overgeneral recollections (see Figure 2.3).

Fitting with both Freud and Beck’s cognitive models of depression, the hypothesised function of this diminished specificity for past events is to blunt the emotional experience of the memory, or to passively avoid it altogether (Raes et al.,
Williams et al (2007) extend Conway & Pleydell-Pearce’s model, arguing that truncated autobiographic memory retrieval in mood disturbance stems from:

- Triggering of ruminative processes, which co-opts available cognitive resources needed for further search and retrieval;
- ‘Functional avoidance’ (i.e., repression of the search) when autobiographic material threatens to cause emotional distress, and;
- Depleted executive control that limits an individual's ability to remain focused on retrieval.

This final mechanism is consistent with research showing cognitive control to be a key element of autobiographical memory retrieval. A review by Dalgleish and colleagues (2007) revealed that performances on measures of autobiographical recall are associated with the integrity of cognitive control independent of the depressed mood state, and that deficits in cognitive control and its subordinate processes like working memory largely underpin the relationship between depression and autobiographic memory impairments. This poverty of cognitive control and resultant skeletal autobiographical recall is thought to foster rumination, intrusive thoughts, and deficits in imagining future events, thereby handicapping adaptive coping (Raes et al., 2006).

Overgeneral memory is a compelling cognitive vulnerability factor for depression. Gibbs and Rude (2004) showed in a nonclinical sample that an overgeneral autobiographic memory style at baseline interacted with the occurrence of stressful life events to predict the development of depressive symptoms 4-6 weeks later, and more recently Young et al (2013) showed that individuals at high familial risk of developing MDD have autobiographic memory impairments that are associated with the same altered patterns of functional activation in the mesial prefrontal cortex (PFC) exhibited by people with active MDD. Together, these findings indicate that overgeneral memory is a trait-like vulnerability factor for developing depression. In clinical samples it is likely to be a long-term cognitive style that persists into remission, with autobiographic memory found to be reliably impaired in patients with unipolar depression over a 7-month period, despite significant clinical improvement in the sample (Peeters et al., 2002).

Moreover, overgeneral autobiographic memory is believed to be a maintaining factor in the mood disorder, leading to poorer prognosis and long-term adjustment issues.
Naylor & Clare, 2008). A meta-analysis of 15 studies looking at autobiographic memory in depression found that fewer specific memories and more overgeneral memories at initial assessment was associated with worse depressive symptoms at follow-up, and predicted poorer prognosis more so than initial depressive symptoms. The prognostication between overgeneral memory and poorer outcomes in depression was most evident as the age of participants increased (Sumner et al., 2010).

### 2.3.3.2 Depression and subjective memory complaints

Experimental evidence suggests that subjective complaints about memory functioning become more prominent in the context of low mood. Studies of both young and older healthy individuals robustly show that emotional state—particularly depressive symptoms—are better predictors of subjective memory ratings than objective memory performance (e.g., Smith et al., 1996; Vestberg et al., 2007; Mendes et al., 2008). Age, education, and sex seem to have little impact on these effects (Slavin et al., 2010).

This relationship is also evident in pathological depressive states. In an insightful longitudinal study, Antikainen et al (2001) showed that at baseline, patients with clinical depression (n=174) complaining of memory disturbances endorsed more depressive symptoms than patients not complaining of memory problems. Complaints of memory problems, however, decreased during six months of follow-up and treatment, a change associated with improved mood but not with cognitive performance. Similarly, Coleman et al (1996) assessed the subjective memory of 70 severely depressed patients before and after a course of electroconvulsive therapy (ECT). Marked improvement in the patients' self-appraisal of their cognitive ability was evident within one week of receiving ECT, with subjective memory complaints comparable to those of healthy controls (n=18) by two months post-treatment. At all time points, the severity of depressive symptoms was strongly associated with patient reports of memory dysfunction. This is despite evidence showing that ECT can result in short-term anterograde and retrograde memory impairments (Ingram et al., 2008), suggesting that as in healthy people from the community, subjective memory complaints from people with clinical depression may be a marker of a depressed mood state rather than reflective of actual cognitive functioning. It is likely that these subjective experiences of forgetfulness in depression stem from lapses in concentration.
2.3.3.3 Depression and psychometric cognitive impairments: reduced cognitive control

Formal neuropsychological assessment provides a framework for empirically measuring cognitive changes associated with depression. According to a review by Clark et al. (2009), the neuropsychological profile of depression consistently discloses reduced cognitive control. Cognitive control is a broad term used to capture higher-order supervisory processes subserved by the anterior frontal lobes. It encompasses strategic retrieval, verification, monitoring, and maintenance of on-line information in order to accomplish a goal (Conway et al., 2001; Svoboda et al., 2006; Spreng & Grady, 2010), and synthesises memory and sensory-perceptual processing subserved by posterior association cortices (Luria, 1974; Baddeley & Della Sala, 1996; D'Esposito & Badre, 2011). The higher-order dysfunction seen in depression often takes the form of circumscribed deficits in working memory, cognitive flexibility, and inhibition of prepotent responses (Austin et al., 2001). This executive dysfunction has meaningful impacts on patient quality of life. Specifically, executive faculties are fundamental to maintaining social relationships, with social dysfunction the major factor decreasing quality of life in depressed patients (Kasper et al., 2011).

According to the Beck model of depression, reduced agency to exert executive control in the context of depressive core beliefs about the self and the world leads to pathological biases in information processing. Specifically, poor cognitive control underpins difficulties disengaging from negative stimuli, difficulty inhibiting a critical self-focus, and unfettered elaboration of negative material (Gotlib & Joormann, 2010; Hamilton, Furman et al., 2011). This biased information processing style is hypothesised to form the basis of metacognitive features of depression such as pessimism, hopelessness, blame, self-criticism, delusions of worthlessness, misplaced guilt, and suicidality. The ensuing rumination occupies the limited capacity of the working memory system and overloads it (Hamilton, Furman et al., 2011). This causes patients to become easily distracted and potentially leads to “memory” complaints. Moreover, the monopoly on cognitive resources by introspection leaves insufficient resources available for concentration, weighing up decisions, and explicit and implicit learning and recall. In conjunction with apathy, this may give rise to a clinical picture of global psychometric difficulties (Hall et al., 2011).
Neurochemically, noradrenaline plays a key role in the cognitive symptoms of depression, modulating prefrontal psychological faculties such as cognitive control. Reduced noradrenaline transmission is well-described in people with depression (Goddard et al., 2009), and results in decreased alertness, inattention and poor concentration, decreased motivation, and reduced cognitive resources (see Moret & Briley, 2011, for a review).

Figure 2.4. Saggittal section of the human brain, showing the principal noradrenergic pathways (Source: Moret & Briley, 2011)

In this thesis, the neuropsychology of depression is interpreted within a hierarchical organisation of neurocognitive function that has been modelled from the preceding literature. This framework recognises that higher-order prefrontal executive functions responsible for synthesising and organising incoming information co-ordinate lower-order modal-specific gnostic processing and sensory-perceptual processing subserved by posterior cortices (see Figure 2.5; Luria, 1974; Baddeley & Della Sala, 1996; D'Esposito & Badre, 2011). It integrates both clinical conceptions of depression, such as Beck’s cognitive model, as well as psychometric profiles of depressed individuals.
Figure 2.5. Hierarchical model of cognitive deficits in depression
2.4 Symptom-based subtypes of unipolar depression

There is a longstanding controversy in psychiatry concerning the classification of depression, with disagreement as to whether its polythetic diagnostic criteria suggest a dimensional entity of varying degrees of severity, or a group of two or more discrete illnesses broadly characterised by dysphoric or anhedonic mood but differing in terms of course, prognosis, optimal treatment, and genetics (Rush, 2007). DSM-IV-TR classification criteria give rise to around 200 symptom profiles of depression, some of which may not show any overlap with each another. That is, two individuals can be diagnosed with depression who share no common symptoms. Luyton et al (2006) argue that descriptive taxonomies ignore biological and psychosocial features of depression that are associated with different aetiologies, presentations, and treatment responses, and therefore spuriously group together heterogeneous individuals.

To address the issue of pleomorphism, several attempts have been made to delineate more homogenous subgroups within unipolar depression, including phenotypes characterised by cognitive symptoms. A phenotype is a constellation of observable characteristics or traits that define a disorder. These traits can be behavioural, biochemical, or physiological, acting as a marker of the structural and functional brain systems involved, and reflecting genetic and epigenetic influences (O’Brien, 2002). Commonly, the taxonomy of depressive symptoms has been studied using data-driven statistical methods, with depressed individuals assigned to diagnostic sub-categories based on the similarity of their symptom profiles (Aktas et al., 2010). Given the difficulty in identifying the underlying pathophysiology of mental disorders, symptom concurrence has been employed to suggest a common aetiology. For instance, patients with ‘atypical’ forms of unipolar depression (i.e., reversed vegetative symptoms of both hypersomnia and hyperphagia) may show higher levels of serum C-reactive protein than patients with more archetypal forms of the disorder (Hickman et al., 2013), hinting at a pathological inflammatory response uniquely underlying the atypical phenotype.

2.4.1 Phenotypes in psychiatric populations: ‘Endogenous’ versus ‘Neurotic’ depression

Physician and clergyman Timothie Bright (1550–1615 CE) first distinguished melancholy with and without cause, a notion that evolved into the hotly debated concept
of organic, ‘endogenous’ depression versus psychogenic or reactive ‘neurotic’ depression (Davison, 2006). The term ‘endogenous’ depression has since been used to describe a profile of insomnia, appetite changes, anhedonia, psychomotor reactivity, diurnal variation, and subjective cognitive difficulties. ‘Neurotic’ depression, meanwhile, comprises a phenotype of self-criticism and emotional reactivity triggered by psychosocial stress (Kiloh et al., 1972; Andreasen et al., 1980). These subgroups of depression were derived from physicians’ observation, however, and differentiating them by biological markers has proved largely fruitless, with no differences between patients with endogenous versus neurotic depression on tests of dexamethasone suppression, cortisol levels, growth hormone response, or polygraphic sleep recordings (Berger et al., 1989). Proband and twin studies conducted in previous decades suggested that endogenous forms of depression have a stronger genetic influence than neurotic subtypes, although results were largely dependent on how each subtype was defined (for a review see McGuffin & Katz, 1989). Overall, most data-driven taxonomic research in psychiatric populations has produced clusters in which group members largely differed in the severity or number of depressive symptoms they endorsed, rather than in the qualitative nature of their symptoms (Andreasen et al., 1980; Sullivan et al., 2002; Lincoln et al., 2007; for a recent review, see van Loo et al., 2012).

2.4.2 ‘Cognitive’ versus ‘Somatic’ subtypes of depression

A notable shift away from the endogenous/neurotic dichotomy was a study co-authored by Aaron Beck (Haslam & Beck, 1993). In an algorithmic categorisation of the symptom profiles of 400 outpatients with unipolar depression, Haslam and Beck found a phenotype of depression characterised by primarily cognitive manifestations of affective disturbance, namely self-critical symptoms in the absence of vegetative features. Subsequent review of the subtyping literature suggests that this cognitive phenotype of depression is robustly replicated in large samples from community populations as well as medical cohorts with coronary disease6 (range N= 324 – 2,544), with studies typically clustering symptoms patients have endorsed on self-report questionnaires such as the Beck Depression Inventory. Common features include subjective cognitive difficulties, dysphoria, self-critical cognitions, and suicidality (see Table 2.1 for evidence of their

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6 From across three different research groups.
reproducibility across studies, as well as Appendix Table A for a detailed account of studies describing cognitive subtypes of unipolar depression).

### Table 2.1 Convergent evidence for the typical symptom profile of the ‘Cognitive’ phenotype of depression

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Studies</th>
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</table>

Although a neurobiological basis for the cognitive phenotype of depression has not yet emerged, parallels may be drawn between the phenotype and the hierarchical model of cognitive decrement in depression outlined in Figure 2.5. In particular, the model predicts that the negative cognitive bias, subjective cognitive complaints, and reduced cognitive performance characteristic of the cognitive phenotype is the product of systematic biases in information processing and higher-order executive deficits. These cognitive domains are well-defined and have clear neuroanatomical and functional correlates that could provide novel insights into the pathogenesis of the cognitive form of depression. As is apparent from Table 2.1, however, only Blazer et al (1988) formally tested the cognitive functioning of their participants\(^7\), raising the question of what psychometric deficits might accompany or underpin the phenomenology of the cognitive phenotype of depression, including whether autobiographic memory disturbance or reduced cognitive control might be more common in the cognitive phenotype than in other phenotypes of depression. It also prompts future investigation into whether the cognitive

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\(^7\) however they only used the Mini Mental State Examination
phenotype might be more common in populations with high rates of co-morbid depression and cognitive deficits, such as epilepsy or stroke.

In addition to the cognitive phenotype, subtyping of self-report depressive symptoms in these same samples commonly discloses a phenotype of unipolar depression characterised by prominent vegetative features (‘Somatic’ depression). Across studies, features of this subtype consistently comprise sleep and appetite changes, excessive fatigue, and diminished libido (see Table 2.2), and less commonly, psychomotor retardation/agitation. For instance, Marijnissen et al (2011) conducted a principal components analysis on the depressive symptoms of 1,284 inhabitants of the Netherlands and found that in addition to the cognitive phenotype, a second symptom-based subtype emerged, characterised by a constellation of insomnias, fatigue, loss of appetite, weight loss, somatic preoccupation, and diminished libido. Furthermore, Stewart et al (2007) provides an initial indication that affectively, patients with a somatic phenotype of depression may experience anhedonia rather than dysphoria.

**Table 2.2 Convergent evidence for the typical symptom profile of the ‘Somatic’ phenotype of depression**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Studies</th>
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</table>

This somatic profile is broadly analogous to the concept of ‘melancholic’ or ‘endogenous’ depression (Davison, 2006), and may be more common than the cognitive subtype (Blazer et al, 1988). Consistent with previous attempts to delineate a biological
marker of ‘endogenous’ depression (Section 2.4.1), there is no clear neurobiological understanding of the somatic phenotype. Although speculative, the prominence of vegetative symptoms in conjunction with the link between this phenotype and negative medical outcomes (see below) may suggest that this phenotype stems from dysfunction in brain systems central to somatic regulation such as the HPA-axis and the serotonin and noradrenaline neurotransmitter systems (see Section 2.3.2).

Intriguingly, the cognitive and somatic subtypes of depression seem to confer differential vulnerabilities to negative health outcomes (see Figure 2.6, with details of contributing studies outlined in Appendix Table A). In particular, somatic features of depression are considered to be more cardiotoxic than cognitive or affective symptoms (e.g., Stewart et al., 2007). For example, Marijnissen et al. (2011), showed that the somatic symptom profile was related to sensitive measures of visceral obesity and cardiovascular risk, including increased waist circumference and greater waist-to-hip ratio, whereas overall depression scores and the cognitive symptom profile were only related to body mass index. More sinisterly, Roest et al. (2011) found that after controlling for the index event, a history of myocardial infarction, Killip class$^8$, diabetes, gender, and age, there was a significant association between somatic subtypes of depression and mortality in people who had suffered myocardial infarction ($P < .001$). This risk was not evident in the cognitive phenotype ($P = .73$). In contrast, however, Stewart et al. (2012) showed that only affective symptoms such as dysphoria predicted 5-year incidence of coronary artery calcification, suggesting that there may not be a singular element of depression that is cardiotoxic across all settings.

Further research is needed to examine the negative impact different phenotypes of depression may have on non-cardiac systems, as well as the different psychiatric prognoses associated with cognitive versus somatic depression. Moreover, it is unclear why scientists from other medical populations with high comorbidites of depression have not adopted the same symptom-profiling approach to depressive features employed by cardiac researchers. The extension to diseases such as epilepsy, stroke, and cancer is clear, and may provide novel insights into differential negative health outcomes conferred by different phenotypes of co-morbid depressive disorder in these populations.

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$^8$ i.e., risk of death within 30 days
Together, the studies reviewed here disclose that cognitive disturbances may be a prominent feature of certain subtypes of unipolar depression. Of interest, the existence of phenomenological phenotypes of depression also suggests that the cognitive, somatic, and affective features of the disorder can be separated out, and perhaps are indicative of dissociable neurobiological substrates.

**Figure 2.6.** Graphical summary of the key features of cognitive versus somatic phenotypes of unipolar depression, as well as the differential health-related outcomes potentially associated with each phenotype.
Summary: Cognitive disturbances are a key feature of depression

Cognitive disturbances have been recognised as a core feature of depression for millennia, and currently constitute a formal diagnostic criterion of the disorder. Indeed, some depressed individuals present with a predominately cognitive phenotype of the disorder. Cognitive disturbances in depression can take many forms, including negative distortions and biases in information processing, subjective cognitive deficits, reduced cognitive control, and autobiographic memory impairments. However, the prevalence and potential role of cognitive disturbance in populations with high rates of both cognitive impairment and mood disorder, such as epilepsy, remains unexplored. The systems-level neurobiological account of depression outlined in the following chapter describes some potential mechanisms that may underpin the cognitive features of unipolar depression that may also be vulnerable to neurological disease.
Chapter 3. Cognition-related brain networks and the symptomatology of unipolar depression

A central tenant of the symptom profiling approach to taxonomy described in the preceding section is that different depressive symptoms or symptom clusters reflect different neurobiological substrates (Aktas et al., 2010). The cognitive symptoms seen in certain phenotypes of depression as well as unipolar depressive disorder more broadly indicates that the brain systems underlying cognition may be implicated in the pathogenesis of depression. In support of this, growing evidence points to the fundamental rôle played by cognition-related brain networks in the expression of many of the diverse features of depression, including somatic and affective symptoms as well as cognitive phenomenology (Davidson et al. 2002; Phillips et al. 2003; Ochsner & Gross, 2005; Phan et al. 2005). The current chapter therefore seeks to explore the neurobiology of depressive symptoms from a cognitive systems perspective.

Neurophysiologist Charles Sherrington (1906) was the first to suggest that the brain communicates and functions via a web of neurons, i.e., a network. In parallel, the rôle of individual structures in the brain was being charted that later came to form the nodes of local and large-scale functional networks (Sporns, 2011). Local networks are contained to a focal region of the brain and engaged in modality-specific processing, such as spatial localisation, visual analysis of shape, object identification by taste, et cetera. In contrast, large-scale networks incorporate parallel lines of communication across the whole brain, enabling complex integrative processing (Bullmore & Sporns, 2009). During functional neuroimaging scans, regions that ‘co-activate’ simultaneously with robust replicability during certain tasks are typically linked together to form a network whose function is crucial to the performance of that task e.g., the ‘autobiographic memory network’, the ‘dorsal attention network’ or the ‘singing network’. This capacity is currently thought to arise from static neuronal architecture and connections in conjunction with flexible and dynamic connectivity (Damoiseaux et al., 2006).

Studies using structural and functional magnetic resonance imaging (MRI) in both healthy individuals and people with unipolar depression have identified a web of prefrontal-midline-limbic regions thought to underpin deficits in cognition that relate to a range of negative affective experiences (Bremner et al., 2004; Levin et al., 2007;
McDermott & Ebmeier, 2009; Cocchi et al., 2014). Moreover, altered functioning of cognitive brain networks has been hypothesised to impair the downregulation of cortico-subcortical mood networks, potentially accounting for some of the more somatic features and phenotypes of unipolar depression (Ochsner & Gross, 2005; Wilson, 2011).

The functional neuroimaging research reviewed here links many of the diverse symptoms of depression to two abnormal cognition-related brain networks. The Autobiographic Memory Network (AMN) focuses on internal mental states but in depression is overactive, leading to pathological introspection and symptoms such as rumination and distorted information processing. In contrast, the externally-focused Cognitive Control Network (CCN) is underengaged in depression, leading to characteristic difficulties in efficiently attending and responding to environmental demands. The anatomical and functional configurations of these two networks can change between individuals and over time, plausibly accounting for both the idiosyncratic symptom presentation of depressive disorders and their often-fluctuating course.

The current chapter focuses on functional neuroimaging of unipolar depression, namely patterns of regional co-activation and how they are altered in depressed patients. The structural neuroanatomical changes associated with mood disturbance have been expertly reviewed in several recent articles (see Hasler & Northoff, 2011; Price & Dreverts, 2012), and therefore will not be re-examined here. In order to characterise the rôle of cognitive networks in depressive symptomatology, inclusion criteria for neuroimaging studies were: (i) studies describing original research or meta-analyses, and (ii) functional activation neuroimaging (e.g., PET, fMRI, SPECT) of neurocognitive networks OR neuroimaging relevant for understanding the neurobiological basis of depressive symptoms, and (iii) comparing adult patients with unipolar depression to healthy adult controls. Studies of late-onset (>50 years) depression were excluded, as current evidence suggests that unique pathophysiologies underpin early-onset versus late-onset depression (Naismith et al, 2012). In addition, since the existential symptoms of depression cannot be reproduced in animal models (Krishnan & Nestler, 2008), functional neuroimaging studies of animals were excluded under criteria (iii). In integrating suitable studies, this chapter sought to characterise the abnormal co-activation patterns of cognitive networks in people with depression, and relate altered function and dynamics to depressive symptomatology.
3.1 General comments on regional coactivation versus resting state networks

‘Functional brain networks’ are stationary snapshots of fluctuating neural activity, derived by averaging the brain’s connectivity or activation across a time series of neuroimaging data (Sporns, 2011). This stationarity can be captured during a pre-defined cognitive task, or while the participant is resting in the scanner with no specified task to execute; the so-called ‘resting state’.

Resting state networks comprise a set of intrinsic networks characterised by very low frequency neuronal oscillations (< .1 Hz) that synchronise functionally diverse brain regions (Mantini et al., 2007). Independent component analysis objectively reveals at least half a dozen resting-state networks, some of which seem be involved in cognitive domains such as sensorimotor planning, executive control, language, and episodic memory (Smith et al., 2009). One of these networks is often referred to as the default mode network and commonly deactivates during task-based fMRI experiments.

In contrast, when participants are asked to do a cognitive task in the scanner, patterns of regional co-activation emerge that form the basis of specialist neurocognitive networks: for instance, an occipital network important for perception, a central network for action, and a network in a similar distribution to the autobiographic memory network that processes tasks with an emotional valence (Crossley et al., 2013). Crossley and colleagues’ meta-analysis of fMRI and PET studies also confirmed a so-called ‘rich club’ of densely interconnected, bilateral regions in mesial parietal and prefrontal cortices that are coactivated by a diverse range of experimental tasks (van den Heuvel & Sporns, 2011).

It should be noted that stationarity is a statistical technique that rigidly maps functional networks onto a brain that is dynamically changing over time. In other words, it is a heuristic, as in reality networks and rich clubs flexibly reconfigure their connections in response to internal and external demands (Sporns, 2011). For example, when faced with cognitive challenge, cognition-related networks co-activate and become strongly connected, and when the demand eases they become less hub-like, allowing resting state networks to re-group and dominate brain function.
3.2 The autobiographic memory network

The AMN is the most well-described functional network in the human brain. Commonly known in its resting state form as the default mode network, it can also be activated in a more targeted manner by tasks requiring self-referential cognitive processing, including autobiographic memory, autonoetic consciousness, social cognition, daydreaming, and introspection (Andreasen et al., 1995; Gusnard et al. 2001; Fossati et al. 2003; Saxe & Kanwisher, 2003; Ochsner et al. 2005; Mitchell et al. 2006; Buckner et al., 2008; Spreng & Grady, 2009; Chun et al. 2011; Andrews-Hanna, 2012). In the current thesis it is referred to as the AMN rather than the ‘default-mode network’ for two reasons: (i) to more specifically reflect its known function, and (ii) to avoid conflation of the default mode network with other resting-state networks, as occurs occasionally in the neuroimaging literature (for expert commentary on this topic, see Buckner, 2012). The research reviewed here examines the AMN in both its task-state and resting state forms.

Key nodes of the bilateral AMN comprise the orbitomesial prefrontal cortex (omPFC), dorsomesial PFC (dmPFC)/rostral anterior cingulate cortex (rACC), hippocampal formation, posterior cingulate and retrosplenial cortex, the precuneus, and parietal regions important for mental imagery (see Figure 3.1; Gusnard & Raichle 2001; Vogt & Laureys, 2005; Cavanna & Trimble, 2006; Buckner et al., 2008; Smith et al., 2009). Two interacting but distinct subsystems are encompassed within the AMN: (i) a mesial temporal lobe circuit recruited during autobiographical recollection, and (ii) a dmPFC/rACC circuit most strongly activated when people think about their present mental states (Buckner et al., 2008; Andrews-Hanna et al., 2010). These two subsystems converge on the mesial core of the midline of the brain, which is activated when people make emotionally-valenced, self-focused decisions (Andrews-Hanna et al., 2010). Given the tonic nature of depressive
symptoms, the resting-state AMN is commonly used to explore the pathophysiological mechanisms underlying depression (Zeng et al., 2012).

3.2.1 Depression’s hyperactive AMN

Compared to healthy controls, however, individuals with unipolar depression show significantly increased activation of the AMN during self-referential cogitation, emotional processing, and at rest (see Table 3.1, or Appendix Table B for full details; Lemogne et al., 2009; Johnson et al., 2009; Sheline et al., 2009; Grimm et al., 2011; Hamilton, Chen et al., 2011). Reduced deactivation is evident in the same regions when depressed patients attempt to perform externally-focused tasks (Grimm et al., 2009; Johnson et al., 2009; Nugent et al., 2011; Muller et al., 2013), giving the impression that the self-focused AMN is pathologically hyperactive in depression (see Figure 3.2). AMN hyperactivity correlates with the severity of depression and feelings of hopelessness (Grimm et al., 2009). This neuroimaging pattern is likely to be a marker of the morbid state of being depressed, given that a meta-analysis of emotional activation studies suggests that antidepressant pharmacotherapy restores normal deactivation of the AMN in patients being treated for depression (Delaveau et al., 2011). This was true for selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants such as bupropion (Delaveau et al., 2011), revealing that there may be multiple neurochemical modulators of AMN regions involved in both tonic resting state activity and emotional processing.

Connectivity within the AMN is also abnormal in depression. There is growing evidence of intensified intra-network connectivity between PFC and ACC nodes of the AMN, as well as between the posterior cingulate, hippocampus, retrosplenial cortex, and lateral parietal cortex (Zeng et al., 2012; Sambataro et al., 2013). Hyperconnectivity within the AMN is also evident in unmedicated patients with Dysthymic Disorder (Posner et al., 2013). To better map this hyperconnectivity, a graph theory study using resting-state fMRI (30 patients with unipolar depression; 63 controls) revealed that the AMN is organised differently in depressed individuals, with key nodes overly prominent and densely connected (Zhang et al., 2011). This feature, known as network centrality, is a metric of network connectedness (Bullmore & Sporns, 2012) that in Zhang et al.’s study was correlated with disease severity and duration. Hyperconnectivity of the AMN in dysthymic patients has been shown to normalise after treatment with SNRIs (Posner et
al., 2013), suggesting that AMN hyperconnectivity supports AMN hyperactivity as a causal mechanism of depressive disorder.

**A. Healthy controls**

![Brain diagram](image1)

<table>
<thead>
<tr>
<th>High activation = CCN</th>
<th>Suppressed activation = AN</th>
<th>Deactivation = AMN</th>
</tr>
</thead>
</table>

**B. Depressed Individuals**

![Brain diagram](image2)

<table>
<thead>
<tr>
<th>Hyperactivation = AMN</th>
<th>Activation = AN</th>
<th>Deactivation = CCN</th>
</tr>
</thead>
</table>

**Figure 3.2.** Engagement of the cognitive control network during a nonself focused task in healthy controls (A) and people with depression (B). (A): In healthy controls, activation of the CCN (red) downregulates the AN (green) and is anticorrelated with the AMN (blue). This allows for efficient completion of externally-focused tasks. (B): In people with depression, the introspective AMN is pathologically engaged (red), suppressing the activation of the CCN (blue) and leading to uninhibited activation of the AN (orange). In the context of maladaptive core beliefs about the self and the world, this gives rise to symptoms of depression such as rumination, dysphoria, poor concentration, diminished work performance, and self critical information processing. ACC = anterior cingulate cortex; AMN = autobiographic memory network; AN = affective network; CCN = cognitive control network; dACC = dorsal anterior cingulate cortex; dLFC = dorsolateral PFC; omPFC = orbitomesial prefrontal cortex; rACC = rostral anterior cingulate cortex.

Clinically, over-activity and hyperconnectivity of the AMN has been associated with a characteristic feature of depression: failure to down-regulate introspective
thinking. For instance, in a resting state fMRI study of 17 patients with unipolar depression (cf. 17 controls), individuals with depression showed increasing levels of AMN activity was associated with increasing levels of maladaptive, depressive rumination (Hamilton, Furman et al., 2011). In another study, patients with depression (n=15) were less likely to show a healthy attribution style (i.e., internal attribution of positive life events, and external attribution of negative events) than controls (n=15) out of scanner (Seidel et al., 2012). Forcing patients to adopt the more adaptive attributional style in-scanner –thereby producing a self-related response conflict- resulted in relative hyperactivation of AMN nodes such as the temporal pole and dmPFC. Such studies provide potential neurobiological substrates in the AMN for features of depression such as increased self-focus, brooding, inner conflict, less self-serving attribution styles, and rumination (Grimm et al., 2011; Hamilton, Chen et al., 2011; Marchand et al., 2012; Seidel et al., 2012).

Altered AMN functioning may also undermine the formation of a healthy identity in people with depression. Task-related fMRI revealed differential activity in the hippocampal and prefrontal nodes of the AMN in 12 unmedicated people with unipolar depression relative to 14 controls, which were related to deficits in the formation of emotionally meaningful autobiographical memories (Young et al, 2013). Impoverished episodic memory is a robust behavioural vulnerability factor for developing depression and its recurrence (Gibbs & Rude, 2004; Naylor & Clare, 2008), and altered AMN activation is evident during autobiographical memory processing in patients with both first-episode and remitted depressive disorder (van Eijndhoven et al., 2011). Consistent with psychodynamic and Beckian cognitive models of depression, the hypothesised function of this diminished specificity for past events is to blunt the emotional experience of the memory, or to passively avoid it altogether (Raes et al., 2003).

Combined, findings to date consistently suggest that the AMN of people with depression is over-active and shows altered internal connectivity. These features have been associated with disordered thinking characteristic of unipolar depression and are seemingly reversible with antidepressant pharmacotherapy.
Table 3.1 Summary of key functional neuroimaging studies finding altered activation in the Autobiographic Memory Network (AMN) in adults with depression relative to healthy controls

<table>
<thead>
<tr>
<th>Authors</th>
<th>Key finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beauregard et al (1998)</td>
<td>Transient sadness triggers AMN hyperactivation</td>
</tr>
<tr>
<td>de Kwaasteniet et al (2013)</td>
<td>Functional connectivity within AMN intensified, related to (i) decreased structural integrity in the uncinate and (ii) more severe depressive symptoms</td>
</tr>
<tr>
<td>Delaveau et al (2011)</td>
<td>Clinical improvement following psychopharmacotherapy associated with decreased hyperactivation in the AMN</td>
</tr>
<tr>
<td>Desseilles et al (2009)</td>
<td>Hyperactivation in AMN, modulated by attentional load</td>
</tr>
<tr>
<td>Epstein et al (2011)</td>
<td>AMN not segregated from networks important for emotional processing</td>
</tr>
<tr>
<td>Fang et al (2012)</td>
<td>86.4% of patients correctly classified as depressed based on hyperconnectivity of AMN</td>
</tr>
<tr>
<td>Grimm et al (2009)</td>
<td>Decreased task-related deactivation in AMN correlated with symptom severity and feelings of hopelessness</td>
</tr>
<tr>
<td>Grimm et al (2011)</td>
<td>Decreased deactivation in AMN during self-related emotional judgements</td>
</tr>
<tr>
<td>Liu et al (2012)</td>
<td>Reduced connectivity between the AMN and cerebellum in patients</td>
</tr>
<tr>
<td>Ma et al (2013)</td>
<td>90.6% of patients correctly classified as depressed based on altered connectivity between AMN-cerebellum</td>
</tr>
<tr>
<td>Mayberg et al (1997)</td>
<td>Patients who respond well to psychopharmacotherapy show AMN hypermetabolism</td>
</tr>
<tr>
<td>Muller et al (2013)</td>
<td>Failure to deactivate AMN in response to emotional stimuli</td>
</tr>
<tr>
<td>Peng et al (2012)</td>
<td>Increased connectivity within the AMN in medication-naïve, first-episode patients</td>
</tr>
<tr>
<td>Ritchey et al (2011)</td>
<td>Prior to a course of Cognitive Behavioural Therapy (CBT), hyperactivation in left AMN in response to negative stimuli. CBT-related symptom improvement linked to a reversal of this valence effect in the AMN</td>
</tr>
<tr>
<td>Seidel et al (2012)</td>
<td>Hyperactivation of AMN during self-serving attributions and weaker connectivity between AMN and regions important for emotion regulation during same task</td>
</tr>
<tr>
<td>Sheline et al (2010)</td>
<td>Hyperconnectivity between AMN and networks important for cognitive control and emotion regulation in patients</td>
</tr>
<tr>
<td>van Eijndhoven et al (2011)</td>
<td>Relative to patients in remission, patients with an active first episode of depression showed hyperactivation in the left AMN during episodic memory formation</td>
</tr>
<tr>
<td>Wang et al (2012)</td>
<td>Decreased low-frequency oscillations (declining spontaneous activity) in the AMN of patients</td>
</tr>
<tr>
<td>Zeng et al (2012)</td>
<td>100% of all patients correctly classified as depressed based on high discrimination power of AMN connectivity</td>
</tr>
<tr>
<td>Zhang et al (2011)</td>
<td>Higher randomisation in AMN, including increased node centrality correlated with disease duration and severity</td>
</tr>
</tbody>
</table>
3.3 The cognitive control network

The CCN recruits a bilateral circuit of midline frontocingulate structures, including the dorsolateral PFC (dlPFC) and dorsal ACC (dACC), as well as auxiliary regions in the mesial temporal lobe and intraparietal sulcus (see Figure 3.3; Smith et al., 2009; Sheline et al., 2010; Pizzagalli, 2011). The CCN is also known as the ‘task-positive’ network, due to its activation during externally-focused and goal-directed behaviours (Fox et al., 2005). It supports working memory, selective attention to relevant tasks, flexible switching between cognitive tasks, and sustained attention (Corbetta & Shulman, 2002; Badre, 2008; Gläscher et al., 2012).

3.3.1 Depression’s lacklustre CCN

The functional neuroimaging literature in depression reveals that people with unipolar depression typically exhibit abnormally decreased task-related activity throughout the CCN (see Figure 3.2 and Table 3.2, or else Appendix Table B for full details; Elliott et al., 1997; Davidson et al., 2002; Kaiser et al., 2003; Okada et al., 2003; Seigle et al 2007; Walsh et al., 2007; Fitzgerald, Laird et al., 2008a), with diminished activation in the prefrontal and cingulate nodes related to poorer task performance (Okada et al., 2003; Thomas & Elliot, 2009). Moreover, individuals with depression need heightened CCN activation to achieve a similar level of cognitive performance to healthy controls (Harvey et al., 2005; Wagner et al., 2006; Matsuo et al., 2007; Fitzgerald, Srithiran et al., 2008b; Kanske et al., 2012), the amplification especially evident in depressed patients with a co-morbid cognitive impairment (Bench et al., 1992). To date, connectivity of the CCN in depression remains equivocal, with some studies reporting within-network CCN hyperconnectivity (e.g., Vasic et al, 2009) and others reporting CCN hypoconnectivity (e.g., Veer et al., 2010).
Numerous cognitive features of unipolar depression are associated with reduced CCN activation, including higher-order attentional impairments, reduced inhibition of irrelevant stimuli, insufficiency in generating novel strategies, poor planning, and working memory deficits (Dolan et al., 1993; Fitzgerald, Laird et al., 2008a; Nusslock et al., 2011). These features can be extrapolated to account for clinical features of depression such as indecisiveness, impulsive thinking, poor concentration, and feelings of guilt and worthlessness (Beck, 2008). For instance, Foland-Ross et al (2013) demonstrated with fMRI that relative to healthy controls (n=15), patients with unipolar depression (n=14) show anomalous activation of the CCN during a task requiring them to expel negative material from their working memory, providing a putative neural basis for the cognitive distortions typical of depression such as selective abstraction, as well as for negative automatic thoughts and rumination.

Notably, PET and fMRI studies show that underactivation of the CCN can normalise after psychological or pharmacological treatment (Brody et al., 2001), including treatment with SSRIIs (Mayberg et al., 2000; Walsh et al., 2007; Fitzgerald, Laird et al., 2008a). When this normalisation occurs, it is associated with clinical improvement of symptoms (Mayberg et al., 2000). For instance, a FDG-PET study of 39 patients with unipolar depression showed that increasing dIPFC metabolism after treatment with an SSRI or interpersonal psychotherapy was associated with remission of cognitive symptoms such as guilt, suicidality, depersonalisation, paranoia, and obsessive-compulsive behaviours (Brody et al., 2001). However, significantly attenuated activation in the dIPFC and dACC may not always normalise with the remission of depressive symptoms (Bermpohl et al., 2009; Schöning et al., 2009), consistent with the view that prefrontal CCN hypoactivation can be a trait-like marker of vulnerability to depression (Baxter et al. 1989; Bench et al., 1992; Mayberg et al., 1999; Kimbrell et al. 2002).
Table 3.2 Summary of key functional neuroimaging studies finding altered activation in the Cognitive Control Network (CCN) in adults with depression relative to healthy controls

<table>
<thead>
<tr>
<th>Authors</th>
<th>Key finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bench et al (1992)</td>
<td>Decreased resting-state activation in CCN; pattern exacerbated in patients with co-morbid cognitive impairment</td>
</tr>
<tr>
<td>Davey et al (2012)</td>
<td>Reduced task-related functional connectivity within the CCN</td>
</tr>
<tr>
<td>Delaveau et al (2011)</td>
<td>Clinical improvement after psychopharmacotherapy linked to increased CCN activity during emotion tasks</td>
</tr>
<tr>
<td>Foland-Ross et al (2013)</td>
<td>Improved activation in CCN when negative valence removed from working memory load</td>
</tr>
<tr>
<td>Harvey et al (2005)</td>
<td>No behavioural difference in working memory performances, but greater activation of the CCN in patients</td>
</tr>
<tr>
<td>Liu et al (2012)</td>
<td>Reduced functional connectivity between CCN-cerebellum correlated with higher depression scores</td>
</tr>
<tr>
<td>Matsuo et al (2007)</td>
<td>No behavioural difference in working memory performances, but greater activation of the CCN in patients</td>
</tr>
<tr>
<td>Matthews et al (2008)</td>
<td>Reduced co-activation of the CCN during emotion regulation; reduced functional connectivity between CCN-amygada related to greater depressive symptom severity</td>
</tr>
<tr>
<td>Naismith et al (2010)</td>
<td>Reduced CCN activation during implicit learning and greater CCN node activation during motor learning</td>
</tr>
<tr>
<td>Ritchey et al (2011)</td>
<td>Prior to Cognitive Behavioural Therapy (CBT), reduced CCN activity but enhanced reactivity to negative stimuli; CBT-related clinical improvement linked to increased CCN activation compared to baseline</td>
</tr>
<tr>
<td>Schlosser et al (2008)</td>
<td>Heightened connectivity in CCN; Enhanced connectivity between anterior cingulate cortex nodes of the Autobiographic Memory Network and CCN and hyperactivation in same regions during a cognitive inhibition task</td>
</tr>
<tr>
<td>Schoning et al (2009)</td>
<td>Heightened activation in an isolated node of CCN during working memory task in patients with remitted depression; no other differences in performance or activation pattern between remitted depression patients and controls</td>
</tr>
<tr>
<td>Sheline et al (2010)</td>
<td>Hyperconnectivity between CCN and networks important for autobiographic memory and emotion regulation</td>
</tr>
<tr>
<td>van Eijndhoven et al (2011)</td>
<td>Relative to patients in remission, patients with an active first episode of depression showed hyperactivation in the left CCN during episodic memory formation</td>
</tr>
<tr>
<td>Veer et al (2010)</td>
<td>Reduced resting-state connectivity in the CCN</td>
</tr>
<tr>
<td>Walsh et al (2007)</td>
<td>Greater response to increasing working memory load in the CCN; greater psychopharmacotherapeutic response predicted by lower response to increasing working memory load in the CCN at baseline</td>
</tr>
</tbody>
</table>
Research to date thus makes it clear that depression is associated with a characteristic pattern of under-activation throughout the CCN, which undermines the patient’s ability to perform a wide range of goal-directed tasks. Moreover, it is associated with biased cognitive processing central to depressive disorder. Specifically, deficits in cognitive flexibility occurring in the context of depressive core beliefs about the self and the world lead to secondary systematic biases in information processing, namely difficulties disengaging from negative stimuli, increased self-focus, rumination, and increased elaboration of negative material.

3.4 AMN and CCN dysregulation in depression: heightened anti-correlation

Functional neuroimaging reveals a dichotomous, anti-correlated relationship between cognition-related networks in the healthy population. In attentionally-demanding tasks, the CCN is activated to marshal the necessary cognitive resources to that task. Activation of the CCN suppresses self-referential processing and leads to deactivation of the AMN, suggesting that in situations requiring top-down direction of cognitive processing, introspection is replaced by increased alertness to external stimuli. This is consistent with the popular notion that we can ‘lose ourselves’ in a task at hand. Conversely, an activated AMN inhibits the CCN and depletes cognitive resources (Smith et al., 2009; Pizzagalli, 2011), suggesting that self-focused brooding and introspection reduces our executive cognitive resources. In a refinement of this model, Spreng et al (2010) added a frontoparietal subnetwork that links AMN activity to prefrontal executive functions like planning. This subnetwork couples the AMN and CCN in a flexible manner to facilitate self-related, external tasks such as planning one’s upcoming social schedule. Using resting-state fMRI in conjunction with PET, Dang et al (2012) disclosed that endogenous dopamine is necessary for the efficient activation of this frontoparietal subnetwork.

The anti-correlated relationship between the AMN and CCN appears to be part of the intrinsic organisation of the human brain, with spontaneous anti-correlation observable even in the absence of any overt task or behaviour (Fox et al., 2005). The neurochemical modulators of AMN versus CCN engagement include serotonin (Hahn et al., 2012) and dopamine (Nagano-Saito et al., 2009; Tomasi et al., 2009), key targets of antidepressant medication (Stahl, 2008).
3.4.1 Altered dynamics between neurocognitive networks in depression

In unipolar depression, the anti-correlated relationship between the CCN and AMN appears to become pathologically imbalanced. Using fMRI with seeds in the prefrontal cortex, Korgaonkar et al (2013) showed that when performing working memory and emotion processing tasks, medication-naïve patients with depression (n=30) exhibited simultaneously decreased activation in the CCN and increased activation of the AMN, the opposite pattern to that observable in healthy controls during tasks (n=30). Specifically, the task-dependent ‘biosignature’ of depression involved hypoactivation of the right dlPFC (i.e., CCN) during working memory updating and negative emotion processing, hyperactivation of the dmPFC/rACC (i.e., AMN) during working memory and inhibition of prepotent responses, and hypoactivation of the dmPFC/rACC during processing of positive emotions. That is, individuals with depression were unable to disengage the introspective AMN and successfully recruit the CCN. This model of dysfunctional AMN-CCN dynamics is strongly underscored by the body of research that emerged from our literature search, separately showing AMN overactivation and CCN underactivation in unipolar depression.

This compelling convergence of findings corroborates this neurocognitive account of depression. Functional MRI studies show that in patients with unipolar depressive disorders, AMN activation fails to attenuate when the CCN is engaged (Sheline et al., 2009; Johnson et al., 2009; Hamilton, Furman et al., 2011), which dynamic causal modelling suggests may be related to high connectivity between the AMN and CCN in the anterior cingulate (Schlosser et al., 2008). The imbalance in cognition-related networks in depression is also evident intrinsically i.e., during rest (Marchetti et al., 2012).

It has been hypothesised that impaired ability of people with unipolar depression to deactivate the AMN and successfully engage the CCN impairs working memory and undermines response inhibition, with clinical correlates that include a dysfunctionally self-focused cognitive style and a failure to attenuate introspection when a job needs to be performed (Sheline et al., 2009; Sheline et al., 2010; Marchetti et al., 2012). It has been proposed that the persistence of this pattern during the remission phase of depression may confer ongoing cognitive risk factors for recurrence (Marchetti et al., 2012), such as negative attentional control and recall biases. Beck (2008) suggests that selective focus on the negative aspects of experience results in cognitive distortions such as exaggeration,
personalisation, and overgenerality, and the formation of dysfunctional attitudes regarding personal adequacy and worth that form the basis of depression.

### 3.4.2 The impact of neurocognitive network dysregulation on affective networks

Disturbed dynamics between the AMN and CCN has the secondary effect of destabilising the ‘top-down’, or cognitive regulation of emotion in the Affective Network (AN; Ochsner & Gross, 2005). The anatomy of the AN overlaps in part with nodes of the AMN and CCN, as well as the reward network and hypothalamic-pituitary-adrenal (HPA) axis. Hyperactivity of the HPA-axis is one of the most consistent biological findings in unipolar depression (Nemeroff & Vale, 2005), with clinical correlates consistent with its somatic features (see Section 2.3.2). The AN includes bilateral subgenual and pregenual cingulate, mesial orbitofrontal PFC, and connected regions of the amygdala, entorhinal cortex, hypothalamus, striatum, midbrain, and nucleus accumbens (LeDoux, 2000; Ongür et al., 2003; Milak et al., 2005; Nugent et al., 2011). These cortico-subcortical pathways are interconnected in a way that supports reward processing and visceral monitoring, namely appetite, libido, sleep, diurnal variation, and vigilance, disturbance to which underpins vegetative, dysphoric, and anhedonic symptoms of depression (Deuschle et al., 1997; Milak et al., 2005; Hasler et al., 2008; Sheline et al., 2010; Nugent et al., 2011).

#### 3.4.2.1 Decoupling of the CCN and the Affective Network

Successful control of affect partly depends on an individual’s capacity to modulate negative emotional responses using cognitive strategies (Beck, 2008), and is reliant on the CCN downregulating the AN (see section A of Figure 3.1; Ochsner et al, 2002; Lutz et al, 2014). This is illustrated by an fMRI study of 14 healthy individuals, whereby the volitional control of negative affect evoked by highly arousing and aversive pictures produced enhanced activation in PFC and dACC (i.e., CCN), and attenuation of AN nodes such as the nucleus accumbens and amygdala (Phan et al, 2005). This gives the impression that in the healthy brain, emotional processing is kept in check by the CCN.

In unipolar depression, however, poor engagement of the CCN is associated with dysregulation of the AN. Specifically, decreased CCN activity occurring simultaneously with increased AN activity is linked to negative affect regulation (Fitzgerald, Laird et al.,
2008a) and poor attention-modulated reward processing (Bermpohl et al., 2009; Hamilton et al., 2012; see Buhle et al 2013 for a recent meta-analysis). For example, during an in-scanner emotional processing task, unmedicated patients with current depression (n=15) showed increased task-related co-activation of the AN (amygdala-subgenual ACC) and decoupling of the CCN from the AN (amygdala-dACC), the latter being associated with greater depressive symptom severity (Matthews et al., 2008). This suggests that depressed individuals failed to co-activate a higher-order cognitive control network to downregulate affective processing. This pattern is evident even in nondepressed individuals with a cognitive vulnerability to depression (Zhong et al., 2011). Tao et al (2013) speculate that the decoupling of the CCN from nodes of the AN that they observed in 39 depressed patients (15 first-episode; 24 treatment resistant) reflects reduced control over hateful feelings towards the self. This could account for the self-loathing common to depressed individuals.

The clinical implications of CCN-AN decoupling are further illustrated in a study by Galynker et al (1998), who used SPECT to compare the regional cerebral blood flow (rCBF) of 11 inpatients with unipolar depressive disorder being treated pharmacologically to that of 15 healthy controls. They found that patients had significantly lower rCBF in nodes of the CCN, such as the bilateral dlPFC and cingulate (i.e., hypofrontality), but also observed altered perfusion in nodes of the AN – specifically the cingulate and orbitofrontal PFC. This related to more severe anergia, anhedonia, psychomotor retardation, and avolition, suggesting that failed regulation of the CCN and AN may give rise to negative symptoms of depression characterised by poor reward processing and vegetative disturbance (Pizzagalli et al., 2009). Successful psychological treatment of depressive symptoms (n=12) has been associated with normalised downregulation of the AN during emotionally-valenced cognitive control tasks in an fMRI study (Dichter et al., 2010).

3.4.2.2 Strengthened coupling of the AMN and the Affective Network.

Abnormal AMN function in unipolar depression has also been linked to altered AN function. Functional connectivity techniques show that in people with depression, the AMN has stronger coupling with nodes of the AN such as the subgenual cingulate, with enhanced connectivity correlating positively with the length of the current depressive
episode (Grecius et al., 2007) and its severity (de Kwaasteniet et al., 2013). The refractoriness of depressive symptoms may therefore be attributable to overrecruitment of emotion-processing regions into the AMN (Broyd et al., 2009). In support of this interpretation, Zeng et al (2012) analysed whole-brain resting-state fMRI using multivariate pattern analysis to correctly classify 24 unmedicated patients with depression from 29 demographically-matched healthy controls (P < .0001). They found that the most discriminating feature was increased connectivity in nodes of the AMN (parahippocampal gyrus and hippocampus, ACC, posterior cingulate, mesial PFC) with those of the AN (amygdala, basal ganglia, insula, superior temporal gyrus). Although somewhat speculative, this might be conceptualised as the AN ‘hijacking’ cognitive networks and disrupting their function (see also Epstein et al., 2011; Fang et al., 2012; Peng et al., 2012). Increased AN connectivity in unipolar depression can normalise with SSRI treatment (Mayberg et al., 2000; Fu et al., 2004; Anand et al., 2005; however see Kanske et al., 2012 for a null result), suggesting that abnormal downregulation of the AN might form a state-dependent pathogenic mechanism of unipolar depression.

In sum, disordered emotional processing in depression implicates neurocognitive mechanisms. Collectively, studies show (i) increased activity in the AN in response to poor activation of the CCN as well as (ii) increased connectivity between the AN and AMN. It has been speculated that the diminished cognitive control of emotion evident in vivo may lead to reduced cognitive downregulation of negative affective responses and unchecked negative emotion when dealing with stressors (Mayberg, 2003), as well as aberrant reward processing. The latter may underpin the distorted emotional regulation characteristic of unipolar depression, such as dysphoria and anhedonia (Phillips et al., 2003; Pizzagalli et al., 2005; Fales et al., 2008; Hasler et al., 2008; Bermpohl et al., 2009; Epstein et al., 2011; Hamilton, Chen et al., 2011; Hamilton et al., 2012). This substantive dysfunction of the mood regulating circuitry is at least in part modifiable with successful pharmacological or psychological therapy (Dichter et al., 2010; Delaveau et al., 2011), and may provide biomarkers of depression with which to monitor the progress of treatment.
3.5 The neurocognitive network model of depression

The neuroimaging studies reviewed in this chapter suggest that many of the characteristic features of unipolar depressive disorders—anhedonia, emotional dysregulation, rumination, intrusive negative thoughts, affectively biased cognitive processing, and reduced goal-directed behaviour—can be attributed to skewed dynamics between two key cognition-related networks. This model of depression (see Figure 3.1) was developed as a theoretical framework for the current thesis and holds that the network responsible for self-focused introspection is pathologically dominant over the network responsible for interacting with the external world. Downstream effects of this imbalance include reduced regulation of affect. The general structure of this neurocognitive model broadly corresponds with those previously proposed by Northoff et al (2011), Whitfield-Gabrieli and Ford (2012), and Marchetti et al (2012). It suggests that the atypical dynamics between neurocognitive and affective networks accounts for the heterogeneous cooccurrence of many depressive features, whereby its two cardinal affective symptoms and nine associated somatic and cognitive features give rise to nearly 200 idiosyncratic configurations of presenting symptoms. Moreover, initial evidence suggests that these aberrant dynamics may be intrinsic to the organisation of the brain, are evident at the first episode of illness, and could represent a vulnerability factor for refractory or recurrent depressive illness.

This model of depression has the advantage of being able to map the abnormal function of complex brain systems to the clinical reality: a patient consumed by a maladaptive internal monologue, too lethargic from poor sleep and nutrition and too self-focused to efficiently marshal their cognitive resources and appropriately engage in the world. Understanding these neurobiological-clinical links opens the door to greater precision in psychiatric medicine. It does this by broadening diagnostic parameters in depression research, providing fresh insights for the development of new and more targeted psychological, physiological, and pharmacological treatments, as well as helping the clinician better tailor clinical management to the individual patient.

3.6. Broadening the psychiatric concept of depression

Acknowledging the role that cognitive networks play in shaping the behavioural manifestations of depression could have far-reaching implications for the diagnosis and
study of this disorder. The current symptom-based nosology of unipolar depression used clinically and in research was based on expert consensus and popularised by the American Psychiatric Association and World Health Organization (see Chapter 2). These nosologies have been criticised for basing the diagnosis of depression on the patient’s endorsement of an arbitrary number of symptoms that do not necessarily describe a homogenous disorder, purportedly contributing to difficulties in finding genes and biomarkers for depression. As in other neurological and psychiatric disorders, it is seen as increasingly likely that diagnoses of depression reflect a common final pathway of various pathophysiological processes (Charney et al., 2002).

Descriptive taxonomies, moreover, are seen by many to ignore psychological, social, and biological factors associated with different aetiologies, presentations, and treatment responses, resulting in arbitrary groupings of heterogeneous individuals under the umbrella term of ‘depression’ (Luyton et al., 2006). Against this background, there are calls to broaden our classification of depression to include its neurobiological and psychosocial correlates.

While symptom-based nosologies of unipolar depression implicate neural systems involved in memory, attention, emotion, autonomic function, and reward processing, they do not yet integrate empirical findings from clinical neuroscience (Insel et al., 2010). One approach to unifying the clinical phenomenology of mood disturbance with its neurocognitive correlates involves increasing the level of neurobiological detail in classification criteria (Insel et al., 2010), aligning the signs and symptoms of depression to their environmental and developmental contexts, neuroimaging patterns, and genetic and molecular substrates (see Table 3.3 for an example). The following section shows that by classifying depressive disease according to a broader structure that incorporates direct measures of network-level brain function, the revised psychiatric construct of depression may be of use to researchers and clinicians alike.
Table 3.3 Example of a nosology of depression inclusive of cognitive networks

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptomatology</th>
<th>Neurocognitive Networks Involved</th>
<th>Molecular Genetic Substrate</th>
<th>Psychosocial Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Symptoms</td>
<td>Overgeneral episodic memory retrieval; Attention and concentration difficulties; Indecisiveness; Rumination; Feelings of worthlessness and/or inappropriate guilt; Egocentric theory of mind</td>
<td>Increasing dominance of the AMN over the CCN</td>
<td>Short form serotonin transporter gene (5-HTTLPR short allele variant; Hayden et al., 2008)</td>
<td>e.g., dysfunctional family dynamics, health problems, work stress, relationship breakdown, social isolation, etc.</td>
</tr>
</tbody>
</table>

3.6.1 The neurocognitive network model of depression: Implications for future research and clinical practice

3.6.1.1. Broadening research parameters

A neurocognitive network model of depression may facilitate novel investigation into the pathogenesis of a broader range of depressive disorders than is allowed by research guided by descriptive taxonomies, opening up research into subclinical forms of depression that may share neurobiological similarities to “major” depression but are excluded from conventional research protocols due to failure to meet symptom-based cut-off scores. For instance, mapping the clinical and genetic differences between people with and without the neurocognitive signature of depression revealed by this review – regardless of their “official” DSM-V/ICD-10 label– may lead to important insights into the mechanisms that underpin vulnerability to depressive symptomatology more generally, rather than only severe mood disturbance. This type of research has compelling clinical meaning, as subclinical or atypical forms of depression are associated with significant psychosocial morbidity and illness chronicity (Kessler et al., 1997), and are common in neurological disease.
3.6.1.2 Advancing development of new treatments

Neurocognitive network models of depressive illness may provide a framework for advancing translational research. Despite growing insight into the neurobiological bases of depression, there has been minimal progress in how the illness is treated (Chubb, 2012). Delineating the cognition-related network processes associated with depression may inform the development of novel psychopharmacological and psychotherapeutic treatments (Mayberg, 1997), as well as neurophysiological devices such as transcortical motor stimulation (TMS) or deep brain stimulation. For instance, dampening of CCN activation has been shown to dysregulate the mesostriatal dopamine system (Hamilton, Chen et al., 2011), potentially providing insights into region-specific neurotransmitter systems that may be targeted in the development of future pharmacotherapies.

3.6.2 Facilitating patient-tailored clinical management: toward precision medicine in psychiatry

Network models of depression may improve patient outcomes in the future by facilitating a management framework in which an individual’s neurobiological profile informs clinician choices. A recurring criticism of the diagnosis of depression reified by DSM-V and ICD-10 is that idiosyncratic symptom profiles are too heterogeneous to be predictive of treatment responses (Insel et al., 2010; Luyten et al., 2006; Mayberg, 2003; Nemeroff et al., 2003). Using neuroimaging with cognitive paradigms, future research could try to identify functional profiles that are regionalised in the brain and can (i) predict outcome with different treatments or (ii) be used as markers of treatment response. Although speculative, such an approach may yield brain biomarkers that can both identify which patients are likely to respond to a given intervention, and predict which patients are vulnerable to relapse during the maintenance stage of treatment. Treating clinicians would then be able to order auxiliary diagnostic tests such as fMRI or neuropsychological assessment to evaluate the presence or absence of neurocognitive profiles that are associated with specific clinical courses and/or treatment responses. This would allow the clinician to tailor an individualised approach to psychotherapy or pharmacotherapy, and facilitate the segregation of genes relevant to depressive susceptibility. This is analogous to what is done routinely in most other areas of medicine today (Insel et al., 2010).
Summary: The neurocognitive model of unipolar depression, potential links to depression in epilepsy

Many of the affective, somatic, and cognitive features of unipolar depression can be attributed to a systems-level pathological imbalance between cognition-related networks. This neurocognitive network model has the potential to extend the current formulation of mental illness as a vaguely-defined “disorder of brain circuits” (Insel et al., 2010) and provide a more rigorous model for furthering neuroscientific research into phenotypes of mood disorder. In particular, thinking about depression within a neurocognitive network framework may facilitate the translation of group-level neuroscientific research into meaningful individual-level patient outcomes. It also facilitates novel thinking into the neurobiological basis of depressive symptoms in populations such as epilepsy, a disease characterised by disruption to the functioning of brain networks and accompanied by high rates of mood disorder and cognitive impairment.
Chapter 4. Depression in Epilepsy

4.1 Focal epilepsy: a model of network disorder

4.1.1 Seizure classification

Seizures and seizure disorders are grouped according to a taxonomy crafted by the International League Against Epilepsy (ILAE). Since its formation, the ILAE has sought to compile a list of entities that are recognised as distinct forms of seizure disorders. More recently, it has attempted to flexibly organise this list according to “useful, natural classes” that reflect current understandings of their neurobiology, clinical features, and prognostic implications, using an evidence-based, descriptive methodology (Berg et al., 2010).

The most recent ILAE Commission on Classification and Terminology felt that it was of some pragmatic utility to maintain the terms “focal” and “generalised” in describing both seizures and epilepsies (see Table 4.1), although it was generally acknowledged that these terms likely did not represent a true dichotomy. Generalised seizures were defined as occurring in, and rapidly engaging, bilaterally distributed networks. Focal seizures, in contrast, were defined as occurring within networks limited to one hemisphere of the brain and either discretely localised or more widely distributed (Berg et al., 2010).

<table>
<thead>
<tr>
<th>Table 4.1 Classification of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized seizures</strong></td>
</tr>
<tr>
<td>Tonic–clonic (in any combination)</td>
</tr>
<tr>
<td>Absence</td>
</tr>
<tr>
<td>Typical</td>
</tr>
<tr>
<td>Atypical</td>
</tr>
<tr>
<td>Absence with special features</td>
</tr>
<tr>
<td>Myoclonic absence</td>
</tr>
<tr>
<td>Eyelid myoclonia</td>
</tr>
<tr>
<td>Myoclonic</td>
</tr>
<tr>
<td>Myoclonic</td>
</tr>
<tr>
<td>Myoclonic atonic</td>
</tr>
<tr>
<td>Myoclonic tonic</td>
</tr>
<tr>
<td>Clonic</td>
</tr>
<tr>
<td>Tonic</td>
</tr>
<tr>
<td>Atonic</td>
</tr>
<tr>
<td><strong>Focal seizures</strong></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
</tr>
<tr>
<td>Epileptic spasms</td>
</tr>
</tbody>
</table>


4.1.1.1 Defining focal epilepsy

By their nature, focal seizures are a paroxysmal event. Many people who experience recurrent focal seizures, however, will be diagnosed as having a more chronic focal epilepsy syndrome. Focal epilepsies are disorders characterised by specific constellations of peri-ictal and interictal signs and symptoms, often with therapeutic or prognostic
implications (Loiseau & Duché; 1990). Many of these focal syndromes are classified in part by age of onset and semiology e.g., childhood absence epilepsy, or juvenile myoclonic epilepsy. Focal seizures have also classified as syndromes according to their putative lobar focus e.g., temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE).

In somewhat of a paradigm shift, the 2010 ILAE Commission on Classification and Terminology proposed a nosological approach to focal epilepsy syndrome classification that is based on current genomic technology, neuroimaging and neurophysiologic capabilities, and combined (e.g., coregistration) techniques (Berg et al., 2010). They asserted that not enough evidence exists to classify focal seizures according to naturally occurring classes, such as underlying causes, age at onset, or associated seizure types. Critics disagree, pointing out that ‘natural’ features of epilepsy such as genes, semiology, and EEG findings can distinguish –for example- focal seizures arising in the frontal lobes with motor automatisms (Devinski & Najjar, 2011). The Commission does not provide any examples of focal epilepsy syndromes, and instead recommend that focal seizures be described according to their manifestations (see Table 4.2). Some argue that this approach sacrifices crisp clarity needed for easy communication (Devinski & Najjar, 2011).

<table>
<thead>
<tr>
<th>Table 4.2 Descriptors of focal seizures according to the degree of impairment during a seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Without impairment of consciousness or awareness</td>
</tr>
<tr>
<td>♦ With observable motor or autonomic components. This roughly corresponds to the concept of “simple partial seizure”.</td>
</tr>
<tr>
<td>♦ ”Focal motor” and “autonomic” are terms that may adequately convey this concept depending on the seizure manifestation)</td>
</tr>
<tr>
<td>♦ Involving subjective sensory or psychic phenomena only</td>
</tr>
<tr>
<td>♦ With impairment of consciousness or awareness. This roughly corresponds to the concept of complex partial seizure. “Dyscognitive” is a term that has been proposed for this concept</td>
</tr>
<tr>
<td>♦ Evolving to a bilateral, convulsive seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term “secondarily generalised seizure”</td>
</tr>
</tbody>
</table>

*Reproduced from Berg et al (2010)*
4.1.2 Epidemiology

Latest estimates suggest that around 70 million people worldwide have epilepsy. In developed countries, approximately 6 per 1000 people will develop epilepsy during their lifetime, with 45 people per 100 000 developing new-onset epilepsy annually. In developing countries this figure is often double, due to the higher risk of experiencing conditions that can lead to permanent brain damage such as obstetric complications and cerebral infection (Brodie et al., 2012). Males and females are equally vulnerable to epilepsy (Olafsson et al., 2005).

The incidence of epilepsy varies with age, with a bimodal distribution peaking in childhood and old age (see Figure 4.1). Approximately 40% of diagnoses comprise focal epilepsy syndromes (Olafsson et al., 2005). The most common form of focal epilepsy is the syndrome widely known as TLE (Téllez-Zenteno & Hernández-Ronquillo, 2012).

![Figure 4.1. Incidence of all unprovoked seizures by age in Iceland from 1995 to 1999 (Source: Olafsson et al., 2005).](image)

4.1.3 Ätiology of focal epilepsy

4.1.3.1 Electroclinical focal epilepsy syndromes

An electroclinical syndrome is a cluster of clinical and EEG features, signs, and symptoms that together define a distinctive, clinically recognisable disorder (Scheffer et al., 2008); moreover, they permit a specific diagnosis and implicate treatment, management, and prognosis. Electroclinical syndromes are often genetic in origin and tend to have a strong relationship to aberrant development of the brain, with onset commonly in infancy or childhood (Parisi et al., 2011). Examples include Dravet Syndrome, Landau-Kleffner Syndrome, and Lennox Gastaut Syndrome (Parisi et al., 2011).
4.1.3.2 Structural-metabolic causes of focal epilepsy

The development of some focal epilepsies is associated with a distinct structural or metabolic condition. Structural lesions include acquired injuries such as stroke, trauma, and infection. They may also be of genetic origin e.g., tuberous sclerosis, malformations of cortical development. The recent ILAE Commission on Classification and Terminology makes clear, however, that there is likely to be a separate disorder mediating the genetic defect and the epilepsy (Berg et al., 2010). A recent structural imaging series by Nguyen et al (2013) suggests that of 806 consecutive patients with focal epilepsy who underwent MRI at their epilepsy centre, 65% had a structural epileptogenic lesion. Lesions included gliosis due to an acquired insult (52%, including 17% with hippocampal atrophy/sclerosis), tumours (29%), vascular malformations (16%), and malformations of cortical development (10%; see Figure 4.2).

![Figure 4.2](Source: Nguyen et al, 2013)

4.1.3.3 Genetics of focal epilepsy

Around 26% of focal epilepsy patients present to tertiary epilepsy centres with negative neuroimaging findings and until lately their ætiology was unclear (Téllez-Zenteno et al., 2010). A gene mutation, however, known as DEPDC5 was recently linked to around 12% of patients with a familial form of nonlesional focal epilepsy (Dibbens et al., 2013). While genes had previously been attributed to generalised forms of epilepsy (e.g., Wallace et
al., 1998), this was the first time that a gene had been linked to a focal epilepsy syndrome. Although the biological role of DEPDC5 and how its mutations lead to seizures remains unclear, this paradigm-shifting discovery has substantially advanced understanding of the pathogenesis of focal epilepsy by implicating a new gene pathway.

4.1.4 Focal epilepsy networks

Central to the latest definitions of generalised and focal seizures is their explicit reconceptualisation as arising out of a disease of brain networks. Network function is conceptualised across three models of interconnection: regular, random, and small-world (see Figure 4.2). Of relevance to epileptology, small world networks are hypothesised to optimise rapid synchronisation, facilitating a balance between local processing and global integration (Meador, 2011). They typically form a functionally and anatomically connected set of bilateral cortical and subcortical brain regions (Spencer, 2002), which rapidly hypersynchronise in a seizure. Simultaneous EEG-fMRI can visualise the epilepsy networks in vivo across the whole brain, documenting changes in brain activity before, during, and after electrical epileptiform discharges (Archer et al., 2003; Flanagan et al., 2009; Carney et al., 2010; Masterton et al., 2010; Dunn et al., 2011; Masterton et al., 2012). Vulnerability to seizure activity in any one part of the network influences activity throughout the rest of the network. In this way, seizures may entrain a large-scale brain network from any given region or node (Spencer, 2002).

The development and organisation of brain networks is modified by epileptic activity. Neurodevelopmental evidence shows delayed age-appropriate increases in white matter networks of children with new-onset epilepsy, which may affect cognitive development through reduced brain connectivity and inefficient transfer of information (Hermann et al., 2010). In adults, recent studies of the mesial TLE connectome before epilepsy surgery suggest that compared with controls (n=18), patients (n=20) show pathological hyperconnectivity within ipsilateral mesial temporal, insular, and frontal structures. Furthermore, patients who did not become seizure-free after surgery showed
lower small-worldness within the ipsilateral temporal lobe i.e., over-integration at the expense of network segregation (Bonilha et al., 2013). This implies that structural network rearrangement is a feature of focal epilepsy, with more extensive network reorganisation associated with poorer clinical outcomes.

4.1.4.1 The relationship between focal epilepsy and neurocognitive networks

The normal organisation of cognitive networks can be disrupted by the paroxysmal excessive neuronal discharges diagnostic of epilepsy (Waites et al., 2006; Wilson et al., 2013). This disorganisation can be imaged using fMRI and related to behavioural patterns of cognitive impairment (Lillywhite et al., 2010; Becker et al., 2013). For instance, TLE has been associated with altered patterns of neural activity within frontoparietal networks supporting attentional processing (Zhang et al., 2009), implying that the disease process can compromise neurocognitive network functioning distal to the primary epileptogenic region. This work has contributed to the contemporary view that seizures and interictal discharges propagate along established cognitive pathways in the brain, and that cognitive dysfunction provides a marker of the underlying epilepsy network (Wilke et al., 2011; Fahoum et al., 2013).

Chapter 3 showed that another disorder of brain function, namely unipolar depression, was associated with altered activation and connectivity in three cognitive networks; moreover, their dysfunction was linked to behavioural features of the disorder. In focal epilepsy, growing evidence indicates that these same three networks are modified by localised epileptic activity. To date, however, there are a limited number of out-of-scanner behavioural studies of this network dysfunction. This thesis seeks to profile the cognitive and behavioural correlates of depression in adult focal epilepsy, using a network framework to explore the impact of seizures on neurocognitive and affective networks.

4.1.4.1.1 Focal epilepsy and the AN. Initial studies suggest that both basal and evoked activity of the AN is altered in people with focal epilepsy. Using a resting-state EEG-fMRI paradigm comparing 23 mesial TLE patients to 23 matched controls, Pittau et al (2012) documented decreased interictal connectivity within the AN bilaterally in people with epilepsy, including the amygdalohippocampal region, pons, and vmPFC. They also noted less interictal connectivity between the AN and the AMN in these patients. This pattern has been replicated during active emotion processing. Broicher et al (2012)
acquired fMRI in 28 mesial TLE patients and 18 healthy controls while participants watched animated fearful faces, finding decreased co-activation within the AN of TLE patients in the same distribution as Pittau et al (2012). Moreover asymmetries in activation were modulated by the side of pathology, meaning that ipsilateral mesial temporal lobe dysfunction can be linked to alterations in remote metencephalic and frontal regions of the AN during emotion processing.

Pathological function of the AN in focal epilepsy has been linked to comorbid symptoms of depression. In a unique study, Chen et al (2012) acquired fMRI in 23 patients with mesial TLE who were treatment-naïve to both antiepileptic and antidepressant medication, compared to 17 matched controls. They found that functional connectivity between the anterior PFC, the limbic system, and the temporal cortex was significantly reduced in patients endorsing depressive symptoms (n=7) relative to both nondepressed patients and healthy controls. Depressed mTLE patients also showed altered resting activity of the left amygdala, right ACC, and bilateral caudate, thalamus, and insula compared to the other two groups, suggesting that depression in focal epilepsy is associated with abnormal activation and intra-connectivity of the AN beyond what is seen in epilepsy alone.

4.1.4.1.2 Focal epilepsy and the AMN. Ictal and interictal epileptiform activity in the AMN is hypothesised to disrupt both its structural and functional integrity. Compared to healthy controls, people with focal epilepsy exhibit decreased activation and functional connectivity bilaterally throughout the AMN, even though only one node of the network is epileptogenic (Laufs et al., 2007; Frings et al., 2009; Liao et al., 2010; Danielson, Guo & Blumenfeld, 2011; Liao et al., 2011; Pittau et al., 2012; Voets et al., 2012; Centeno et al., 2013; Peng et al., 2013; Trotta et al., 2013). Specifically, researchers have observed reduced long-range connections between nodes of the AMN in TLE, taking the form of diminished anteriorly-projecting connections from the precuneus to the vmPFC (Haneef et al., 2012). This occurs in the context of conversely increased local connectivity within the same regions (de Salvo et al., 2013). Alteration in AMN connectivity have been related to the duration of mesial TLE (Liao et al., 2010; Zhang et al., 2010; Morgan et al., 2013), indicating that chronic habitual seizures lead to accumulating damage to the function of this neurocognitive network.
The activation of the AMN is especially impaired during epileptic seizures associated with altered consciousness. Using SPECT, EEG, and fMRI (Blumenfeld et al., 2004; Danielson et al., 2011), altered consciousness during focal seizures has been linked to abnormal engagement and maintenance of the AMN; specifically, to structural and functional connectivity deficits between tracts linking the hippocampus to the PCC (Liao et al., 2010). Danielson et al (2011) contend that brainstem-thalamic arousal systems that modulate AMN activity in consciousness are actively inhibited by epileptiform activity, leading to dyscognitive states and widespread deactivation of frontoparietal cortices. These data suggest that epileptic discharges may deactivate the AMN (Catani et al., 2013).

In support of this interpretation, EEG-fMRI technology shows that deactivation in nodes of the AMN such as the PCC/precuneus and bilateral parietal lobes is evident during interictal epileptiform discharges in patients with focal epilepsy (Kobayashi et al., 2006; Laufs et al., 2007; Fahoum et al., 2012; although see Lui et al., 2008 for a negative result). Deactivation is most marked in patients with TLE (Laufs et al., 2007; Fahoum et al., 2012), thought to be either a result of reduced EEG sensitivity to interictal epileptic discharges in extra-TLE, or differences in the primary pathology. Laufs et al (2007) suggest that transient cognitive impairments and performance deficits associated with TLE may stem from paroxysmal dysfunction of the AMN. This has been directly tested in other clinical populations such as Alzheimer’s disease and autism, where the degree of AMN hypoactivation correlates with the severity of cognitive impairment (see Broyd et al., 2009, for a review).

Together, these studies suggest that the AMN of people with focal epilepsy may be pathologically under-activated and under-engaged, particularly during seizures accompanied by altered conscious awareness. This may lead to cognitive impairments common in focal epilepsies, such as autobiographic memory deficits, impaired theory of mind, and altered self-related processing (Spreng & Grady, 2010), however this has not been directly tested.

4.1.4.1.3 Focal epilepsy and the CCN. Reduced cognitive control is common in focal epilepsy, a finding corroborated by fMRI evidence of CCN dysfunction in these patients. In the first such study, FDG-PET and neuropsychological assessment were used to show
that prefrontal metabolic asymmetry was related to poor performance on measures of
cognitive control in 96 patients with TLE, and was not related to episodic memory,
psychiatric symptoms, or frontal interictal epileptiform discharges (Jokeit et al., 1997).
This seminal study also indicated that epileptic foci distal to the prefrontal hub could
dysregulate the CCN.

More recently, Stretton et al (2012) used a classic ‘n-back’ fMRI cognitive control
paradigm in 38 TLE patients (19 left) and 15 healthy controls, revealing that performance
was impaired in both left and right TLE groups and associated with reduced CCN activity.
Winston et al (2013) extended these findings in 54 TLE patients, relating poor
performances on a cognitive control fMRI task to reduced activation in the parietal nodes
of the bilateral CCN as well as to grey matter loss and diminished white matter integrity
within the frontoparietal CCN. Elsewhere, working memory impairments in focal
epilepsy have been related to reduced functional connectivity within the CCN (Vlooswijk,
Jansen et al., 2011). These studies suggest that the structural substrates of cognitive
control are disrupted by seizures with distal foci, likely accounting for poor CCN
activation as well as attentional and working memory dysfunction in seizure disorders
(Stella & Maciel, 2003).

Preliminary evidence suggests that similar to unipolar depression, epilepsy is
associated with reduced task-related deactivation of the AMN, indexing poor CCN
engagement. Using fMRI, Frings et al (2009) showed that patients with unilateral mesial
TLE (n=14) showed reduced activation of the AMN during a non-self focused task,
relative to healthy controls (n=8). This indirectly suggests that altered temporal dynamics
between the AMN and CCN (seen in unipolar depression) may be observable in epilepsy
patients with co-occurring depression. This is relevant to the current thesis, which
explores the possible contribution of dysfunctional cognitive networks to depression in
epilepsy. To achieve this objective, behavioural data is framed in terms of neurocognitive
network function. For example, reduced autobiographic memory function on
neuropsychological testing will be framed as a behavioural index of dysfunction in the
AMN. This approach will be used to explore whether habitual seizures impact on
autobiographic memory, cognitive control, and mood, implicating altered operation of
their underlying neurobiological systems; namely the AMN, CCN, and AN, respectively.
4.1.5 Cognitive comorbidities in epilepsy

Malfunctioning neurocognitive networks have clear affective and cognitive outworkings in the psychiatric population and the same is true for patients with habitual seizures, even if cognitive findings are not typically presented in a network framework. Cognitive impairment is a common co-morbidity of focal epilepsy. Some degree of impairment can be documented in almost all cases, with regular seizures worsening deficits in the long term (Helmstaedter et al., 2004). Patient ratings suggest that cognitive deficits significantly impact day-to-day functioning and reduce quality of life (Baker et al., 2009).

Research focusing on delineating the clinical factors that contribute to the development of cognitive dysfunction variously emphasise the deleterious rôle of seizure frequency and seizure severity, antiepileptic drug side effects disruption by interictal epileptiform activity, seizure-induced head trauma, and illness chronicity (i.e., young age at onset of epilepsy/long duration of epilepsy; Holmes & Lenck-Santini, 2006; Korman et al., 2013). The finding that cognitive impairments may be evident in untreated patients with newly diagnosed seizures (Taylor et al., 2009; Tosun et al., 2011), however, reveals that the disease can also disrupt the healthy development of cognitive networks in the absence of overt seizures.
Cognitive disturbance in people with focal epilepsy has been broadly linked to abnormal engagement and connectivity of neurocognitive networks. A review of 15 studies investigating the neuroimaging correlates of memory and language in focal epilepsy showed that cognitive dysfunction is often associated with decreased functional connectivity within local and global neurocognitive networks. That is, the altered brain function is not sufficient to maintain normal memory and language processing (Vlooswijk et al., 2010). A few studies Vlooswijk and colleagues reviewed, however, suggest the converse — that functional activation changes were associated with normal cognitive performances— implying that abnormal activation was an efficient compensatory mechanism to preserve cognitive functioning. On balance, these findings suggest that pathologically altered functioning of memory and language in people with epilepsy is accompanied by widespread alterations to neurocognitive networks, which often have adverse effects on patient cognition.

The abnormal brain function that defines focal epilepsy can arise from any region of the cerebrum or cerebellum, and therefore all cognitive domains and networks are vulnerable to epileptiform disturbance (see Helmstaedter et al., 2011). Given that the most common form of focal epilepsy is TLE (Téllez-Zenteno & Hernández-Ronquillo, 2012), most neuropsychological research to date has profiled the cognitive impairments and neurocognitive network function associated with this syndrome; typically in the domain of memory.

4.1.5.1 Memory deficits in focal epilepsy. By the 1950s, neurosurgery had become an acceptable treatment of focal epilepsies. This shift was accompanied by increasing interest in the behavioural sequelae of epilepsy surgery, most famously illustrated by the case of H.M. (1926 – 2008). Patient H.M. underwent a bilateral temporal lobectomy for medically intractable seizures in 1954 at Hartford Hospital in Connecticut (see Figure 4.4). Although a relatively circumscribed excision that spared the parahippocapal structures important for familiarity, the operation produced a dense postoperative anterograde amnesia (Scoville & Milner, 1957), prompting his neuropsychologist, Brenda Milner, to initiate a case series scrupulously detailing the cognitive outcomes of unilateral
temporal lobe excision in patients with bilateral mesial temporal pathology. The resultant study described impaired recent memory function in the context of intact general cognition (Milner & Penfield, 1955), positioning the mesial temporal region as a critical node in the formation and retrieval of recent memories.

Sixty years of subsequent research into memory and epilepsy has ultimately resulted in a more nuanced model of the declarative memory system. Findings that surgical removal of the left hippocampus severely undermined performances on the task of verbal paired-associate learning (Meyer & Yates, 1955) gave rise to a lateralised material-specific model of learning. More recent studies expanded on this concept by showing that neuronal loss and epileptogenic foci in left-lateralised mesial temporal structures commonly leads to impaired learning of arbitrarily-related words (the ‘hard’ pairs of a paired-associate learning task), but spares semantically-rich recall (Rausch & Babb, 1993; Saling et al., 1993). This formed the basis of a model of memory that attributes the task of learning new arbitrarily-related information to the mesial temporal regions of the brain (Saling, 2009); that is, task-specificity, rather than material-specificity. Specifically:

- Verbal memory can be systematically fractionated by left mesial temporal lobe seizure foci;
- The resulting components of memory are localised within different regions of the left temporal lobe; and
- Verbal and non-verbal memory functions are not entirely lateralised

The task-specific model of learning distinguishes mesial (arbitrary forms of learning) from lateral (semantic learning) specialisation within the temporal lobe (Wilson & Engel, 2010), evident in both verbal and nonverbal forms of learning (e.g., Wilson & Saling, 2008). Perirhinal cortices are particularly seen as mediating protosemantic (i.e., free of meaning, arbitrarily-related) associative memory, with impairment of this memory system acting as a proximal neurocognitive marker of mesial temporal epileptogenesis (Saling, 2009).

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9 Dominant neuropsychological model of memory from 1950-2000s, asserting that verbal and non-verbal memory are independent, unitary, and internally homogeneous constructs lateralised to the left and right temporal lobes, respectively.
Memory deficits are not, however, restricted to epilepsy patients with temporal lobe foci. Frontal lobe epilepsies may also be associated with psychometric memory ‘impairments’. Memory deficits observed in frontal lobe injury, however, derive from reduced organisation and strategic control of information during encoding and retrieval (Baldo & Shimamura, 2002). In this way, the PFC forms an auxillary node of the episodic memory network. Higher-order deficits in cognitive control are common in FLE (O’Muircheartaigh & Richardson, 2012) and may secondarily undermine memory retrieval (Matuszewski et al., 2006). Accordingly, when patients with frontal lobe abnormalities are instructed to use strategies to compensate for executive dysfunction, episodic search and recall is significantly improved (Drane et al., 2006; McKinnon et al., 2008; Thaiss & Petrides, 2008). Although these impairments can give the impression of memory deficits in FLE, they do not constitute a primary memory disturbance like in TLE. Together, the well-characterised memory deficits of TLE positions the mesial temporal structures as the key node in arbitrary-associated learning, with nodes in the PFC supporting efficient retrieval in the large-scale AMN.

4.1.5.1.1 Autobiographic memory deficits in epilepsy. It is well-established that autobiographic memory is vulnerable to neurological insult in the temporal lobes (Scoville and Milner, 1957; Vargha-Khadem et al., 1997), including TLE. Individuals with TLE consistently perform more poorly than healthy controls on tasks that require recall of the arbitrary associations between people, time, incidents, and locations that make up a person’s life (Buchanan et al., 2006; Noulhaine et al., 2007; Herfuth et al., 2010). In particular, TLE patients recall fewer details that add richness to autobiographical recollection, such as sensory information and emotion (St Laurent et al., 2009). This provides behavioural evidence for altered AMN function in focal epilepsy, an interpretation validated by fMRI data showing reduced activation throughout the AMN of TLE patients with even mild autobiographic memory impairments (n=11; Addis et al., 2007).

The autobiographic memory deficit of TLE has been attributed to two potential and non-exclusive mechanisms: (1) mesial temporal lobe pathology, which alters the physiology of the declarative memory system and leads to disturbance of the bilateral AMN, and/or (2) recurrent, paroxysmal disturbance of the AMN caused by seizure
activity that interrupts autobiographic memory processing, leading to ‘blanks’ in first-person recollection.

To date, most studies have investigated the first mechanism (e.g., Buchanan et al., 2006; Noulhaine et al., 2007), or confounded it with the second by combining medically-intractable, pre-operative TLE patients with seizure-free anterior temporal lobectomy patients, with limited consideration of seizure variables (e.g., Viskontis et al., 2000; St Laurent et al., 2009; Hurfuth et al., 2010). There is scant research seeking to tease apart the relative contribution of pathology versus seizures. Rayner et al. (2012) presented initial data suggesting that the chronicity of temporal lobe seizures (i.e., younger age at onset and intractability) was associated with the severity of episodic autobiographic memory impairments, while Voltzenvogel et al (2007) used a longitudinal design to show that in the absence of recurrent seizures the autobiographic memory of right TLE patients improved after surgical resection. Together these studies support the view that habitual seizures may contribute to the poor recall of autobiographic events in people with TLE.

To delineate the role of seizures from temporal lobe pathology, one needs to examine the autobiographic memory functioning of medically intractable epilepsy patients with seizure foci outside the temporal lobe. This allows the effect of recurrent seizures to be directly tested. Thaiss and Petrides (2008) compared autobiographic memory in TLE and frontal lobe epilepsy (FLE), arguing that autobiographic memory was fundamentally preserved in patients with FLE, but they were less likely to use an organisational strategy to facilitate recollection. However, this study tested patients who had undergone resective surgery and were mostly seizure-free (L.M. Thaiss, personal communication), preventing the role of habitual extratemporal lobe seizures from being directly explored. Chapter 3 showed that autobiographic memory impairment indexes altered activity and connectivity of the AMN in unipolar depression. This thesis extrapolates these findings to epilepsy research exploring whether similar network dysfunction caused by habitual seizures leads to reduced autobiographic memory function and depressive symptomatology in patients with focal epilepsy.
4.2 Depression in epilepsy

4.2.1 Prevalence and significance

Depressed mood is the most prominent psychiatric symptom of epilepsy (Tellez-Zenteno et al., 2007). Research suggests that between 17-55% of people with medically refractory epilepsy endorse clinically significant depressive symptoms (Mendez et al., 1986; Indaco et al., 1992; Jacoby et al., 1996; Boylan et al., 2004; Jones et al. 2007; Adams et al., 2008; Canuet et al., 2009; Ertekin et al., 2009; Wrench et al., 2004), with 43% higher odds of developing depression than healthy controls when adjusting for demographic factors (Fuller-Thomson & Brennenstuhl, 2009).

Depressed mood in epilepsy can bear a close relationship to the occurrence of seizures (the ‘ictus’), and may present pre-ictally, peri-ictally, post-ictally, or inter-ictally (Scott & Masland, 1953; Weil, 1955; Gaitatzis et al., 2004). The former three refer to transient mood symptoms that occur as part of – or are heightened by – a seizure (Jackson & Turkington, 2005). Depression in epilepsy requires careful assessment of whether depressive symptoms are temporally related to the ictal event, as interictal and peri-ictal depressive disorders may respond differently to pharmacological treatment (Kerr et al., 2011). Interictal depression is the focus of the current thesis, comprising the most common presentation of depression in epilepsy and referring to enduring depressive episodes that manifest between seizures (Kanner & Nieto, 1999; Colman, 2003).

Unipolar depression in epilepsy is of critical clinical concern. It is associated with inflated morbidity and excess mortality, with more deleterious effects on patient quality of life than seizures (Cramer et al., 2003; Gilliam, 2005). Suicidality is up to 25 times more common than is seen in the healthy population (Gaitatzis et al., 2004; Kanner, 2009). Despite this, psychiatric comorbidities of epilepsy remain under-recognised and undertreated (Kanner et al., 2010; Fiest et al., 2014), leading to a call for the prioritisation of their management in recent international consensus clinical practice statements (Kerr et al., 2011).
4.2.2 Phenomenology of depression in epilepsy

There is a longstanding notion in epileptology that unipolar depression presents differently in people with epilepsy than what is seen in psychiatric or community populations (see Figure 4.5). Psychiatrists such as Kraepelin (1923) and Bleuler (1949), as well as neurologists like Henri Gastaut (1953, 1955), noted that patients with epilepsy sometimes develop periodic dysphoria intermixed with bursts of euphoria, anxiety, and somatic symptoms. Stemming from these observations, Dietrich Blumer and colleagues (Blumer et al., 2004) have argued for the recognition of an epilepsy-specific depressive disorder, Interictal Dysphoric Disorder (IDD), which is characterised by intermittent bouts of short-lived dysphoria. Despite this longstanding speculation that the phenotype of depression in people with seizures is different to that seen in the general community, there is still no systematic, data-driven research exploring the existence of phenomenological subtypes of depression in epilepsy that is analogous to what has been achieved in other medical conditions with a high comorbidity of mood disturbance, such as cardiac disease (see Section 2.4.1).

Figure 4.6. Depressive disorders in epilepsy are considered to lie on a spectrum of severity ranging from low-grade ‘sub-syndromic’ depressive episodes to severe, suicidal depression. They may not always fit dominant category-based diagnostic systems such as DSM-IV-TR or ICD-10, but can show overlapping features. Interictal Dysphoric Disorder is postulated to be caused by paroxysmal, subthreshold hypersynchronous neural discharges that produce increasingly inhibitory responses in the mood network. (Source: Rayner & Wilson, 2012)
4.2.2.1 Interictal dysphoric disorder. The eight key symptoms of IDD comprise irritability, low moods, anergia, insomnia, atypical pains, anxiety, fear, and euphoric moods; patients present with an average of five of these symptoms. The bouts of dysphoria occur intermittently, without external triggers, and independent of overt seizures (Blumer et al., 2004). It is thought to be caused by paroxysmal, subthreshold hypersynchronous interictal discharges that produce increasingly inhibitory responses in the mood network (Blumer et al., 2004; see Mula, 2014 for a recent review). Blumer (1991, 1995) has suggested that up to 50% of epilepsy patients seeking medical care suffer from IDD of sufficient severity to require pharmacologic treatment. The identification of IDD as a separate entity, however, has been clinically debated, with work by Marco Mula and colleagues showing that it is not specific to epilepsy, being present in patients with migraine (Mula et al., 2008). Further research is needed to resolve the issue.

4.2.2.2 Subsyndromic depression. The existence of “subsyndromic”, “subthreshold” or “subclinical” forms of unipolar depression has long been recognised in the psychiatric realm, and their negative impact on the course and prognosis of the depressive disorder is well-established (Paykel et al., 1995; van Praag et al., 2004; Cuijpers & Smit, 2008). Affected patients endorse high levels of depressive symptoms, but fail to meet threshold criteria for a formal diagnosis of depression. Recently, Kanner et al (2010) extended this notion in a study of 188 people with epilepsy. A diagnosis of subsyndromic unipolar depression was made in 26 patients (14%) based on Beck Depression Inventory-II scores >12 or Centers for Epidemiologic Studies-Depression scores >16, occurring in the absence of any DSM-IV diagnosis of mood disorder. Patients with subsyndromic unipolar depression had a worse quality of life than asymptomatic patients. Worryingly, 41% of epilepsy patients with subsyndromic unipolar depression had previously met criteria for a MDE, and yet 74% were untreated. The authors asserted that despite the failure of DSM criteria to recognise subsyndromic unipolar depression, it is not a benign disorder. Accordingly, they advocate that comorbid epilepsy and subsyndromic unipolar depression needs to be recognised and treated aggressively.

Issues with phenomenology and nomenclature. Central to the debate surrounding the phenomenology of depression in epilepsy is the notion that current psychiatric nomenclature such as DSM-IV-TR may not adequately capture depression as it presents in people with epilepsy (Kanner et al., 2010). Implicit in this suggestion is that
the true prevalence of clinically significant depression in the epilepsy population may be even higher than current research estimates. However, large numbers of studies demonstrate that it is possible to apply standardised criteria in a considerable proportion of patients. The issue of the phenomenology of depression in epilepsy continues to be discussed by scholars such as Blumer and Kanner, however, because of its potential to delineate individualised -and therefore more precise- guidelines for treatment and prognosis (Mula, 2013).

This thesis recognises that data-driven investigation into the existence of phenotypes of depression in epilepsy might also provide initial insights into differential neurobiological underpinnings of the disorder. In particular, phenotypes variously characterised by cognitive or somatic symptoms (as is seen in other populations; see Section 2.4.1) might selectively index unique involvement of the AMN, CCN, or AN, providing new insights into the neural systems involved in the pathogenesis of depression in epilepsy.

**4.2.3 Depression and epilepsy: a bidirectional relationship**

_Melancholics ordinarily become epileptics, and epileptics, melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy_

–Hippocrates, cited in Lewis (1934)

Classical Athenian scholars such as Hippocrates and Aristotle were the first to consider epilepsy and depression to be closely related. One particularly compelling hypothesis is that a shared pathophysiological mechanism accounts for both depression and seizures (Kanner, 2004; Kanner, 2008; Kanner, 2011; Salzberg, 2011). This is driven by the empirical observation that a bidirectional relationship exists between seizures and depression, whereby patients with epilepsy are more likely to develop depression than people in the general population, and sufferers of unipolar depression are at 4- to 7-times greater risk of experiencing an unprovoked seizure (Kanner, 2011).

The bidirectional relationship between depression and epilepsy appears to have important clinical consequences. A 20-year follow-up study of 780 individuals with newly diagnosed epilepsy showed that patients with a history of mood disorder were twice
as likely to develop pharmacoresistant epilepsy as those without such a history (Hitiris et al., 2007). The authors hypothesise that the deleterious neurobiological processes that underpin depression may interact with those producing seizures to increase the burden of brain dysfunction, and thereby increase the morbidity associated with epilepsy. More recent speculation posits that depression and seizures can both be fundamental manifestations of the same underlying disorder (epilepsy), with comorbidity reflective of more extensive disease (Wilson & Baxendale, 2014)

4.2.4 Correlates of depression in epilepsy

Shared mechanisms underlying the heightened comorbidity of mood disturbance and epilepsy must be operant in both conditions (Kanner, 2008). The ætiological agents of comorbid depression and epilepsy have been conceptualised across two broad domains: psychosocial and neurobiological. The latter encompasses epileptological, structural, and functional brain correlates of mood disturbance in epilepsy.

4.2.4.1 Psychosocial features of depression in epilepsy

The psychosocial risk factors of mood disturbance in epilepsy are well-described. Persistent, unpredictable seizures increase financial strain, transform family dynamics, engender perceived and enacted stigma, reduce self-esteem, and limit the ability to complete schooling, retain employment, and acquire a driver’s licence (Wilson et al., 2004; Livneh & Antonak, 2005; Velissaris et al., 2007; Scramber, 2011; Wrench, Rayner et al., 2011; Kerr, 2012). This can hinder personal autonomy and intensify social isolation (Bishop & Allen, 2003).

The psychosocial limitations accompanying epilepsy appear to particularly disadvantage those patients who have lived with seizures since childhood. Taking a developmental perspective, Wilson et al (2012) recently found that as children with TLE transition into adulthood, a significant subset (48%) of them fail to master most normative developmental tasks, the achievement of which allows one to develop a vocational direction, form interpersonal relationships, and obtain financial independence. In this same sample, individuals with childhood-onset focal epilepsy who continued to experience seizures into adulthood showed psychological and social difficulties not shared by their seizure-free peers (Micallef et al., 2010). A psychosocial framework
conceptualises depression in epilepsy as a reactive process that takes place across the lifetime, linked to the ignominies of living with habitual seizures.

Individuals with epilepsy, however, exhibit higher rates of unipolar depression than people with other chronic illnesses whose lifestyles are also restricted. For instance, the prevalence rates of depression seen in people with epilepsy are higher than those seen in patients with conditions such as severe asthma (36.5% versus 27.8%; Ettinger et al., 2004). Implicit in these findings is that there are factors unique to seizure disorders that are depressogenic beyond the usual stressors associated with living with a chronic illness (Jones et al., 2007b).

4.2.4.2 Epileptological features of depression in epilepsy

Clinical factors associated with a heightened risk of depression include illness chronicity, nonlesional focal epilepsy, and the psychotropic effects of some antiepileptic drugs (Jacoby et al., 1996; Anhoury et al., 2000; Quigg et al., 2003; Ettinger, 2006; Adams et al., 2008). Yet results are mixed, with Gilliam et al (2002) finding no association between the type or frequency of seizures and poor quality-of-life scores in a sample of 194 patients with refractory focal epilepsy. Moreover, as is seen with cognition, depressive disorders often antedate the first onset of seizure activity (Hesdorffer et al., 2006; Jones et al., 2007), consistent with the notion in Section 4.2.3 that mood disturbance might represent the initial manifestation of the disease.

4.2.4.3 Neurobiological features of depression in epilepsy

4.2.4.3.1 Neurochemical features. Abnormal neurotransmitter functioning is a robust finding both in epilepsy and depression, implicating systems involving serotonin (Parsey et al., 2006; Drevets et al., 2007; Didelot et al., 2008; Liew et al., 2009), noradrenalin (Jobe & Browning, 2005), glutamate (Sanacora et al., 2004; Huberfeld et al., 2011), and γ-aminobutyric acid (GABA; Möhler, 2012; Kaila et al., 2014). Moreover, abnormal neurotransmitter function has been directly linked to depression in people with epilepsy (Peng et al., 2013). For instance, using PET the degree and distribution of reduced serotonin binding in epilepsy can be correlated with scores on depression scales (Savic et al., 2004; Lothe et al., 2008, Theodore et al., 2012) as well as diagnoses of depression made via semi-structured interview (Hasler et al. 2007). Similarly, reduced N-acetyl aspartate (NAA) in the temporal lobes evident on magnetic resonance spectroscopy
(MRS) correlated significantly with depression in patients with TLE (Gilliam et al., 2000.) A later replication revealed that the extent of voxels in the hippocampus with depleted NAA was linearly associated with severity of depression symptoms (Gilliam et al., 2007). No seizure-related or psychosocial factors could account for the depressive symptoms, suggesting that chronic hyperexcitability of the hippocampus from seizures may be ‘excitotoxic’ and disturb the neurochemical modulators of affect regulation in the mesial temporal network.

4.2.4.3.2 Immunological features. Stress is another prominent theme connecting depression and epilepsy at a neurobiological level. Recent studies link the pathogenesis of depression to the release of inflammatory cytokines during injury, illness, infection, or stress. This inflammatory response is thought to cause dysregulation in mood-regulating cortico-striatal-limbic networks such as the AN and AMN, leading to the behavioural and physiological changes observable in major depression (Piser, 2010). Similarly, inflammation by cytokines in response to epileptiform discharges is clearly seen in animal models of seizure disorder, where animals are subjected to experimental stress (Vezzani et al., 2011).

Actions at several interrelated biological levels might explain the effect of the inflammatory response, including dysregulation of the HPA axis, monocyte gene expression, and abnormal neurogenesis in limbic structures such as the hippocampus (Grosse et al., 2014; for a review, see Koe et al., 2009 or Danzer, 2012). For instance, Pineda et al (2010) showed that in a rat model of TLE, animals developed behaviours congruent with despair and anhedonia that were accompanied by compromised raphe-hippocampal serotonin transmission; with other studies indicating that this pattern of change in the HPA axis stems from an inflammatory response taking the form of enhanced interleukin 1β signalling (Mazarati et al., 2010). An initial link between epilepsy, psychiatric illness, and autoimmune responses in humans has recently been made by Ekizoglu et al (2014), who found neuronal antibodies in the sera of one sixth of patients with focal epilepsy (N=81), with psychosis a frequent comorbidity in the seropositive group.
Anatomical features. The neuroanatomy implicated in depression in epilepsy broadly parallels the regions involved in depression in psychiatric populations, with analogous functional and structural brain changes in the ACC, PFC, amygdala, and hippocampus (see Kanner et al., 2012, for a concise review). The abnormal structures form key nodes in the AMN and CCN, with ongoing epileptiform disease activity likely disrupting the integrity of mood networks bilaterally. A recent review by Wrench, Matsumoto et al (2011) highlighted larger ipsilateral amygdala volumes and larger contralateral subgenual prefrontal cortex volumes as structural findings associated with depression in patients with intractable focal epilepsy. They argued that these structural findings interact with psychosocial and psychiatric factors to increase patient risk of developing mood disturbance in focal epilepsy (see Figure 4.6).

Functional features. There is indirect evidence that mood network dysfunction in depressed patients with epilepsy is related to altered neurocognitive networks. Neuroimaging techniques such as depth EEG, SPECT, and FDG-PET (Theodore et al., 1983; Leib et al., 1991; Bromfield et al. 1992; Schmitz et al. 1997; Salzberg et al., 2006) reveal a relationship among focal epilepsy, depressed mood, and frontal lobe disruption that mirrors the “hypofrontal” CCN seen in unipolar depression. For instance, in Salzberg

Figure 4.7 Neurobiological, psychiatric, and psychosocial markers of depression in medically refractory focal epilepsy. MTLE, mesial temporal lobe epilepsy (adapted from Wrench, Matsumoto et al., 2011 and Wrench, Rayner, et al., 2011)
et al’s (2006) FDG-PET study, TLE patients with a history of depression (n=9) showed focal hypometabolism in ipsilateral orbitofrontal cortex compared with patients who had never been depressed (n=14; P < .001). This is supported by behavioural studies such as the work of Hermann et al (1991), revealing that dysphoric mood symptoms in patients with left-lateralised TLE (n=26) were associated with indices of impaired frontal lobe function (i.e., perseverative responding on a set-shift task, the Wisconsin Card Sorting Test). This relationship was also evident in patients with right-lateralised TLE (n=38), but was nonsignificant. More recently, an fMRI study by Peng et al (2013) observed functional asymmetry in hippocampal-anterior PFC pathways that was associated with depressive symptoms in patients with left-lateralised TLE. Studies such as these suggest that network nodes in the temporal and orbitofrontal regions, already implicated in primary depressive disorders, may also be relevant to the pathophysiology of depression in focal epilepsy.

Initial research also suggests that cognitive and somatic depressive symptom patterns are differentially related to dysfunction of specific systems. Using PET and a 5-HT1A antagonist in 24 patients with lesion-positive TLE, Loethe et al (2008) found that symptoms of psychomotor agitation, anhedonia, and negative cognitions (i.e., ruminating on past failure, feelings of guilt and/or punishment, self-dislike, self-criticalness, feelings of worthlessness) correlated positively with altered serotonergic function in the raphe nuclei and in the contralateral insula, whereas somatic symptoms of depression correlated positively with serotonin binding potential in the epileptogenic hippocampal region, the left mid-cingulate gyrus, and the bilateral inferior dIPFC. This provides preliminary evidence that ongoing epileptiform activity can disrupt functional systems that are known to be pathogenic of depression, with dissociable effects on cognitive versus somatic symptoms. This is supported by an interictal PET study of 40 TLE patients, which found significantly lower levels of serotonin-receptor binding in the ipsilateral hippocampus associated with delayed auditory recall (P < .02) as well as increased BDI scores (Theodore et al., 2012). This hints that altered neurochemical transmission in epilepsy may change the behaviour of neurocognitive networks, giving rise to network disturbances that are accompanied by cognitive impairment. No data exists, however, to indicate whether there are cognitive versus somatic subtypes of depression in epilepsy, as are seen in other chronically ill populations (outlined in Section 2.4.1).
4.2.4.4 Cognitive features

Given that the role of neurocognitive networks in the pathogenesis of depression in epilepsy has not been directly tested, further insights into their altered function can be gleaned from behavioural experiments.

4.2.4.4.1 Objective cognitive impairments. As in depression in the psychiatric realm, cognitive impairments and distortions are common in depressed patients with epilepsy. In a recent study, Brand et al (2012) found that epilepsy patients (N=101) who were younger at age of seizure onset were at the highest risk of mood-congruent cognitive biases when experiencing lowered mood. Specifically, they were more likely to rate neutral or positively-valenced facial expressions as negative. This is consistent with another study showing that illness chronicity in right-lateralised mesial TLE increases depressogenic cognitive distortions in emotion processing (Meletti et al., 2003). Together, these give the impression that chronic epilepsy engenders biases in information processing that are well-recognised risk factors for unipolar depression.

Further insight into the role of neurocognitive networks is shed by the relationships between depression in epilepsy and a particular cognitive function, namely memory. Reduced new learning and delayed recall is most evident in epilepsy patients with major depression, especially in patients with left temporal foci (Paradiso et al., 2001; Helmstaedter et al., 2004; Rösche et al., 2012), with severity of depressive symptoms able to predict the scope of the memory dysfunction (Dulay et al., 2004). These findings provide some evidence that compromised left frontotemporal networks are central to the coupling of mood disorders and memory impairment in epilepsy patients. This laterality effect has been interpreted as reflecting the depletion of cognitive reserve in patients with depression leading to poor verbal elaboration. That is, depression leads to additive changes in the ipsilateral left temporal lobe that undermine memory function above and beyond what is seen in epilepsy alone. This interpretation, however, has not been directly investigated to date, but would be greatly informed by results from a neuroimaging study.

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10 The theory of cognitive reserve suggests that it is the reserve or capacity of the contralateral hippocampus to support function after epilepsy surgery that determines whether changes in memory function will be observed (Chelune, 1995)
designed to delineate the magnitude of functioning of the verbal memory networks in left and right TLE patients with and without major depression relative to healthy controls.

Temporal lobe memory function, however, is not the only cognitive domain to be undermined by mood disturbance in epilepsy. While TLE patients with clinically elevated depressive symptoms evidence greater verbal memory decline after epilepsy surgery (Busch et al., 2011), FLE patients with clinically elevated depressive symptoms show greater reductions in cognitive control (Dulay et al., 2013). These poor cognitive outcomes could not be accounted for by differences in seizure outcome or post-operative mood alone, and could predict cognitive outcome beyond what could be achieved with pre-surgical memory indices alone. This may indicate that cognitive function after epilepsy surgery is more vulnerable in the context of depression, with the nature of the cognitive impairment different for differing focal epilepsy syndromes. Further research, however, is needed to determine whether these cognitive ‘declines’ are reversed when the patients’ psychiatric state improves.

These findings offer initial converging evidence that relative to euthymic patients, depressed patient with epilepsy show depressogenic cognitive biases, worse cognitive impairments, and are at greater risk of cognitive decline after epilepsy surgery if the mood disorder is not treated. Together, they suggest that depression in epilepsy is linked to dysfunction in cognitive networks. The rôle of seizure chronicity and other seizure factors in this relationship, however, remains unclear and will be a focus of the current thesis. Moreover, the link between cognitive networks and depression in epilepsy is nuanced, with some studies unable to show any relationship between memory and mood in this population (e.g., Tracy et al., 2007). The possibility that only certain phenotypes of depression in epilepsy characterised by cognitive dysfunction lead to psychometric memory deficits has not been explored to date and therefore also forms part of the current research objectives.

4.2.4.4.2 Autobiographic memory impairments. As described in Section 4.1.5, impoverished autobiographic memory is considered a life-long risk factor for developing and prolonging depressive disorders (Gibbs & Rude, 2004), and epilepsy patients have deficits in autobiographic memory recall (Gascoigne et al., 2013; St-Laurent et al., 2009). Although potential links between autobiographic memory and depression have not been
investigated in the epilepsy population, it seems reasonable that the relative difficulty focal epilepsy patients show in activating their AMN and accessing autobiographical information may be associated with their increased vulnerability to depression, as it is in the psychiatric population (see Sections 3.3.2 and 2.3.3.1). Specifically, it can be hypothesised that seizure-related disruption to autobiographic memory networks in focal epilepsy would be linked to depressive symptoms and memory disorder.

Autobiographic memory impairment provides a particularly elegant behavioural model for elucidating how depression and cognition-related networks might relate in epilepsy. Autobiographic memory is supported by a widely distributed network with hubs in multiple regions of the brain. Focal seizures propagate along such networks, disrupting processing occurring in distal pathways and nodes. Targeting the AMN is therefore likely to capture neurocognitive markers of depression in epilepsy patients with heterogeneous seizure foci; moreover its anti-correlated relationship with the CCN prompts novel exploration of the interaction between different cognitive networks when profiling depression in epilepsy. This thesis seeks to understand whether depression in epilepsy is associated with disturbed function of cognitive networks, and if so, whether this is due to activity in the epilepsy network.

Summary: Indirect links between depression in epilepsy and disturbance of cognition-related networks

Focal epilepsy is a disease of brain networks that is highly comorbid with mood disorder and cognitive impairment. It has become clear that the networks that are responsible for producing seizures may overlap with the networks underlying depression and autobiographic memory.

Despite high rates of impoverished autobiographic memory and evidence of abnormal AMN functioning in the epilepsy population, there is limited understanding of whether depression in epilepsy is linked to cognitive dysfunction. Evidence of altered functioning of cognition-related brain networks in depressed individuals with epilepsy would give rise to a novel potential mechanism for the pathogenesis of depressive symptoms in epilepsy.
4.3. Aims & Hypotheses

The principal objective of the current thesis was to explore the relationships between depression in epilepsy and autobiographic memory function, for the first time providing a phenomenological account of depression in epilepsy that references seizure-related dysfunction in neurocognitive networks. To achieve this objective, three behavioural experiments were conducted with a large consecutive, prospective cohort of individuals with chronic focal epilepsy (n=85) examined relative to sociodemographically-matched healthy controls (n=72).

Study 1: Behavioural profiles in frontal lobe epilepsy: Autobiographic memory versus mood impairment

The first study reported in this thesis is a preliminary exploration of autobiographic memory and cognitive control in focal epilepsy, and the nature of any relationships between impairment in these domains and affective disturbance. It therefore targeted a case series of patients with seizures focalised to the hub of all three networks of interest; namely, the frontal lobes (Sheline et al., 2010).

It was hypothesised that:

I. At a group level, FLE would be associated with impaired mood and cognition relative to matched controls, reflecting dysfunction in the autobiographic memory, cognitive control, and affective networks

II. Consistent with clinical observations, individuals with FLE would show predominant mood changes or cognitive changes but not both, suggesting that frontal lobe seizures or pathology can selectively disrupt discrete frontal lobe networks.

Study 2: Determinants of autobiographic memory impairment in epilepsy

The second study sought to investigate whether the antecedents of autobiographic memory impairments in epilepsy are influenced by the timing of disease onset (childhood versus adulthood). To achieve this objective, the overall clinical sample was divided into patients with habitual onset of seizures in childhood or adolescence (‘early onset’) versus adulthood (‘late onset’).
It was hypothesised that:

I. Consistent with previous research (see Sections 4.1.5 and 4.2), focal epilepsy patients would show increased rates of psychological and cognitive dysfunction relative to healthy controls, as well as high rates of current and lifetime depressive disorder.

II. The predictors of autobiographic memory impairment would differ between patients with early and late onset epilepsy. Specifically, people with seizures throughout the critical neurodevelopmental period of childhood/adolescence would show links to epilepsy-related factors such as seizure frequency or febrile convulsions; in contrast, reduced autobiographic recollection in recent onset epilepsy would be more strongly linked to non-clinical factors such as depressive symptoms.

Study 3: Cognitive profiling reveals subtypes of depression in focal epilepsy

The third study reported in the thesis aimed to explore if cognitive impairment is a marker of depression in epilepsy. It employed data-driven, symptom-based subtyping of depression in epilepsy in order to identify a phenotype characterised by cognitive dysfunction. This would provide initial behavioural evidence that selected phenotypes of depression uniquely index dysregulation in cognitive brain networks.

It was hypothesised that:

I. As seen in other populations (see Section 2.4), there would be two distinct subgroups of current depressive symptomology in depressed patients with epilepsy reflecting either cognitive network dysfunction, or somatic network dysfunction
   a. These clusters would differ in terms of their epileptological, psychosocial, and psychological features, typical of a true phenotype
   b. Given the high prevalence of cognitive impairment in epilepsy, there would be more patients with the Cognitive presentation of depression than a Somatic presentation
   c. Consistent with disruption to cognitive networks suggested by the symptom profile, depressed patients in the Cognitive symptom cluster
would perform significantly worse on cognitive measures than depressed patients in the Somatic symptom cluster.
Chapter 5. Study One

Behavioural profiles in frontal lobe epilepsy: Autobiographic memory versus mood impairment

Focal epilepsy, including frontal lobe epilepsy (FLE), is currently considered to be a disease that affects brain networks. In particular, the frontal lobes contain hubs for many inter- and intra-hemispheric networks (Goldman-Rakic et al., 1996), including nodes of cognitive networks such as the AMN, the task-positive CCN, and the mood-regulating AN. Reflecting disruption to these networks, FLE has been associated with (i) reduced cognitive flexibility (O’Muircheartaigh & Richardson, 2012) and (ii) high levels of depressive symptomatology (Dulay et al., 2013). Autobiographic memory is presumed to be similarly reduced in FLE; however, this has not been well-studied.

Autobiographic memory impairment is well-established in other focal epilepsies, namely temporal lobe epilepsy (TLE; see section 4.1.5.1.1). Previous studies support the view that habitual seizures may interrupt the functioning of the AMN and contribute to the poor recall of autobiographic events in people with TLE (Rayner et al., 2012; Volzenvogel et al., 2007). In the only FLE research to date, Thaiss and Petrides (2008) reported that autobiographic memory was fundamentally preserved, but patients were less likely to use an organisational strategy to facilitate recollection. However, this study tested patients who had undergone resective surgery and were mostly seizure-free (L.M. Thaiss, personal communication), preventing the disruptive effects of habitual seizures from being explored. Clinical experience in the Comprehensive Epilepsy Programme at Austin Health suggests that selected patients with medically refractory FLE often show difficulties in recalling specific personal memories from across their lives. This is consistent with studies showing compromised autobiographic retrieval in other frontal lobe disorders (Della Sala et al., 1993; McKinnon et al., 2008), although these may reflect different mechanisms.

The purpose of Study One was to perform an exploratory, in-depth characterisation of autobiographical memory in a case series of medically intractable but neurosurgically-naïve FLE patients, relative to a group of matched healthy controls. Each participant underwent extensive clinical investigation, enabling us to consider the effects
of cognitive, neuropsychiatric, and epileptological factors on the nature and extent of any autobiographic memory impairment. This approach is useful for identifying relevant factors that warrant further investigation in future, larger-scale research.

It was hypothesised that at a group level, FLE would be associated with impaired (i) mood and (ii) cognition (i.e., cognitive control and autobiographic memory). Furthermore, individuals with FLE would either have predominant mood changes or autobiographic memory changes but not both, suggesting effects within overlapping but dissociable frontal lobe networks.

5.1 Method

5.1.1 Participants

Nine consecutive patients with medically refractory FLE were prospectively assessed between 2010 and 2014 as part of a wider behavioural study in the Comprehensive Epilepsy Programme at Austin Health, Melbourne, Australia. Epileptogenic foci were identified by established methods (Jackson et al., 1990), including clinical history, ictal semiology on video–electroencephalography (EEG) monitoring, 3T MRI, interictal [18F]fluoro-deoxyglucose positron emission tomography (FDG-PET), ictal and interictal blood flow single photon emission computerised tomography (SPECT), and clinical neuropsychological evaluation. From the families of patients we also recruited a control sample of people with no neurologic or psychiatric history (n = 24). Inclusion criteria for all participants were (1) age ≥18 years, (2) a Full Scale IQ (FSIQ) in the normal range, (3) no history of neurosurgery, and (4) a functional level of English. The study was approved by the Austin Health and The University of Melbourne Human Research Ethics Committees, and all patients gave written, informed consent in accordance with the Declaration of Helsinki.

5.1.2 Measures

Demographic and clinical information was collected from patient medical records, including age, sex, neurologic and seizure history, current pharmacotherapy, and clinical neuropsychiatric evaluation. In controls, demographic and medical information was obtained from a self-report medical screen.
5.1.2.1 Psychiatric evaluation

5.1.2.1.1 DSM-IV Axis I diagnoses of mood disorder

In-depth neuropsychiatric evaluation of the patient sample was undertaken using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), which is considered to be the gold standard measure for diagnosing current and past mood disturbance according to the criteria of the DSM-IV (American Psychiatric Association, 2000). The mood modules of the Non-Patient edition, designed for use in non-psychiatric populations, was employed (SCID-I/NP, see Appendix A; First et al., 2002). Controls had been excluded on the basis of any psychiatric history or symptomatology and were therefore not assessed using the SCID.

5.1.2.1.2 Linear measures of current mood symptomatology

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E, see Appendix B; Gilliam et al., 2006) was administered as a linear self-report measure of current depressive symptoms. Its six items canvass symptoms that do not overlap with commonly comorbid cognitive deficits in epilepsy or the adverse effects of antiepileptic drugs, with each item endorsed on a scale of 1=never to 4=always/often. NDDI-E scores of >15 have been shown to have 90% specificity, 81% sensitivity, and a positive predictive value of .62 for a diagnosis of major depression in epilepsy patients (Gilliam et al., 2006).

The Patient Health Questionnaire-Generalised Anxiety Disorder-7-item (PHQ-GAD-7, see Appendix C) was developed to assess the severity of current generalised anxiety disorder symptoms presenting in medical populations and validated in a study of 2740 primary care patients (Spitzer et al., 2006). It also has good sensitivity and specificity as a screen for panic, social anxiety, and posttraumatic stress disorder (Kroenke et al., 2007). Participants assign scores of 0, 1, 2, and 3, to the response categories of ‘not at all’, ‘several days’, ‘more than half the days’, and ‘nearly every day’, respectively. PHQ-GAD-7 total scores for the seven items range from 0 to 21. Scores of 5, 10, and 15 represent markers of mild, moderate, and severe anxiety, respectively.
5.1.2.2 Neuropsychological evaluation

5.1.2.2.1 Autobiographic memory

The Autobiographical Memory Interview (AMI, see Appendix D; Kopelman et al., 1990) is a semi-structured interview that assesses personal memories sampled from three time periods: childhood, early adulthood, and recent life. The AMI is designed on the premise that semantic and episodic autobiographic memories interact synergistically during everyday life, but reflect dissociable information processing streams that can be measured independently. The Personal Semantic Schedule requires participants to recall personally relevant facts from across their lives (e.g., classmates’ names, former addresses). Each of the three time-points are scored out of 21 (maximum=63), with a score of ≤47 associated with an amnestic syndrome and a score of 48-49 indicative of a probable amnestic syndrome. The Autobiographical Incident Schedule asks participants to recall three personal episodes from each time period (e.g., primary school, a wedding). Where a participant fails to recall anything, some prompts may be used and it is permissible to encourage the participant to elaborate on information they have already provided. Episodic memories are scored from 0 - 3 (maximum=27) based on both their richness in detail and how precisely the incident is located in place and time, with a total score of ≤12 associated with an amnestic syndrome and a score of 13-15 indicative of a probable amnestic syndrome. Inter-rater reliability on the AMI was found to lie between r = .83–.86, with good sensitivity to organic diseases such as Wernicke-Korsakoff, TLE, and dementia (Kopelman et al., 1994).

5.1.2.2.2 Broader memory function

Neuropsychological evaluation of broader cognitive functioning was assessed using the Wechsler Memory Scale-fourth edition (WMS-IV, see Appendix E11; Wechsler, 2009) and encompassed domains of auditory-verbal learning and recall, visual learning and recall, as well as the executive function of working memory. Specifically, auditory-verbal memory was assessed with immediate and delayed recall indices of the Verbal Paired Associates subtest, visual learning was assessed using the immediate and delayed recall indices of the Design Memory subtest, and working memory was assessed using the Symbol Span subtest. All subtests were scored according to age-scaled normative data.

11 Please note, due to copyright restrictions the actual test material cannot be included in the Appendix
supplied with the battery (M=10; SD=3). Some patients had data missing from the WMS-IV due to seizures interrupting the assessment.

For Study One only, neuropsychological variables of interest also included extra measures of working memory, cognitive control, and auditory-verbal and visual memory gathered during the formal diagnostic neuropsychological assessment conducted by the clinical neuropsychologist in the CEP of Austin Health (Dr. David Weintrob). All of these psychometric tests have well-established validity, reliability, and normative data (Strauss et al., 2006; see Table 5.1).

Table 5.1 Measures of cognitive functioning employed in Study One

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Specific Cognitive Processes</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual ability</td>
<td>• Extent of lexical vocabulary</td>
<td>• Wechsler Test of Adult Reading (Wechsler, 2001)</td>
</tr>
<tr>
<td>Auditory-Verbal Memory</td>
<td>• Immediate and delayed recall of verbally-mediated information</td>
<td>• Verbal Paired Associates subtest, Wechsler Memory Scale – IV (Wechsler, 2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Immediate and delayed recall of verbally-mediated information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rey Auditory Verbal Learning Test (Strauss et al., 2006)</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>• Immediate and delayed recall of visually-mediated information</td>
<td>• Design Memory subtest, Wechsler Memory Scale – IV (Wechsler, 2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Copy and delayed recall of a visual pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rey-Osterreith Complex Figure Test (Strauss et al., 2006)</td>
</tr>
<tr>
<td>Cognitive Control</td>
<td>• Working memory and mental manipulation of visual information</td>
<td>• Symbol Span subtest, Wechsler Memory Scale – IV (Wechsler, 2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Strategic orthographic lexical retrieval; inhibition of rule-breaking responses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Controlled Oral Word Association Test (total, FAS Strauss et al., 2006)</td>
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</tbody>
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5.1.3 Statistical analyses

Analyses were run using IBM SPSS Statistics 22.0 with a statistical significance criterion set at $P \leq 0.05$ (two-tailed). Where the assumptions of parametric tests were not upheld, more conservative nonparametric alternatives were employed.

To characterise the cognitive and psychiatric profiles of patients relative to controls, we first examined differences in autobiographic memory using one-way analysis of variance. The performance of the patients on subtests of verbal and visual memory, as well as working memory, were compared to levels of normal task performance ($M=10$, $SD=3$) using a one-sample t-test. Finally, a Mann-Whitney U test was used to assess differences between patients and controls on the self-report measure of depression.

5.2 Results

Patients with focal epilepsy did not differ from healthy controls in sex, age, FSIQ, or years of education ($P > 0.05$). A summary of the key demographic and clinical features of the nine FLE patients is contained in Table 5.2. The mean age at the onset of seizures in the FLE group was 14.6 years (range = 1.5–35.0 years), with a mean duration of epilepsy of 24.6 years (range = 6–41 years). On average, the FLE patients experienced 48.4 seizures per month (range = 1–105). Seven out of nine cases had a structural frontal lobe lesion evident on MRI. The location, laterality, and nature of these lesions was heterogeneous.
Table 5.2 Key demographic and epileptological features of the nine FLE cases

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
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<td>Sex</td>
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<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
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<tr>
<td>Age (years)</td>
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<td>38</td>
<td>41</td>
<td>41</td>
<td>38</td>
<td>42</td>
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<td>Age at seizure onset (years)</td>
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<td>35</td>
<td>34</td>
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<td>3.5</td>
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<td>Duration of epilepsy (years)</td>
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<td>6</td>
<td>7</td>
<td>37</td>
<td>39</td>
<td>27</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Seizure frequency (monthly average)</td>
<td>5</td>
<td>90</td>
<td>60</td>
<td>&lt;1</td>
<td>30</td>
<td>30</td>
<td>40</td>
<td>75</td>
<td>105</td>
</tr>
<tr>
<td>Location of lesion</td>
<td>Frontopolar region; ant. MFG</td>
<td>MFG; sup. frontal sulcus</td>
<td>midline suprasellar; basal ganglia; OPFC; mPFC</td>
<td>ant. frontal atrophy</td>
<td>Piriform cortex; OPFC</td>
<td>sup. frontal region</td>
<td>diffuse frontal atrophy</td>
<td>OPFC</td>
<td>Frontopolar region</td>
</tr>
<tr>
<td>Evidence</td>
<td>EEG, MRI, PET, SPECT</td>
<td>EEG, MRI, PET</td>
<td>EEG, MRI, PET</td>
<td>EEG, MRI, PET</td>
<td>EEG, SPECT, PET</td>
<td>EEG, MRI, PET</td>
<td>MRI</td>
<td>EEG; EEG, fMRI, MRI, PET</td>
<td>EEG, MRI, PET</td>
</tr>
<tr>
<td>Laterisation</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Bilateral</td>
<td>Right</td>
<td>Right</td>
<td>Bilateral</td>
<td>Right</td>
<td>Right</td>
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<tr>
<td>Pharmacotherapy</td>
<td>CLB; LTG</td>
<td>LEV; LTG; TPM; VPA</td>
<td>CLZ; LTG</td>
<td>TPM; VPA</td>
<td>CBZ; CLB; CLZ; LEV; PHT</td>
<td>CBZ; TPM</td>
<td>LEV; VPA</td>
<td>VPA</td>
<td>CBZ, LCM, LEV, VPA</td>
</tr>
</tbody>
</table>

‘Impaired Cognition’ = Patients who scored in the ‘Definitely Abnormal’ range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview (Kopelman et al., 1990); ‘Impaired Mood’ = Patients who scored in the normal range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview (Kopelman et al., 1990), but evidenced past or current mood symptoms.

P = patient, M = male, F = female; Ant. = anterior; MFG = middle frontal gyrus; mPFC=mesial prefrontal cortex; OPFC=orbitofrontal prefrontal cortex; Sup. = superior; CBZ = carbamazepine; CLB=clobazam; CLZ=clonazepam; LCM=lacosamide; LEV=levetiracetam; LTG = lamotrigine; PHT= phenytoin; TPM=topiramate; VPA=sodium valproate
5.2.1 FLE patients have worse autobiographic memory than controls

Group level comparisons revealed that FLE patients performed significantly worse on measures of semantic autobiographic memory than healthy controls \([F_{(1,31)} = 9.37, P = 0.005, \eta^2 = 0.23, \text{large effect}]\) (Table 5.3). Similarly, FLE patients exhibited significantly worse episodic autobiographic memory function than healthy controls \([F_{(1,31)} = 26.51, P < 0.001, \eta^2 = 0.46, \text{large effect}]\) (Table 5.3 and Figure 5.1). Patients did not differ from normative data on measures of auditory-verbal memory, visual memory, and working memory from the WMS-IV \((P > 0.05; \text{Table 5.3})\).

<table>
<thead>
<tr>
<th>Table 5.3 Cognitive and psychiatric scores: patients versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autobiographic Memory</strong></td>
</tr>
<tr>
<td>AMI Episodic Score</td>
</tr>
<tr>
<td>12.33 ± 4.42</td>
</tr>
<tr>
<td>AMI, Semantic Score</td>
</tr>
<tr>
<td>51.61 ± 5.52</td>
</tr>
<tr>
<td>AMI</td>
</tr>
<tr>
<td>20.13 ± 3.67**</td>
</tr>
<tr>
<td>56.96 ± 4.04**</td>
</tr>
<tr>
<td><strong>Intellectual Ability</strong></td>
</tr>
<tr>
<td>WTAR, FSIQ</td>
</tr>
<tr>
<td>96.88 ± 8.43</td>
</tr>
<tr>
<td>103.71 ± 14.67</td>
</tr>
<tr>
<td><strong>Auditory-Verbal Memory</strong></td>
</tr>
<tr>
<td>WMS-IV, VPA Immediate SS</td>
</tr>
<tr>
<td>8.67 ± 3.08</td>
</tr>
<tr>
<td>10 ± 3\textsuperscript{a}</td>
</tr>
<tr>
<td>WMS-IV, VPA Delayed SS</td>
</tr>
<tr>
<td>9.33 ± 2.34</td>
</tr>
<tr>
<td><strong>Visual Memory</strong></td>
</tr>
<tr>
<td>WMS-IV, Designs Immediate SS</td>
</tr>
<tr>
<td>6.67 ± 3.20</td>
</tr>
<tr>
<td>10 ± 3\textsuperscript{a}</td>
</tr>
<tr>
<td>WMS-IV, Designs Delayed SS</td>
</tr>
<tr>
<td>9.00 ± 2.45</td>
</tr>
<tr>
<td><strong>Cognitive Control</strong></td>
</tr>
<tr>
<td>WMS-IV, Symbol Span SS</td>
</tr>
<tr>
<td>8.50 ± 2.67</td>
</tr>
<tr>
<td>10 ± 3\textsuperscript{a}</td>
</tr>
<tr>
<td><strong>Depression Symptoms</strong></td>
</tr>
<tr>
<td>NDDI-E, total score</td>
</tr>
<tr>
<td>12.63 ± 4.72</td>
</tr>
<tr>
<td>10.0 ± 2.08</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Mean and standard deviation of healthy controls based on normative data provided by the test manual (Wechsler, 2009). \ **P<0.01
AMI = Autobiographical Memory Interview; FSIQ = Full Scale Intelligence Quotient; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; SS = Scale Score (mean of 10 and standard deviation of 3); VPA = Verbal Paired Associates; WMS-IV = Wechsler Memory Scale, 4th Edition; WTAR = Wechsler Test for Adult Reading
Figure 5.1. Mood and memory function of frontal lobe epilepsy (FLE; n=9) patients relative to healthy controls (n=24). Panel A depicts significantly poorer episodic autobiographic memory recall in FLE patients; Panel B shows higher levels of depressive symptoms in FLE patients relative to controls; Panel C plots autobiographic memory against depressive symptoms, showing the clustering of patients with lower memory scores (‘Impaired Cognition’=orange circles) versus higher depression scores (‘Impaired Mood’=blue triangles). Healthy controls largely form their own cluster of normal performance (black squares). Note that in Panel C, there is one patient in the Impaired Cognition group with an NDDI-E score >15 (P3).
5.2.2 High levels of clinical depression in FLE patients

The level of current depressive symptoms endorsed by FLE patients did not differ significantly from controls on the NDDI-E (P > 0.05; Figure 5.1). However based on semi-structured psychiatric interview, 44% of FLE patients met formal criteria for a lifetime history of major depression and 33% met criteria for current depression. While the small sample size inherent in a case series approach necessarily restricts broad generalisations, it is worth noting that this rate of depression seems much higher than a recent estimate of the global point prevalence of major depressive disorder at 4.7% (95% CI=4.4–5.0; Ferrari et al., 2013).

5.2.3 Profiling FLE cases: Impaired Cognition versus Impaired Mood

Inspection of individual patterns of cognitive and psychiatric functioning revealed two distinct profiles (see Appendix F for Case Vignettes). Five out of nine patients (56%) scored in the abnormal range on the Autobiographic Incident Schedule of the AMI (‘Impaired Cognition’ profile) with two of these also scoring in the abnormal range on the Personal Semantic Schedule of the AMI (Table 5.4). Most (4/5) of the patients from the Impaired Cognition profile showed broader deficits in cognitive control and auditory-verbal and visual memory, while only one had experienced recurrent mood disturbance.

The remaining four patients (44%) scored within the normal range on the Autobiographical Incident and Personal Semantic Schedules of the AMI, in the context of preserved broader cognitive functioning. In contrast to the Impaired Cognition profile, these patients primarily presented with a history of depressive disorder and/or current depressive symptoms (‘Impaired Mood’ profile; Table 5.5).
### Table 5.4. Autobiographic memory and general cognitive functioning of the nine cases

<table>
<thead>
<tr>
<th></th>
<th>Impaired Cognition Profile</th>
<th>Impaired Mood Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1</td>
<td>P2</td>
</tr>
<tr>
<td>Autobiographic Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI Episodic Score</td>
<td>8*</td>
<td>9*</td>
</tr>
<tr>
<td>AMI, Semantic Score</td>
<td>54.5</td>
<td>49.5</td>
</tr>
<tr>
<td>Intellectual Ability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WTAR, FSIQ</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>Auditory-Verbal Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-IV, VPA Immediate SS</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>WMS-IV, VPA Delayed SS</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>RAVLT, ∑ Trials A1-A5</td>
<td>54</td>
<td>67</td>
</tr>
<tr>
<td>RAVLT, Delay</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Visual Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-IV, Designs Immediate SS</td>
<td>11</td>
<td>3*</td>
</tr>
<tr>
<td>WMS-IV, Designs Delayed SS</td>
<td>12</td>
<td>7*</td>
</tr>
<tr>
<td>RCFT, Delay</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Cognitive Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-IV, Symbol Span SS</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>FAS, Total</td>
<td>34</td>
<td>26*</td>
</tr>
</tbody>
</table>

*At least one standard deviation below age-expected levels of task performance (i.e., impaired)

‘Impaired Cognition’ = Patients who scored in the ‘Definitely Abnormal’ range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview (Kopelman et al., 1990) ‘Impaired Mood’ = Patients who scored in the normal range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview (Kopelman et al., 1990) but evidenced past or current mood symptoms; AMI = Autobiographical Memory Interview; FAS = orthographic lexical retrieval component of the Controlled Oral Word Association Test; FSIQ = Full Scale Intelligence Quotient; P = Patient; RAVLT = Rey Auditory-Verbal Learning Test; SS = Scale Score (mean of 10 and standard deviation of 3); VPA = Verbal Paired Associates; WMS-IV = Wechsler Memory Scale, 4th Edition; WTAR = Wechsler Test for Adult Reading; Normative data for the Autobiographic Memory Interview taken from Kopelman et al. (1990); Normative data for the Wechsler Test of Adult Reading taken from Wechsler (2001); Normative data for the Wechsler Memory Scale–4th Edition taken from Wechsler (2009); Normative data for the Rey Auditory-Verbal Learning Test taken from Senior (2012), Australian data stratified by age and years of education; Normative data for the Rey-Osterreith Complex Figure Test taken from Strauss et al (2006), stratified for age; Normative data for the FAS, total score, taken from Tombaugh et al (1999), stratified for age and years of education; Shaded area indicates two cases that have been grouped according to their overall cognitive and behavioural profile, but whose psychometric psychiatric performances are recognised to be either subclinical (P6) or less commensurate with a dichotomous grouping (P5)
### Table 5.5. Mood profile of the nine FLE cases

<table>
<thead>
<tr>
<th>SCID-I/NP Diagnoses</th>
<th>Impaired Cognition Profile</th>
<th>Impaired Mood Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P1  P2  P3  P4</td>
<td>P5</td>
</tr>
<tr>
<td>SCID-I/NP Diagnoses</td>
<td>Nil  Nil  Nil  Nil</td>
<td>Current MDE, Past MDE</td>
</tr>
<tr>
<td>Score</td>
<td>11   6   16*   12</td>
<td>—</td>
</tr>
</tbody>
</table>

*Level of endorsed depressive symptoms suggests that the patient is at risk of a current MDE (Gilliam et al., 2006)

‘Impaired Cognition’ profile = Patients who scored in the ‘Definitely Abnormal’ range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview; ‘Impaired Mood’ profile = Patients who scored in the normal range on the Autobiographical Incident Schedule of the Autobiographical Memory Interview, but evidenced past or current mood symptoms (Kopelman et al., 1990)

DDNOS = Depressive Disorder Not Otherwise Specified; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; MDE = Major Depressive Episode; MDD = Major Depressive Disorder; P = Patient; SCID-I/NP = Structured Clinical Interview for DSM-IV Axis I Disorders, non-patient edition

Shaded area indicates two cases that have been grouped according to their overall cognitive and behavioural profile, but whose psychometric psychiatric performances are recognised to be either subclinical (P6) or less commensurate with a dichotomous grouping (P5)
5.2.4 Characterising the two profiles: Impaired Cognition versus Impaired Mood

5.2.4.1 Seizure-related factors

The onset of habitual seizures and subsequent duration of epilepsy were broadly similar for the ‘Impaired Cognition’ and ‘Impaired Mood’ profiles. For the five patients with a profile of Impaired Cognition, mean age at seizure onset was 15.5 years (range = 1.5-35 years) and mean duration of epilepsy was 20.8 years (range = 6–37 years). For the four patients with the Impaired Mood profile, mean age at onset was slightly younger than the Impaired Cognition group at 9.13 years (range = 3-22 years), with mean duration of epilepsy concordantly longer at 33.6 years (range = 27–41 years). Clinically, all of the FLE patients were experiencing ongoing seizures, with the Impaired Mood group reporting a higher average number of seizures per month (62.5 ± 17.14) compared to the Impaired Cognition group (37.2 ± 16.9).

5.2.4.2 Broader cognitive factors

Four out of five patients with a profile of Impaired Cognition (Cases 2-5) exhibited deficits in cognitive control, such as reduced maintenance and manipulation of visual details in working memory. They also showed deficits on the immediate and delayed recall components of visual memory. Three out of five patients showed reduced auditory-verbal memory on indices of both immediate and delayed recall (Cases 3-5). Only Case 1 showed intact general cognitive functioning in the context of impaired episodic autobiographic memory.

In contrast, broader cognitive functioning was largely intact for the ‘Impaired Mood’ profile. One patient (Case 6) showed reduced immediate recall, however, clinically this appeared to be secondary to bradyphrenia (see Appendix F Case Vignettes). Another patient with preserved episodic autobiographic memory (Case 7) had an isolated deficit in orthographic lexical retrieval, whereas all other aspects of auditory-verbal memory, visual memory, and cognitive control were within the normal range.

5.2.4.3 Mood-related factors

Only one of the patients with impaired episodic autobiographic memory (Case 3) met criteria for a DSM-IV mood disorder (Table 5.4). In contrast, two of the four FLE patients with an Impaired Mood profile met criteria for previous major depression and current
minor depression, the third endorsed high but subclinical levels of current depressive symptoms, and the final patient met criteria for a previous major depressive episode (fully resolved). No other sociodemographic or clinical variables differed between the two profiles.

5.3 Discussion

Study One describes a consecutive case series of nine people with medically-refractory FLE. As a group, FLE was found to be associated with worse semantic and episodic autobiographic memory compared to controls, and showed higher rates of depression than seen in the general population. Analysis of the individual data revealed that five cases (56%) evidenced significant impairments on measures of episodic autobiographic memory, generally occurring in the context of broader cognitive deficits. In contrast, the remaining four patients showed largely intact autobiographical recollection and cognition but high rates of depression. Whilst previous studies have documented autobiographic memory deficits in people with frontal lobe insults (Della Sala et al., 1993; McKinnon et al., 2008) or other focal epilepsies (Huruth et al., 2010), this is the first attempt to characterise the neurological, neuropsychological, and neuropsychiatric correlates of impaired versus preserved autobiographic memory functioning in FLE patients with active seizures. These initial findings highlight the need for larger-scale studies investigating the cognitive and psychiatric comorbidities of FLE.

5.3.1 Brain networks supporting autobiographic memory may be disturbed by an active frontal lobe seizure focus

Our finding of impoverished autobiographic memory in medically-intractable FLE contrasts with the study by Thaiss and Petrides (2008) reporting preserved autobiographic recall in seizure-free FLE patients post-surgical resection. This discrepancy may indicate that an active frontal lobe seizure focus can disrupt the normal functioning of brain networks that regulate cognition, including autobiographic memory. After epilepsy surgery, fMRI studies demonstrate that the lesion-free and seizure-free brain is capable of significant functional reorganisation (Bonelli et al., 2013; Wilson et al., 2013). Although speculative, intact autobiographic memory described by Thaiss and Petrides may represent functional normalisation of cognitive networks in the absence of disruptive seizure activity.
The negative impact that active epilepsy has on cognitive networks is well described. Recent EEG-fMRI findings demonstrate that cortical lesions can be co-activated with cognition-related networks during epileptogenic discharges (Pillay et al., 2013), over time altering the functioning and connectivity of these networks (Laufs et al., 2007; Liao et al., 2011; Voets et al., 2012). Poor cognition in FLE may therefore index abnormal organisation in prefrontal regions of cognition-related networks, including the AMN and CCN (Vaessen et al., 2013; Dulay et al., 2013). Since alterations in AMN connectivity have been found to relate to the duration of focal epilepsy (Zhang et al., 2010), habitual frontal lobe seizures may deepen and extend abnormalities in neurocognitive networks over the long-term (Centeno et al., 2012). This converging set of findings supports our preliminary observation that disruption by frontal lobe disease and seizures may undermine neurocognitive networks that underpin episodic autobiographic memory function.

The high co-occurrence of impaired cognitive control and autobiographic memory in the FLE patients may also point to a fundamental disturbance of the network regulating cognitive control. The CCN recruits a circuit of midline prefronto-cingulate structures that are important for executive functions essential to the retrieval of memory (Baddeley & Della Sala, 1996). Cognitive control is commonly impaired in FLE (O’Muircheartaigh & Richardson, 2012), and has secondary downstream effects on the efficiency of autobiographic recollection (McKinnon et al., 2008; Drane et al., 2006). Thus the difficulty in retrieving singular incidences that was exhibited by the five FLE patients with Impaired Cognition in the current study may reflect dysregulation of the prefrontal CCN, rather than an amnestic disorder per se. This, in turn, would account for the broad range of cognitive difficulties seen in this group of patients. An alternative hypothesis is that the anticorrelation between the AMN and CCN is altered, disrupting the function of both. The presence of one patient with impaired autobiographic memory but intact cognitive control, however, raises the possibility that seizure activity may primarily undermine the AMN as well.
5.3.2 Dissociation of semantic and episodic autobiographic memory

In contrast to episodic recall, semantic autobiographic memory was largely preserved across the case series, consistent with previously described double dissociations between semantic and episodic autobiographic memory in patients with severe frontal lobe damage (McKinnon et al., 2008; Squire & Zola, 1998) and paediatric TLE (Smith & Lah, 2011). A strong case exists for the view that this dissociation reflects the fundamentally different processes and neural substrates that support episodic and semantic memory. Semantic knowledge may be entirely decontextualized (Saling, 2009) and relies upon left temporoparietal and parietofrontal circuits (Levine et al., 2004). In contrast, episodic autobiographic memory requires recollection of events in context (Wheeler et al., 1997) and engages a more anterior, bilateral network (Levine et al., 2004; Spreng & Grady, 2010), making it more vulnerable to frontal lobe dysregulation.

5.3.3 Dissociation of autobiographic memory and depression

In striking contrast to findings from the psychiatric literature, only one of the five ‘Impaired Cognition’ patients had a history of mood disorder. Autobiographic memory dysfunction has previously been considered a trait-like vulnerability for developing and prolonging unipolar depression (Gibbs & Rude, 2004), with over-activity of the introspective AMN associated with increased self-focus and rumination characteristic of depression (Hamilton et al., 2011). However the second profile in the current case series, characterised by a high rate of depression but intact autobiographic memory, may provide preliminary evidence that epileptiform disruption to the prefrontal-subcortical AN responsible for emotional regulation (Sheline et al., 2007) does not necessarily result in autobiographic memory disturbance. This would imply that recurrent seizures can differentially dysregulate brain networks that support discrete psychological processes, giving rise to different cognitive and mood profiles in active FLE (Figure 5.2).
Figure 5.2. Proposed effect of an active seizure focus on cognitive [blue arrows] and affective [teal arrows] functions regulated by brain networks with nodes in the prefrontal cortex, suggesting that autobiographic memory dysfunction in frontal lobe epilepsy can stem from either primary disruption to the Autobiographic Memory Network (AMN), or via secondary disruption to the AMN caused by altered function of the Cognitive Control Network (CCN).

Of interest, a recent study of patients with FLE (n=64) suggested that clinically elevated depressive symptoms before epilepsy surgery were a risk factor for developing post-operative executive dysfunction—including reduced cognitive control (Dulay et al., 2013). This is consistent with the idea that disruption to functional systems in the frontal lobes can impact on networks that support higher-order cognition and mood in different ways. It also supports the view that there may be some anatomical overlap between the AMN, CCN and AN in the mesial prefrontal cortex that dynamically shifts across neurological states and at different time points (Sheline et al., 2007).

5.3.4 Differential markers of network dysfunction: future directions

This preliminary study is the first to suggest that neurocognitive and affective networks that are in part regulated by prefrontal structures may be independently affected by an active seizure focus. Although the case series methodology is limited by small sample size, the findings described here are strengthened by the heterogeneity of the patients’ epileptological features, which reflects the heterogeneity evident in the broader FLE population. While the findings require replication in a large behavioural cohort of depressed and euthymic FLE patients and controls, they take the first steps in generating new ideas for future research. These include developing task-based fMRI activation
paradigms targeting the AMN, CCN, and AN to directly evaluate the functioning of these networks in patients with FLE relative to controls. The link between the chronicity of seizures and the nature and extent of network dysfunction also warrants attention, examining in-scanner activation and connectivity measures relative to out-of-scanner measures of epileptological, neuropsychological, and psychiatric functioning to assess how the AMN, CCN, and AN function in different phenotypes of FLE. Finally, neuroimaging the extent of network reorganisation after frontal lobe surgery and its impact on cognition and mood is warranted.

5.3.5 Study One conclusions

This case series is the first study to describe the autobiographic memory functioning of chronic FLE patients. It provides initial evidence that an active frontal lobe seizure focus may leave epilepsy patients vulnerable to (i) episodic autobiographic memory deficits, likely secondary to reduced cognitive control, or (ii) low mood. These two preliminary profiles suggest that FLE may differentially affect brain networks that support cognitive and affective psychological functions. Such behavioural profiles may prove useful as localising markers of network dysfunction for pre-surgical planning and evaluation, and inform psychoeducation and support provided to patients and families affected by such difficulties.

**Study One** showed that frontal lobe epilepsy is a network disease that is alternately associated with impaired autobiographic memory and depression. The dissociation between impaired autobiographic memory and depression in this case series suggests that at an individual level, epilepsy can selectively affect discrete brain networks.

**Study Two** builds on these findings, exploring whether epileptological markers of disease chronicity are linked to impoverished autobiographic memory in a large sample of patients with heterogeneous focal epilepsy, which would suggest that poor cognition is a marker of network disease chronicity and that habitual, longstanding seizures disrupt the normal development of cognitive networks. Moreover, although autobiographic memory and mood are largely dissociable in FLE, Study Two investigates whether their networks substrates might be intertwined in other syndromes of epilepsy such as TLE.
Chapter 6. Study Two

Memories are made of this: Determinants of impaired autobiographical memory in epilepsy

Autobiographic memory encompasses our knowledge and recollection of self-related events from across the lifespan, forming the basis of personal identity and psychological wellbeing (Blinder, 2007). Accordingly, deficits in autobiographic memory are robustly associated with psychiatric disturbances such as depression (Williams, 2006; see Section 2.3.3.1). Neurobiologically, depression is associated with abnormal hyperactivity and hyperconnectivity of the AMN (see Section 3.3.2). As previously outlined, impoverished autobiographical recall is also common in neurological diseases that affect the AMN, including epilepsy. These marked autobiographic memory deficits often occur in the context of broader, more mild decrements in auditory-verbal and visual learning and recall (Herfuth et al., 2010; Noulhaine et al., 2007), indicating that autobiographical impairments can be the most prominent cognitive feature of epilepsy. Autobiographic memory, however, is not routinely assessed in neuropsychological evaluations of people with epilepsy and the mechanisms that underpin it remain unclear.

Neurobiological investigation into the autobiographic memory impairment in epilepsy is largely limited to the null effect of foci laterality (Herfuth et al., 2010; Noulhaine et al., 2007), and despite evidence of deficits in extratemporal lobe epilepsies (see Study One, Chapter 5) most research to date assumes that mesial temporal lobe pathology or resection is the cause of reduced autobiographic recall in epilepsy (Buchanan et al., 2006; Noulhaine et al., 2007; St Laurent et al., 2009). Another potential neurobiological mechanism, however, is that recurrent damage to the AMN by seizures interrupts autobiographical processing, leading to impoverished first-person recollection. In particular, the onset of seizures in childhood—but not adulthood—is linked to abnormal neurodevelopment such as poor cognitive function, reduced brain mass, and delayed white matter increases (Hermann et al., 2006; Hermann et al., 2010). Cognitive vulnerability in childhood-onset epilepsy persists across the lifespan (Baxendale et al., 2010; Hermann et al., 2002), but may be ameliorated in the context of seizure freedom (Helmstaedter et al., 2003), providing indirect evidence that habitual disturbance of
neurocognitive networks during brain development may undermine cognition in people with epilepsy. The impact of chronic seizures on autobiographic memory, however, has never been explored and the possible psychiatric and cognitive correlates of autobiographic memory impairment in epilepsy also remain unknown, giving rise to the current research.

The aim of Study Two was to investigate what gives rise to autobiographic memory impairments in a disease of brain networks, namely focal epilepsy. To achieve this aim, the finding that focal epilepsy is associated with reduced semantic and episodic autobiographic memory function was to be replicated in a large behavioural sample of epilepsy patients and socio-demographically matched healthy controls. The core component of the study investigated whether the antecedents of autobiographic memory impairments in epilepsy are influenced by the timing of disease onset (childhood versus adulthood). To do this, the correlates of impaired autobiographical recall in patients with early onset of seizures (childhood or adolescence) were contrasted to those with late onset (adulthood). It was expected that impoverished autobiographic memory in people with seizures throughout the critical neurodevelopmental period of childhood/adolescence would be linked to epilepsy-related factors such as seizure frequency or febrile convulsions. In contrast, reduced autobiographic recollection in recent onset epilepsy would be more strongly linked to non-clinical factors such as depressive symptoms.

6.1 Methods

6.1.1 Participants

A total of 157 adults participated in this study between 2010-2014. The patient sample comprised 85 individuals with focal epilepsy recruited via the Comprehensive Epilepsy Programme at Austin Health, Melbourne. Epileptogenic foci were identified by established methods from our group (see Study One). Of the 85 patients, 63 (74%) were deemed to have seizures arising from the temporal lobe (47% left hemisphere, 56% lesion positive), and 22 (26%) from either the frontal or parietal lobe (27% left hemisphere, 72% lesion positive). Epileptological and demographic features of the group are summarised in Table 6.1.
Table 6.1. Demographic and clinical profile of the sample (N=157)

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy Patients (n=85)</th>
<th>Healthy Controls (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), $M \pm SD$</td>
<td>40.94 ± 12.98</td>
<td>44.93 ± 15.48</td>
</tr>
<tr>
<td>Range</td>
<td>20-69</td>
<td>21-69</td>
</tr>
<tr>
<td>Sex</td>
<td>Female (%)</td>
<td>51 (60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 (61%)</td>
</tr>
<tr>
<td>Education (years), $M \pm SD$</td>
<td>13.59 ± 3.25</td>
<td>14.00 ± 3.28</td>
</tr>
<tr>
<td>Range</td>
<td>5-24</td>
<td>9-21</td>
</tr>
<tr>
<td>Full-Scale IQ, $M \pm SD$</td>
<td>101.62 ± 11.48$^a$</td>
<td>107.08 ± 12.28$^{b*}$</td>
</tr>
<tr>
<td>Range</td>
<td>72-132</td>
<td>71-132</td>
</tr>
<tr>
<td>Handedness</td>
<td>Right (%)</td>
<td>80 (95%)$^c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62 (87%)$^d$</td>
</tr>
<tr>
<td>Age of seizure onset (years), $M \pm SD$</td>
<td>22.3 ± 13.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Range</td>
<td>1.5 - 63</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of epilepsy (years), $M \pm SD$</td>
<td>18.9 ± 13.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Range</td>
<td>2 - 52</td>
<td>N/A</td>
</tr>
<tr>
<td>Monthly average seizure frequency, $M \pm SD$</td>
<td>22.2 ± 52.0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>$\leq$1/month</td>
<td>21 (25%)</td>
</tr>
<tr>
<td></td>
<td>Fortnightly (2-3/month)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td></td>
<td>Weekly (4-15 month)</td>
<td>32 (38%)</td>
</tr>
<tr>
<td></td>
<td>Daily (≥16/month)</td>
<td>19 (22%)</td>
</tr>
<tr>
<td>Side of epilepsy focus</td>
<td>Left (%)</td>
<td>35 (41%)</td>
</tr>
<tr>
<td></td>
<td>Right (%)</td>
<td>41 (48%)</td>
</tr>
<tr>
<td></td>
<td>Bilateral/Unclear (%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Lesion positive</td>
<td>Yes (%)</td>
<td>52 (61%)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Anti-epileptic drug monotherapy</td>
<td>Yes (%)</td>
<td>19 (22%)</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

$^a$= four cases of missing data; $^b$= eight cases of missing data; $^c$= two cases of missing data; $^d$= one case of missing data

$^{*}$= P<.05

A group of 72 healthy individuals with no neurological or psychiatric history was recruited from the patients’ families and the broader community to provide a sociodemographically-matched control sample. Patients with focal epilepsy did not differ from healthy controls in sex, age, or years of education (P > .05; see Table 6.1). The control sample had a slightly higher mean FSIQ than the patient group $[t_{(142)} = -2.75, P < .05, \eta^2 = .05$, small-moderate effect size]; however mean scores for both groups fell within the “Average” range of intelligence (Wechsler, 2001). Although the difference in FSIQ between patients and controls was a small-sized effect, a linear relationship between autobiographic memory indices and FSIQ in patients was nonetheless assessed using...
scatterplots and Pearson Product-Moment correlations and rejected, negating any need to covary for the effect of FSIQ.

Inclusion criteria for all participants were: (1) age 18 years or older, (2) FSIQ ≥ 70, (3) no previous history of neurosurgery, and (4) a functional level of English. Patients with a comorbid psychiatric diagnosis outside of mood or anxiety disorder (e.g., postictal psychosis) were also excluded. The study had approval from the relevant Human Research Ethics Committees and all participants provided written informed consent in accordance with the Declaration of Helsinki.

6.1.2 Measures

As outlined in Study One (see Chapter 5).

6.1.3 Statistical analyses

**Initial analyses.** Analyses were run using IBM SPSS Statistics 22.0 with a statistical significance criterion set at P < .05 (two-tailed). Where the assumptions of parametric tests were not upheld, more conservative nonparametric alternatives were employed.

To characterise the cognitive and psychiatric profiles of patients relative to controls, differences in semantic (AMI total score, Personal Semantic Schedule) and episodic (AMI total score, Autobiographical Incident Schedule) autobiographic memory were first examined using independent samples t-tests. Odds ratios with 95% confidence intervals were also calculated to determine the patients’ likelihood of showing amnestic-level memory impairments relative to controls. The performance of the patients on subtests of verbal and visual memory, as well as working memory, were compared to ‘Average’ levels of task performance (M=10, SD=3) using one-sample t-tests. Finally, Mann-Whitney U tests and independent samples t-tests were used to assess differences between patients and controls on measures of mood.

**Core analyses.** The predictors of impaired autobiographical recall of patients with onset of epilepsy in childhood/adolescence (‘early onset’; n=43) were then contrasted to those whose onset of seizures was in adulthood (‘late onset’; n=42). Definitions of developmental period were taken from World Health Organization criteria (2014): childhood = 0-8 years, adolescence = 9-19 years (i.e., ‘early onset’= 0-19 years),
adulthood (‘adult onset’) = >19 years. Each of the following analyses was run separately for patients with early onset and late onset epilepsy:

(i) To identify variables most likely to be predictors of episodic and semantic autobiographic memory in each of the developmental groups, bivariate two-tailed Pearson product–moment correlations were performed for each group between autobiographic memory and seizure variables, auditory-verbal memory, visual memory, working memory, and current mood. This was done separately for the semantic and episodic indices of autobiographic memory function. Univariate ANOVAs or independent samples t-tests were also used to assess the strength of relationships between semantic and episodic autobiographic memory scores and dichotomous variables such as history of depression, pharmacotherapy, and laterality of seizure focus.

(ii) Variables that were significantly associated with autobiographic memory functioning at P < .05 were then entered into hierarchical multiple regression analyses to examine their comparative importance in predicting the semantic and episodic index scores from the AMI for each group, resulting in four regression models (early onset-semantic; early-episodic; late-semantic; late-episodic). Preliminary analyses ensured no violation of the assumptions of normality, linearity, multicollinearity, or homoscedasticity. The predictive value of the models can be cross-validated using adjusted $R^2$.

6.2 Results

6.2.1 Focal epilepsy patients have pervasive memory impairments

Relative to healthy controls, individuals with focal epilepsy showed impoverished learning and recall across multiple domains of memory (see Table 6.2). Specifically, patients were significantly less able to recall personally relevant semantic knowledge than the healthy controls ($t_{(140)} = -4.2$, $P < .001$; $\eta^2 = .11$, large effect size), and were significantly less able to recall personally relevant events from their lives ($t_{(140)} = -6.2$, $P < .001$; $\eta^2 = .10$, large effect size). This was true for all life periods ($P < .001$), except childhood semantic ($P > .05$). Odds ratio analyses suggested that patients were 4.39 times more likely than controls to have ‘amnestic’ or ‘probably amnestic’ grade semantic
autobiographical impairments (95% CI = 1.02 – 18.89), and 4.02 times more likely have ‘amnestic’ or ‘probably amnestic’ grade episodic impairments (95% CI = 1.80 – 8.99).

Table 6.2 Cognitive and psychiatric profile of patients versus controls

<table>
<thead>
<tr>
<th>Overall sample</th>
<th>Epilepsy Patients (n=85)</th>
<th>Healthy Controls (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI Semantic Total, M ± SD</td>
<td>54.77 ± 5.56&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58.23 ± 3.96&lt;sup&gt;b,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>32.5 – 63.0</td>
<td>46.5 – 63.0</td>
</tr>
<tr>
<td>AMI Episodic Total, M ± SD</td>
<td>16.61 ± 4.86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21.65 ± 4.69&lt;sup&gt;b,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>4 - 27</td>
<td>8 - 27</td>
</tr>
<tr>
<td>Verbal Paired Associates-I, M ± SD</td>
<td>8.91 ± 3.28&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 ± 3.0&lt;sup&gt;e,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>3 - 17</td>
<td></td>
</tr>
<tr>
<td>Verbal Paired Associates-II, M ± SD</td>
<td>8.62 ± 3.11&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 ± 3.0&lt;sup&gt;e,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>1 - 14</td>
<td></td>
</tr>
<tr>
<td>Design Memory-I, M ± SD</td>
<td>9.00 ± 2.96&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 ± 3.0&lt;sup&gt;e,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>2 - 16</td>
<td></td>
</tr>
<tr>
<td>Design Memory-II, M ± SD</td>
<td>9.16 ± 2.37&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 ± 3.0&lt;sup&gt;e,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>3 - 16</td>
<td></td>
</tr>
<tr>
<td>Symbol Span, M ± SD</td>
<td>10.19 ± 2.71&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10 ± 3.0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>5 - 17</td>
<td></td>
</tr>
<tr>
<td>NDDIE, M ± SD</td>
<td>12.55 ± 3.59&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10.36 ± 3.00&lt;sup&gt;f,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>6-20</td>
<td>6-19</td>
</tr>
<tr>
<td>PHQ-GAD-7, M ± SD</td>
<td>5.57 ± 4.76&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.79 ± 4.16&lt;sup&gt;f,***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 19</td>
<td>0 - 16</td>
</tr>
</tbody>
</table>

Patient performances by age at onset

<table>
<thead>
<tr>
<th>Early n=43</th>
<th>Late n=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI Semantic Total, M ± SD</td>
<td>54.53 ± 4.84</td>
</tr>
<tr>
<td>Range</td>
<td>41.0 – 62.5</td>
</tr>
<tr>
<td>AMI Episodic Total, M ± SD</td>
<td>16.02 ± 5.06</td>
</tr>
<tr>
<td>Range</td>
<td>4.0 – 23.0</td>
</tr>
<tr>
<td>NDDIE, M ± SD</td>
<td>12.62 ± 4.02&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>6-20</td>
</tr>
<tr>
<td>PHQ-GAD-7, M ± SD</td>
<td>4.95 ± 4.15&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range</td>
<td>0 - 18</td>
</tr>
</tbody>
</table>

<sup>a</sup>= three cases of missing data; <sup>b</sup>= twelve cases of missing data; <sup>c</sup>= normal levels of task performance provided by age-stratified norms; <sup>d</sup>= fourteen cases of missing data; <sup>e</sup>= thirteen cases of missing data; <sup>f</sup>= ten cases of missing data; <sup>g</sup>=four cases of missing data; <sup>h</sup>= five cases of missing data; <sup>i</sup>=six cases of missing data; <sup>j</sup>=seven cases of missing data; AMI = Autobiographic Memory Interview; NDDIE = Neurological Disorders Depression Inventory for Epilepsy; PHQ-GAD-7 = Patient Health Questionnaire Generalised Anxiety Disorder 7-item

*= P<.05, **= P<.01, ***P<.001
Compared to age-stratified normative data, individuals with focal epilepsy also demonstrated significantly reduced auditory-verbal learning \((t_{(68)} = -2.7, P < .01, \eta^2 = .10, \text{large effect size})\) and recall \((t_{(68)} = -3.7, P < .001, \eta^2 = .17, \text{large effect size})\) compared to age-expected levels, although the mean score on these indices fell within a standard deviation of the mean. Similarly, patients showed significantly reduced visual learning \((t_{(70)} = -2.9, P < .01, \eta^2 = .11, \text{large effect size})\) and recall \((t_{(69)} = -2.9, P < .01, \eta^2 = .11, \text{large effect size})\) compared to age-expected levels; mean scores, again, fell within a standard deviation of the mean. Patient performances on the working memory task did not significantly differ from normative levels \((P > .05)\).

### 6.2.2 Patients have high rates of depressive disorder and symptoms

Psychiatric evaluation revealed that 36 (43%) epilepsy patients met DSM-IV criteria for a lifetime history of either MDD or DDNOS. Moreover, 21 (25%) currently met formal criteria for a unipolar depressive disorder. This is appreciably higher than the global point prevalence for MDD of 4.7% \((95\% \text{ CI} = 4.4-5.0\%\) recently reported by Ferrari et al (2013). Commensurate with this high rate of psychiatric morbidity, individuals with focal epilepsy endorsed significantly higher rates of current depressive symptoms on the NDDI-E than controls \((t_{(140)} = 3.91, P < .001, \eta^2 = .10, \text{large effect size})\), as well as significantly higher rates of current anxiety symptoms \((U = 1645.00, P = .008; \text{see Table 6.2})\).

### 6.2.3 Neurodevelopmental context of autobiographic memory predictors

The correlates of autobiographic memory impairment in epilepsy were explored within the neurodevelopmental context of early versus late onset of epilepsy. Although individuals with early onset \((n=43; \text{Mean current age}=37.0, \text{SD}=12.7)\) were younger at testing than patients whose onset was in adulthood \((n=42; \text{M}=44.9, \text{SD}=12.2; t_{(83)} = -2.96, P = .004, \eta^2 = .10, \text{large effect size})\), they had a longer duration of epilepsy \((\text{M}=25.3 \text{ years, SD}=13.8 \text{ versus M}=12.4, \text{SD}=8.6; t_{(83)} = 5.15, P < .001, \eta^2 = .24, \text{very large effect size})\). The two patient groups did not differ on any other variables \((P>.05)\).

Potential epileptological, demographic, cognitive, and psychiatric contributors to poor autobiographic memory were explored. Significant correlates of reduced semantic
and episodic autobiographic memory were entered into separate hierarchical regression analyses to investigate their differential predictive value for early versus late onset epilepsy.

6.2.3.1 Autobiographic impairments in early onset epilepsy are related to disease chronicity

In patients with early onset of seizures, their poor recall of personally relevant semantic facts was associated with a higher monthly average seizure frequency ($r = -.32$, $P = .02$, medium strength). Adding monthly average seizure frequency to a hierarchical multiple regression disclosed that it accounted for 10% of the unadjusted variance in predicting semantic memory impairment in early onset epilepsy, $F_{(1,42)} = 4.53$, $P = .04$; adjusted $R^2 = .07$ (see Figure 6.1).

Figure 6.1. Impaired autobiographic memory recall in patients with early onset of epilepsy is linked to indices of increased seizure chronicity and reduced working memory, while the impairment seen in patients with late onset epilepsy is largely predicted by elevated symptoms of depression ($N=85$). $\beta$ = standardised coefficient

The poor recall of salient life events in people with early onset epilepsy was found to be associated with younger age at the onset of seizures ($r = .29$, $P = .03$, medium strength effect), and lower Symbol Span score ($r = .34$, $P = .022$, medium strength effect), reflecting reduced working memory. Adding Symbol Span and the age at onset sequentially to a hierarchical multiple regression established that with just Symbol Span scores in the equation, the model accounted for 11.3% of the unadjusted
variance, $F_{(1,34)} = 4.21, P = .048$. Symbol Span and age at onset together, however, gave rise to a stronger model that accounted for 18% of the unadjusted variance for predicting episodic autobiographic memory impairment in early onset epilepsy, $F_{(1,34)} = 3.59, P = .039$, adjusted $R^2 = .13$ (see Figure 6.1).

6.2.3.2 Autobiographic impairments in late onset epilepsy are linked to depression

In contrast, the poor semantic memory of patients with late onset epilepsy was associated with higher self-reported depression scores on the NDDI-E ($r = -.39, P = .010$, medium-large effect size). Cognitive correlates included lower scaled scores for Designs-I immediate visual learning ($r = .43, P = .006$, medium-large effect size), Designs-II delayed recall ($r = .36, P = .020$, medium effect size), as well as Symbol Span ($r = .36, P = .021$, medium effect size). Being lesion positive also resulted in poorer knowledge of autobiographical facts ($M=53.47, SD=7.14$ versus lesion negative: $M=57.53, SD=3.64$; $t_{(37)} = -2.03, P = .049$, $r = .33$, medium effect size). Inspection of hierarchical regression diagnostics suggested that the cognitive variables were highly collinear, and therefore on a priori theoretical grounds (see Section 5.3.1), only Symbol Span was retained. $R$ was significantly different from zero at the end of each step, however Symbol Span did not add any unique variance to the original model and was omitted. With just NDDI-E scores in the equation, the model accounted for 15% of the unadjusted variance, $F_{(1,34)} = 5.93, P = .02$, adjusted $R^2 = -.13$. Depressive symptoms and lesion status together, however, accounted for 30% of the unadjusted variance, $F_{(2,34)} = 6.73, P = .004$, adjusted $R^2 = .25$, indicating that a significant increment in $R^2$ was gained by including lesion status as a predictor of semantic recall ($P = .016$; see Figure 6.1).

Poor recollection of episodic autobiographical memories in the late onset group was also associated with higher self-reported depression scores on the NDDI-E ($r=.45, P=.004$, large effect size). Cognitive correlates comprised reduced scaled scores for Verbal Paired Associates-I ($r=.34, P=.033$, medium effect size), Verbal Paired Associates-II ($r=.38, P=.018$, medium-large effect size), Designs-I ($r=.29, P=.047$, medium effect size), Designs-II ($r=.39, P=.012$, medium-large effect size), as well as Symbol Span ($r=.32, P=.033$, medium effect size). Again, the cognitive variables were highly collinear and only Symbol Span was retained. $R$ was significantly different from zero at the end of each step but Symbol Span did not add any unique variance and was
omitted from the final model. Depression scores accounted for 20% of the unadjusted variance in predicting episodic impairments in late onset patients, $F_{(1,33)} = 8.16$, $P = .007$, adjusted $R^2 = -.17$ (see Figure 6.1).

6.3 Discussion

Study Two explores the determinants of impaired autobiographic memory in a disease of brain networks, namely epilepsy. It takes into account cognitive and psychiatric correlates of autobiographic memory impairment, as well as neurological factors. This neurodevelopmental approach allows exploration of the impact of seizures and network disease on evolving memory function. It revealed that impoverished semantic and episodic autobiographic memory in epilepsy are multidetermined, and that they differ between patients with early versus late onset of habitual seizures.

6.3.1 Neurocognitive impact of disease chronicity in early onset epilepsy

In patients whose seizures began as children or teenagers, impoverished autobiographic memory was largely associated with indices of disease chronicity. Specifically, poor semantic autobiographic knowledge was linked to increased seizure frequency while impoverished episodic recall was underpinned by younger age at the onset of epilepsy and reduced working memory. This suggests that the chronic longstanding seizures of early onset epilepsy have a negative impact on neurocognitive networks such as the AMN, as well as networks regulating executive function. Moreover, the differential predictors of semantic and episodic recall corroborates the notion that while these two memory systems are highly interdependent, they are vulnerable to different disease mechanisms (Buckley et al., 2014).

The research literature supports the observation that habitual seizures commencing early in life have an adverse effect on the healthy development of cognitive function. Indeed, deficits in the cognitive substrate are not only exacerbated by earlier age at seizure onset in childhood epilepsy (Baxendale et al., 2010; Hermann, Seidenberg & Bell, 2002), but can antedate the onset of seizures (for a review see Hermann & Seidenberg, 2007). These early cognitive impairments are often accompanied by altered brain development, such as reduced hippocampal volumes (Hermann et al., 2002). Such findings may indicate that children and adolescents with epilepsy have reduced neurocognitive reserve with which to resist the cumulative impact of longstanding
seizures on cognitive networks such as the AMN. The apparently rapid emergence of persistent cognitive impairments and altered neurodevelopment around seizure onset also lends support to a growing view that cognitive and behavioural disturbances might also be considered primary manifestations of the disease (epilepsy), giving rise to seizures (Wilson & Baxendale, 2014).

In the context of reduced cognitive integrity stemming from early onset epilepsy, the finding that increased seizure frequency contributed to poor recall of personal facts indicates that the semantic component of the AMN is vulnerable to disruption by ongoing seizures. The impact of active epilepsy on cognitive networks is well described. Recent EEG-fMRI findings demonstrate that cognition-related networks can be co-activated during epileptogenic discharges (Pillay et al., 2013), over time altering their functioning and connectivity (Laufs et al., 2007; Liao et al., 2011; Voets et al., 2012), including in the AMN (Zhang et al., 2010). Behaviourally, the intractability of focal seizures (i.e., AED polypharmacotherapy) has been related to the severity of episodic autobiographic memory impairments (Rayner et al. 2012), while longitudinal designs show that in the absence of recurrent seizures, the autobiographic recall of TLE patients improves after successful surgical resection (Voltzenlogel et al., 2007). Together, these studies suggest that habitual seizures may deepen and extend abnormalities in the AMN over the long-term, undermining first-person recollection in people with early onset epilepsy.

### 6.3.1.1 Key role of working memory in autobiographic retrieval

The episodic memory deficit observed in patients with early onset epilepsy was also associated with reduced working memory. Behavioural studies show that autobiographic recall heavily relies on efficient cognitive control—including working memory—to select and retrieve personal memories in a goal-directed manner (Baldo & Shimamura, 2002; Dalgleish et al., 2007). These processes are mediated by the midline prefronto-cingulate structures of the CCN (Fox et al., 2005). Cognitive control and working memory are fundamental executive functions that are commonly impaired in focal epilepsy (Dulay et al., 2013; Stretton et al., 2013), with secondary or ‘downstream’ effects on the efficiency of autobiographic recollection (Drane et al., 2006). For instance, autobiographical impairments were linked to reduced working memory in Study One of the current thesis,
with other studies demonstrating that FLE patients fail to utilise working memory strategies to enhance autobiographic recall (Thaiss & Petrides, 2008). These findings indicate that epilepsy during childhood may dysregulate the typical development of the CCN, undermining the efficient, goal-directed retrieval of autobiographical memories in patients with early onset of seizures.

**6.3.2 The cognitive impact of adjusting to seizures in adulthood**

In contrast, the semantic and episodic autobiographic memory impairments evidenced by people with late onset seizures were largely underpinned by depressive symptoms. This is commensurate with other studies showing a co-occurrence of memory impairments and depressive symptoms in people with epilepsy. Compellingly, the severity of depressive symptoms is able to predict the scope of memory dysfunction in focal epilepsy (Dulay et al., 2004), with neuroimaging demonstrating that depression in epilepsy leads to changes in the ipsilateral left frontotemporal region that undermines verbal elaboration of remembrances above and beyond what is seen in epilepsy alone (Paradiso et al., 2001; Rösche et al., 2012; Helmstaedter et al., 2004). Together, these studies provide initial evidence that depression and memory impairments can co-occur and lead to additive neurological changes in epilepsy, suggesting that they might share a network substrate that is undermined by the disease.

Behavioural parallels between late onset epilepsy and unipolar depression may flag that brain network changes that are seen in depression are likely to occur in epilepsy. As noted in Section 2.3.3.1 people with depressive disorders more readily recall negative memories than positive, and proffer vague, poorly localised, and overgeneral recollections (Williams, 2006). Given that the late onset epilepsy group does not endorse higher rates of depressive symptoms than early onset patients, it suggests that they alone have a behavioural profile analogous to psychiatric patients with unipolar depression. Although autobiographic memory in depression is vague, recollections become excessively focused upon and the AMN becomes hyperactive, leading to maladaptive symptoms such as pathological rumination, increased self-focus, brooding, and self-biased attribution styles (see Chapter 3). The extension of this to epilepsy is feasible: research shows that patients with late onset seizures go through a period of intense, self-focused psychological adjustment following the diagnosis of epilepsy (Velissaris et al.,
2007; Velissaris et al., 2012). Although speculative, the findings of Study Two may indicate that adult onset epilepsy patients engage introspective autobiographical processes as part of their psychological adjustment to their seizure disorder, serving the cognitive reframing process we know is undertaken as late onset patients struggle with pervasive feelings of loss of control and altered self-identity after the sudden onset of seizures (Velissaris et al., 2007).

6.3.2.1 Is lesional focal epilepsy a cognitive vulnerability factor in late onset epilepsy?

In addition to elevated depressive symptoms, the episodic autobiographic memory impairment exhibited by people with late onset focal epilepsy was partially predicted by the presence of a lesion on MRI, around a third of which were hippocampal sclerosis and the remainder miscellaneous abnormalities such as dysembryoplastic neuroepithelial tumours and cortical dysplasias. Lesions associated with epilepsy foci such as hippocampus sclerosis or cortical dysplasia carry an additive risk of cognitive dysfunction compared to being lesion negative, (Klein et al., 2000; Miller et al., 1993), and over the long term can have increasingly deleterious effects on cognitive networks (Fuerst et al., 2001). Moreover, any lesion evident on imaging after diagnosis of epilepsy in adulthood may represent a structural abnormality that developed in or before childhood but did not cause seizures for some years. Despite being epileptologically ‘dormant’, these lesions may have impacted on the development of functional cognitive networks important for autobiographic memory (Bell et al., 2011). Exploring whether autobiographic memory dysfunction—or cognitive disturbance more broadly- antedates the emergence of seizures in late onset epilepsy and reflects a subtle underlying developmental disorder (Pardoe et al., 2013; Lillywhite et al., 2009) represents an important challenge to future studies seeking to investigate this issue more precisely.

6.3.3 Implications for practice and research across neurological disorders

Study Two sought to map cognitive impairments to a network model of brain dysfunction. It demonstrates that the recent conceptualisation of epilepsy as a disease of brain networks makes it an increasingly useful model with which to dissect its cognitive and psychiatric features (Berg et al., 2011). In particular, cognitive and psychiatric features of epilepsy can now be viewed as primary symptoms of the same network disease that gives rise to
seizures. This implies a common neurobiological substrate, in addition to the secondary effects of a lesion, pharmacotherapy, psychosocial limitations or other factors (Wilson & Baxendale, 2014). This makes neurocognitive and neurobehavioural symptoms potential markers of brain network disturbance, with implications for both research and clinical practice across the neurological spectrum.

The rapidly advancing technological ability to image and evaluate brain networks provides increasingly targeted indices of the anatomical and neurochemical systems implicated in a neurological disorder (Sporns, 2011, Farquarson et al., 2013). When adopted in research, this may reveal more precise metrics of patient outcome. Future phenotyping could assess how neurocognitive markers of epilepsy might map onto neuroimaging or genetics patterns (Wandschneider et al., 2014; Berkovic & Jackson, 2014), potentially guiding the development of novel pharmacological and psychological treatments of the neurological illness and its neuropsychological features. Alternatively, it remains to be seen how neurocognitive markers might be used to predict the cognitive, behavioural, or clinical prognosis in an individual. For instance, the phenotypes of early versus late onset epilepsy provided by the current study could give rise to longitudinal explorations of the prognostic value of autobiographic memory network dysfunction in predicting psychiatric outcomes of people with adult onset seizures. The parsimonious way in which the network model of brain function can be applied to the neuropsychology of epilepsy challenges scientists working with other neurological or neuropsychiatric populations to explore the value of a similar framework in their own work.

The downstream effects of this paradigm shift in research to the clinical coalface are clear. Integration of network-level phenotypes into epilepsy classification systems will make these classifications more precise reflections of the disease process taking place in the individual along with the intrinsic brain networks that this abnormality acts through or arises from. For example, an early onset epilepsy syndrome associated with reduced autobiographic memory and working memory indexes specific cognitive, anatomical, and neurochemical systems that future research may link to tailored treatment options. Such an approach makes clinical management plans more patient-centred, with consideration given to the significance of neurological, cognitive, and neuropsychiatric features of the disorder.
6.3.4 Study Two conclusions

The results of Study Two support a lifespan approach to understanding the cognitive impairments common to epilepsy, taking into account the deleterious effects of seizures on the developing brain’s structure and function, as well as psychological processes associated with adjusting to a chronic illness. Multifactorial predictors of autobiographic memory network dysfunction revealed in different epilepsy syndromes supports the use of neurocognitive phenotyping as a valid method to generate more individualised neurological research. Crucially, the close interrelation of autobiographic memory, working memory, and depression in this study suggests that these functions may share neural networks that are vulnerable to seizures and network disease.

**Study Two** illustrated that epilepsy is a disease that can alter the normal development of complex cognitive networks that occurs during childhood and adolescence. In early onset epilepsy disease markers of seizure chronicity and reduced working memory are linked to impoverished autobiographic recall, whereas behavioural profiles of late onset epilepsy suggest that dysfunctional autobiographic memory and mood are interrelated and independent of seizure chronicity, providing initial evidence that cognitive deficits and affective symptoms in epilepsy may be primary manifestations of the network disease, rather than secondary effects of seizures.

**Study Three** extends these findings, by exploring in greater detail whether depressive disorder in people with epilepsy is linked to cognitive disturbance; specifically, whether a phenotype of the disorder characterised by predominant cognitive impairment exists. This would implicate cognitive networks in the pathogenesis of depression in epilepsy, as in seen in psychiatric populations.
Chapter 7. Study Three

Data-driven profiling identifies a cognitive subtype of depression in epilepsy

Depressed mood is the most prominent psychiatric feature of epilepsy (Tellez-Zenteno et al., 2007; see Section 4.2), with patients showing 43% higher odds of developing unipolar depression than healthy controls (Fuller-Thomson & Brennenstuhl, 2009). Moreover, this relationship is apparently bidirectional, with a history of depressive disorder linked to increased risk for developing seizures (Hesdorffer et al., 2006; see Section 4.2.3). Neurobiological efforts to understand the heightened association between depression and epilepsy suggest that shared neurochemical or neuroanatomical abnormalities underpin both seizures and mood disturbance (see Kanner et al., 2012 for a review).

More recently, the conceptualisation of epilepsy as a disease of brain networks has given rise to the notion that depressive symptoms accompanying epilepsy may stem from the same malfunctioning network that is propagating seizures (Berg, 2011). Initial evidence suggests that these shared networks may relate to cognitive function. This is based on research in unipolar depression, where depressive symptoms are linked to abnormal functioning of three networks: specifically, the AMN, CCN, and AN (see Chapter 3). This has direct relevance for exploring potential mechanisms of depression in epilepsy, given that cognitive impairments are a common and prominent accompaniment to habitual seizures (Saling, 2009) and can index the underlying epilepsy network (Lillywhite et al., 2009).

Understanding the links between mood and cognitive networks in epilepsy, however, has received limited investigation to date. Interest has perhaps been muted by the belief that the presentation of depression in epilepsy is neither well-captured by psychiatric criteria nor homogenous (Blumer et al., 2004; Kanner et al., 2010; see Section 4.2.2), and is therefore not suited to the binary grouping of patients as depressed versus euthymic in cognitive studies. However, this impression is largely untested by empirical methods, and the extent to which there exists distinct phenotypes of depression in epilepsy remains unclear. In the psychiatric field, symptom concurrence has been employed as a
method to identify phenotypes of depression with presumed common ætiologies (Aktas et al., 2010; see Section 2.4).

The current study aimed to profile the presenting symptoms of depression in people with chronic focal epilepsy, using data-driven methods to investigate the presence of different subtypes of the condition. The clinical, cognitive (psychometrically measured), and psychosocial correlates of any resultant subtypes were also identified. Given the manifold links between behavioural, cognitive, and seizure disorders, it was expected that there would be a commonly-occurring phenotype of depression in epilepsy characterised by cognitive depressive symptoms and accompanied by more prominent psychometric cognitive impairments relative to other phenotypes.

7.1 Method

7.1.1 Participants

Overall, 156 people participated in the current study; this comprises the entire patient sample outlined in Study Two (Chapter 6), excluding one TLE patient with one previous episode of postictal psychosis. Of the 84 patients in Study Three, 62 (74%) were deemed to have seizures arising from the temporal lobe (47% left hemisphere, 56% lesion positive), and 22 (26%) from either the frontal or parietal lobe (27% left hemisphere, 72% lesion positive). Epileptological and demographic features of the group are summarised in Table 7.1.

All 72 healthy controls detailed in Study Two participated in this study. Patients with focal epilepsy did not differ from healthy controls in sex, age, or years of education (P > .05; see Table 7.1). The control sample had a slightly higher mean FSIQ than the patient group [t(142) = -2.75, P < .05, η² = .05, small-moderate effect size]; however mean scores for both groups fell within the “Average” range of intelligence (Wechsler, 2001).
Table 7.1. Demographic and clinical profile of the sample (N=156)

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy Patients (n=84)</th>
<th>Healthy Controls (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), ( M \pm SD )</strong></td>
<td>41.14 ± 12.92</td>
<td>44.93 ± 15.48</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>20-69</td>
<td>21-69</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>51 (61%)</td>
<td>44 (61%)</td>
</tr>
<tr>
<td><strong>Education (years), ( M \pm SD )</strong></td>
<td>13.59 ± 3.27</td>
<td>14.00 ± 3.28</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>5-24</td>
<td>9-21</td>
</tr>
<tr>
<td><strong>Full-Scale IQ, ( M \pm SD )</strong></td>
<td>101.61 ± 11.49(^a)</td>
<td>107.08 ± 12.28(^b^*)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>72-132</td>
<td>71-132</td>
</tr>
<tr>
<td><strong>Handedness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right (%)</td>
<td>79 (94%)(^c)</td>
<td>62 (87%)(^d)</td>
</tr>
<tr>
<td><strong>Age of seizure onset (years), ( M \pm SD )</strong></td>
<td>22.37 ± 13.63</td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>1.5 – 63.0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Duration of epilepsy (years), ( M \pm SD )</strong></td>
<td>19.07 ± 13.16</td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>2 - 52</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Monthly average seizure frequency, ( M \pm SD )</strong></td>
<td>22.40 ± 52.28</td>
<td></td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>1 - 400</td>
<td></td>
</tr>
<tr>
<td>( \leq 1/\text{month} )</td>
<td>20 (24%)</td>
<td></td>
</tr>
<tr>
<td>Fortnightly (2-3/month)</td>
<td>13 (16%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Weekly (4-15 month)</td>
<td>32 (38%)</td>
<td></td>
</tr>
<tr>
<td>Daily (( \geq 16/\text{month} ))</td>
<td>19 (23%)</td>
<td></td>
</tr>
<tr>
<td><strong>Side of epilepsy focus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left (%)</td>
<td>35 (42%)</td>
<td></td>
</tr>
<tr>
<td>Right (%)</td>
<td>40 (48%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bilateral/Unclear (%)</td>
<td>9 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Lobar focus, Temporal (%)</strong></td>
<td>62 (74%)</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>51 (61%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Anti-epileptic drug monotherapy</strong></td>
<td>19 (23%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^a\)= four cases of missing data; \(^b\)= eight cases of missing data; \(^c\)= two cases of missing data; \(^d\)= one case of missing data

*= P<.05

7.1.2 Materials

In addition to the materials outlined in Study One (Chapter 5), the current study also employed the Epilepsy Surgery Inventory, 55-item (ESI-55; Vickery et al., 1992) as a measure of health-related quality of life in the patient group. It was specifically designed for patients with medically refractory focal epilepsy to assess outcome after epilepsy surgery, and takes approximately 15 minutes to complete. The ESI-55 includes the
following scales: health perceptions, energy/fatigue, overall quality of life, social function, emotional well-being, cognitive function, physical function, and pain, as well as three separate scales of role limitations due to emotional, physical, or memory problems. Findings by Vickery et al. (1992) indicate that the ESI-55 is reliable, valid, and sensitive to differences in seizure status, and since its development it has been widely used as a quality of life measure in this population.

The Family Adaptability and Cohesion Scale (FACES-IV; Olson, 2011) is the latest version of a brief (10-15 minutes) self-report assessment of family functioning focusing on family cohesion, flexibility, and communication, as well as how happy family members are with their family system. The FACES IV questionnaire consists of 84 items across six scales; two ‘that measure ‘balanced’ or healthy dynamics, and four ‘unbalanced’ scales designed to tap low and high cohesion (disengaged and enmeshed) and flexibility (rigid and chaotic). Participants were required to respond to questions assessing each of the domains on a six point Likert scale. The FACES-IV was used to measure to gauge patient satisfaction with their family dynamics and functioning.

7.1.3 Statistical analyses

Analyses were performed using IBM SPSS Statistics 22.0, with the statistical significance criterion set at P < .05 (two-tailed). Where data did not meet assumptions for parametric analyses, more conservative non-parametric alternatives were employed (Tabachnick & Fidell, 2007).

To test the hypothesis that there would be two distinct subgroups of current depressive symptomology in depressed patients with epilepsy reflecting either cognitive network dysfunction or somatic network dysfunction, cluster analysis was used to measure endorsed symptom association in order to classify depressive symptoms into clusters. The nine items describing different depressive symptoms on the SCID were selected as the indicator variables. A two-step Ward Method cluster analysis was used, with squared Euclidian distances as the similarity measure. A two-cluster solution was selected a priori in line with the results of community studies and the medical literature identifying two clusters of depressive symptoms (Marijnissen et al., 2007). Each cluster then represents a homogeneous group of patients who share similar responses to the model parameters (i.e., the SCID symptoms).
To test the hypothesis that these clusters would differ in terms of their epileptological, psychosocial, and psychological features, typical of a true phenotype, covariates associated with cluster membership in bivariate descriptive analyses were used to compare the two clusters, or where power was too low, inspected frequency trends across groups. Chi-squared analyses employed a conservative Continuity Correction with Fisher’s Exact Test.

7.2 Results

The neuropsychological and psychiatric functioning of the overall cohort was described in Study Two (see Chapter 6). In brief, epilepsy patients performed significantly worse on measures of both semantic and episodic autobiographic memory (P < .001) as well as auditory-verbal and visual recall (P < .01), and had substantially higher rates of depressive symptoms (P < .001). Commensurate with this, psychiatric evaluation in the current study revealed that 35 (42%) epilepsy patients met DSM-IV criteria for a lifetime history of unipolar Depressive Disorder. Moreover, 21 (25%) currently met criteria for a Major Depressive Disorder or Depressive Disorder Not Otherwise Specified. This is appreciably higher than the global point prevalence for Depressive Disorder of 4.7% (95% CI = 4.4-5.0%) recently reported by Ferrari et al (2013).

7.2.1 Two subtypes of depression in epilepsy

Cluster analysis revealed the presence of two distinct subtypes of depression amongst the 21 currently depressed patients with epilepsy (see Table 7.2). Patients in the first cluster, labelled ‘Cognitive Depression’ (n=15), were characterised by high rates of metacognitive symptoms such as parasuicidal or suicidal thoughts, and feelings of worthlessness and guilt ($\chi^2(1) = 2.79$, Fisher’s Exact P = .05). They were also more likely to experience dysphoric mood compared to patients in the other cluster ($\chi^2(1) = 2.79$, Fisher’s Exact P = .05), and endorsed low rates of somatic symptoms and anhedonia. In contrast, the second cluster, named ‘Somatic Depression’ (n=6), were significantly more likely than the Cognitive Depression patients to feel anhedonic ($\chi^2(1) = 6.56$, Fisher’s Exact P = .006). They also endorsed significantly higher rates of biological symptoms such as appetite change ($\chi^2(1) = 6.53$, Fisher’s Exact P = .004), and sleep disturbance ($\chi^2(1) = 6.56$, Fisher’s Exact P = .006), and were less likely to endorse cognitive symptoms (P > .05). The two subtypes endorsed similarly high rates of excessive fatigue and subjective
cognitive difficulties (P > .05). Of note, this fatigue and disturbed subjective cognition was not attributed to the primary effect of seizures or anticonvulsant medication.

Table 7.2. Cluster analysis of DSM-IV symptoms reveals two profiles of current depression in epilepsy

<table>
<thead>
<tr>
<th>DSM-IV Symptoms of Depression</th>
<th>Depression Subtype</th>
</tr>
</thead>
</table>
|                               | Cognitive  
|                               | (n = 15)          |
|                               | Somatic  
|                               | (n = 6)          |
| Affective Symptoms            | Dysphoria          | 93% ^           |
|                               | Anhedonia          | 13%             |
| Somatic Symptoms              | Appetite Change    | 27%             |
|                               | Sleep Change       | 13%             |
|                               | Psychomotor Agitation | 13%         |
|                               | Fatigue            | 60%             |
| Cognitive Symptoms            | Worthlessness & Guilt | 93% ^        |
|                               | Subjective Cognitive Difficulties | 87% |
|                               | Suicidality        | 67%             |

^P=.05 (i.e., trend); **P<.01

7.2.2 Correlates of Cognitive versus Somatic subtypes of depression in epilepsy

7.2.2.1 Cognitive features

The Cognitive phenotype of depression was characterised by poor memory function (see Table 7.3 & Figure 7.1). Relative to healthy controls, patients in this cluster exhibited significantly reduced autobiographic memory across all life periods, including childhood episodic recall, early adulthood semantic and episodic recall, recent life semantic and episodic recall, as well as significantly worse overall semantic and episodic recollection. There was also a trend for worse childhood semantic memory. In addition, patients with the Cognitive subtype showed significantly reduced delayed recall across both auditory-verbal and visual domains of memory. In contrast, patients with Somatic Depression
showed a more muted and restricted profile of reduced memory, with poorer performances than controls only in childhood episodic, early adulthood semantic, overall episodic, and delayed visual recall (see Table 7.3).

Table 7.3. Cognitive profile of Cognitive vs Somatic subtype of depression relative to controls

<table>
<thead>
<tr>
<th></th>
<th>Cognitive Depression n = 15</th>
<th>Healthy Controls n = 60a</th>
<th>Somatic Depression n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood semantic AM, M±SD</td>
<td>17.17 ± 3.18 P=.05</td>
<td>18.68 ± 2.63</td>
<td>18.00 ± 1.38 p=.56</td>
</tr>
<tr>
<td></td>
<td>trend</td>
<td></td>
<td>n.s</td>
</tr>
<tr>
<td>Childhood episodic AM, M±SD</td>
<td>5.73 ± 1.98** P=.008</td>
<td>7.20 ± 1.72</td>
<td>4.83 ± 2.79** P=.004</td>
</tr>
<tr>
<td></td>
<td>d=.79; large ES</td>
<td></td>
<td>d=1.02; large ES</td>
</tr>
<tr>
<td>Early adult semantic AM, M±SD</td>
<td>17.60 ± 2.23** P=.001</td>
<td>20.17 ± 1.04</td>
<td>18.25 ± 1.41* P=.019</td>
</tr>
<tr>
<td></td>
<td>d=1.48; v. large ES</td>
<td></td>
<td>d=1.54; v. large ES</td>
</tr>
<tr>
<td>Early adult episodic AM, M±SD</td>
<td>5.60 ± 2.29* P=.017</td>
<td>7.27 ± 18.56</td>
<td>5.00 ± 3.23 P=.15</td>
</tr>
<tr>
<td></td>
<td>d=.12; small ES</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Recent life semantic AM, M±SD</td>
<td>18.27 ± 1.91* P=.012</td>
<td>19.45 ± 1.57</td>
<td>18.17 ± .75 P=.68</td>
</tr>
<tr>
<td></td>
<td>d=.67; medium ES</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Recent life episodic AM, M±SD</td>
<td>5.20 ± 1.97*** P&lt;.001</td>
<td>7.18 ± 1.86</td>
<td>6.17 ± 2.04 P=.21</td>
</tr>
<tr>
<td></td>
<td>d=1.03; large ES</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall semantic AM, M±SD</td>
<td>52.83 ± 6.72*** P&lt;.001</td>
<td>58.28 ± 3.96</td>
<td>55.42 ± 2.38 P=.14</td>
</tr>
<tr>
<td></td>
<td>d=0.98; large ES</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall episodic AM, M±SD</td>
<td>16.53 ± 4.92** P=.001</td>
<td>21.65 ± 4.69</td>
<td>16.00 ± 7.56* P=.01</td>
</tr>
<tr>
<td></td>
<td>d=1.07; large ES</td>
<td></td>
<td>d=.89; large ES</td>
</tr>
<tr>
<td>Verbal Paired Associates, M±SD</td>
<td>7.30 ± 3.53* P=.039</td>
<td>10 ± 3</td>
<td>9.00 ± 2.45 P=.41</td>
</tr>
<tr>
<td>(delayed recall)</td>
<td>d=.82; large ES</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Design Memory, M ± SD</td>
<td>7.70 ± 1.64** P=.002</td>
<td>10 ± 3</td>
<td>8.40 ± 1.14* P=.035</td>
</tr>
<tr>
<td>(delayed recall)</td>
<td>d=.95; large ES</td>
<td></td>
<td>d=.71; medium ES</td>
</tr>
</tbody>
</table>

N.B. immediate recall and working memory indices from WMS-IV not reported here as they did not differentiate the Cognitive versus Somatic profile (P>.05); *P<.05; **P<.01; ***P<.001; a = 12 missing cases; AM = autobiographic memory; d= Cohen’s d; SD= standard deviation; ES = effect size; M=mean
Figure 7.1. Reduced neuropsychological functioning of the two depression phenotypes relative to a baseline of normal task performance provided by the control group (z score = 0). Patients with the Cognitive phenotype perform worse than those with Somatic depression across nearly all cognitive domains. Somatic patients, however, endorse elevated symptoms of anxiety.

7.2.2.2 Psychosocial and demographic features

Inspection of group trends suggested that depressed patients with the Somatic phenotype were more likely to be female (84%) than was seen in the Cognitive subtype (47%; see Table 7.4). Epileptologically, patients with a Somatic phenotype had more frequent seizures than the Cognitive phenotype (49 per month, versus 13) with greater variability in their seizure frequency. Psychosocially, individuals with the Somatic phenotype reported lower levels of family satisfaction than patients with the Cognitive phenotype, and endorsed higher symptoms of anxiety.

The Cognitive subtype was somewhat more likely to have a longer duration of epilepsy than the Somatic subtype (18 years versus 13). They also endorsed subtly lower epilepsy-related quality of life. Otherwise, patients with Somatic and Cognitive subtypes of depression were comparable in terms of age, seizure focus, and FSIQ, with no differences between the two subtypes in their severity of self-reported depressive symptoms. Of concern, only five patients (33%) with Cognitive Depression were being actively treated with psychotropic medication, however their symptoms were better recognised than the Somatic Depression phenotype, none of whom were being treated psychologically or pharmacologically for depression. This is broadly consistent with the results of a recent city-wide psychiatric evaluation of people with epilepsy, which found
only 29.7% of depressed patients were receiving psychological or psychotropic treatment (Fiest et al., 2014).

Table 7.4. Demographic & psychosocial profile of Cognitive vs Somatic subtypes of depression

<table>
<thead>
<tr>
<th></th>
<th>Cognitive Depression</th>
<th>Somatic Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), M ± SD</strong></td>
<td>38.47 ± 11.76</td>
<td>34.33 ± 7.53</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>23 – 57</td>
<td>27 – 42</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>7 (47%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td><strong>Relationship status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single (%)</td>
<td>6 (40%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td><strong>Full-Scale IQ, M ± SD</strong></td>
<td>98.71 ± 9.45</td>
<td>97.75 ± 9.18</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>92 – 113</td>
<td>84 - 103</td>
</tr>
<tr>
<td><strong>Age of seizure onset (years), M ± SD</strong></td>
<td>20.73 ± 11.56</td>
<td>21.25 ± 14.40</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>8 – 41</td>
<td>9 - 37</td>
</tr>
<tr>
<td><strong>Duration of epilepsy (years), M ± SD</strong></td>
<td>17.53 ± 10.5</td>
<td>12.92 ± 13.29</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>6 – 41</td>
<td>2 - 18</td>
</tr>
<tr>
<td><strong>Monthly seizure frequency, M ± SD</strong></td>
<td>12.50 ± 20.8</td>
<td>48.5 ± 76.6</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>1 – 75</td>
<td>1 - 200</td>
</tr>
<tr>
<td><strong>Lobar focus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal (%)</td>
<td>11 (73%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td><strong>Side of epilepsy focus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left (%)</td>
<td>10 (67%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Right (%)</td>
<td>4 (27%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Bilateral/Unclear (%)</td>
<td>1 (7%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>NDDI-E score, M ± SD</strong></td>
<td>15.92 ± 2.91</td>
<td>14.25 ± 4.99</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>12 – 20</td>
<td>9 - 19</td>
</tr>
<tr>
<td><strong>PHQ-GAD-7 score, M ± SD</strong></td>
<td>8.83 ± 5.73</td>
<td>11 ± 5.72</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>1 – 18</td>
<td>6 - 19</td>
</tr>
<tr>
<td><strong>ESI-55 overall QOL, M ± SD</strong></td>
<td>45.00 ± 13.37</td>
<td>53.00 ± 16.14</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>25 – 75</td>
<td>50 – 77.5</td>
</tr>
<tr>
<td><strong>Psychotropic medication</strong></td>
<td>Yes (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (33%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>FACES-IV family satisfaction, M ± SD</strong></td>
<td>59.29 ± 22.11</td>
<td>38.80 ± 27.85</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>13 – 92</td>
<td>10 - 71</td>
</tr>
</tbody>
</table>
7.3 Discussion

In the first data-driven attempt to develop a typology of depressive disorder in a neurological population, phenotyping revealed two clinically-distinct, symptom-based subtypes of the condition in people with focal epilepsy. The first, Cognitive Depression, was a more frequently occurring subtype characterised by cognitive symptoms of depression, dysphoria, and prominent memory deficits. The second, Somatic Depression, was a less common subtype typified by somatic or vegetative features, anhedonia, elevated anxiety, frequent seizures, and unsatisfactory family dynamics. The ubiquity of subjective cognitive difficulties and excessive fatigue across the two subtypes also suggests some homogeneity in the presentation of depression in epilepsy. This typology provides insights into the neurocognitive network basis of depression in epilepsy, and has immediate clinical relevance in the form of a clear description of how depression presents in the busy neurology clinic.

7.3.1 Unique profiles of network disruption

Psychiatry has long used phenotyping of presenting symptoms to systematically classify mental disorders, first to validate observational diagnoses, and more recently to infer common neurobiological mechanisms (Aktas et al., 2010; Hickman et al., 2013). In the current study, cognitive and somatic phenotypes potentially provide differential markers of brain network dysregulation.

7.3.1.1 Cognitive phenotype networks

Distorted self-related cognitive processing and memory disturbance common to the Cognitive subtype has been shown to reflect dysregulation of the AMN and CCN. In brief, the CCN is important for goal-directed behaviour, while the antipodal AMN is considered central to self-reflection through personal life memories (Sheline et al., 2010). Neuroimaging suggests that both networks function abnormally in focal epilepsy (Levine et al., 2004; Zhang et al., 2009). In unipolar depression, the AMN becomes chronically hyperactivated, leading to pathologically introspective brooding and rumination. It also suppresses the CCN, leading to diminished performances on externally-focused tasks (see Chapter 3). This pattern of distorted self-related processing and reduced cognitive function is entirely consistent with the presentation of the Cognitive phenotype described
here (see Figure 7.2), and may implicate similarly altered regulation of the CCN and AMN. The lack of a clear correlation between seizure severity and Cognitive depression discounts a secondary effect of seizures on behaviour, instead implying that a common network disease may underpin the depressive symptoms, seizures, and memory impairments seen in this phenotype (Berg et al., 2011; Wilson & Baxendale, 2014).

**Figure 7.2.** Symptom profiles of the two phenotypes of depression in epilepsy, together with their psychosocial and cognitive correlates and putative underlying networks

### 7.3.1.2 Somatic phenotype networks

In contrast, the Somatic profile of depression in epilepsy appears to index dysregulation of subnetworks that support emotional processing and visceral monitoring, together referred to as the AN (Ochsner & Gross, 2005). The interconnected cortico-subcortical regions of the AN support appetite, libido, sleep, reward processing and vigilance, disturbance to which underpins the vegetative and anhedonic symptoms of depression that are predominant in the Somatic phenotype (Sheline et al., 2010; Ochsner & Gross, 2005). Although speculative, the link between the Somatic profile and more frequent seizures may reflect involvement of the piriform component of the AN (see Figure 7.3). The piriform cortex is highly epileptogenic and a key region in hedonic processing (Vaughan & Jackson, under review; see Stone et al., 2006 for a review). It lies at the junction of the temporal and frontal lobes, and it is contiguous with structures
fundamental to emotion and memory: namely, the amygdaloid nuclei and perirhinal/entorhinal cortices (Vaughan & Jackson, under review).

Figure 7.3. The “piriform axis”. T1-weighted image of a 37 year old man, displayed in a (a) parasagittal and (b) oblique-axial orientation, approximately +20° relative to the anterior commissure-posterior commissure axis. This orientation allows the relationship between the piriform cortex (Pir), amygdala (Am) and hippocampus (Hip) to be seen. The arrow indicates the position of the middle cerebral artery (MCA) within the endorhinal sulcus. (Source: Vaughan & Jackson, 2014)

7.3.2 Cognitive & Somatic phenotypes of depression in other populations

The delineation of Cognitive and Somatic phenotypes supports the view that depression in epilepsy is not a homogeneous condition with a canonical presentation (Blumer et al., 2004; Kanner et al., 2012, Rayner & Wilson, 2012). However, the phenotypes emerging from the current study are not unique to epilepsy. For instance, Haslam and Beck (1993) categorised the depressive symptoms of 400 outpatients with major depression. Of the four syndromal subtypes to emerge, one had prominent anhedonic and vegetative symptoms (c.f., Somatic phenotype), while another had a marked lack of vegetative features but prominent self-critical cognitions (c.f., Cognitive phenotype). Data-driven subtyping of depressive symptoms in community and medical samples also discloses phenotypes with predominantly somatic or cognitive features (Blazer et al., 1988; Marijnissen et al., 2011; Stewart et al., 2012; see Section 2.4.1). This convergence of findings across psychiatric, community, and other medical populations underscores the robustness of the Somatic and Cognitive profiles as phenotypes of depressive disorder.

What is unique about these phenotypes in epilepsy, however, is their relative frequency. Inversely to what is seen in psychiatric studies, the Somatic subtype was uncommon. Instead, the higher frequency of the Cognitive phenotype in individuals with
epilepsy may suggest that disease in the CCN and AMN neurocognitive networks could be the commonest cause of depressive symptoms in epilepsy. Again, this supports the long-held idea that depression in epilepsy presents differently from primary psychiatric patients (Blumer et al., 2004), and implicates the AMN and CCN as viable targets for future research seeking to understand the pathophysiology of depression. Although speculative, the involvement of the AMN and CCN may suggest that there is something about these two anti-correlated networks that is more epileptogenic than other brain networks.

7.3.3 Clinical implications

Classification remains the primary goal of psychopathology, so that clinical features that reliably cluster together might more precisely predict the prognosis and treatment response of individuals (Haslam & Beck, 1993; Aktas et al., 2010). In other populations, Cognitive and Somatic subtypes of depression confer a differential vulnerability to negative health outcomes. In particular, Somatic phenotypes are more cardiotoxic (Stewart et al., 2007; Stewart et al., 2009), and relate to sensitive measures of visceral obesity and cardiovascular risk (Marijnissen et al, 2011). This raises the possibility that epilepsy patients with different phenotypes of depression may be at differential risk of long-term negative health outcomes in addition to those conferred by their seizures. This is particularly concerning, given that in this sample mood disorders were often untreated prior to inpatient monitoring. This hypothesis, however, requires substantiation with more extensive research.

The ubiquity of subjective memory complaints across the two phenotypes of depression may hold more immediate clinical utility. Rather than a veridical assessment of current cognitive ability, this characteristic feature of the depressed cohort may be better viewed as a sensitive marker of mood disturbance in epilepsy. This is commensurate with the finding that bitter memory complaints offered by people with epilepsy are reliably linked to symptoms of depression and anxiety (Giovagnoli et al., 1997; Au et al., 2006; Rayner et al., 2010). As in our Cognitive depression patients, however, subgroups within the epilepsy population (such as patients with a mesial temporal lobe focus) may report cognitive difficulties that are verified by empirical testing (Rayner et al., 2010), supporting the notion that subjective memory complaints
are the product of a complex interaction of mood disturbance and objective memory deficits. It remains useful, therefore, for clinicians to view these complaints as potential markers of psychiatric or neuropsychological disturbance that warrant further assessment.

Despite increasing recognition of the significance of depression in epilepsy (Kanner et al., 2012), the paucity of epilepsy patients being treated for depression indicates that management of the disorder in the context of the busy neurology clinic may require a shift in thinking (Fiest et al., 2014). While subjective memory complaints might provide a “quick and dirty” impetus for further questioning around a patient’s mood, recognition of symptom subtypes might also improve diagnosis and treatment. In particular, the Somatic phenotype is characterised by symptoms that overlap with the side-effects of seizures and anticonvulsant use, potentially leading to an incorrect attribution of (for example) appetite loss to medication rather than depression. Recognition that the features of depression in epilepsy can mimic the cognitive or vegetative correlates of seizures and anticonvulsant medications may serve as a prompt for more detailed questioning around the emergence of cardinal diagnostic symptoms such as anhedonia and dysphoria. Moreover, lack of a proconvulsant effect in newer generation antidepressant medications should reassure clinicians as to their safety in people with epilepsy (Johannessen-Landmark et al., 2014).

7.3.4 Future directions

The current study is an initial description of the phenotypes of depression in individuals with epilepsy, and raises interesting questions for future research. The small sample size of the Somatic phenotype reflects that it was an uncommon presentation, but which needs validation in a larger sample, in addition to investigation the presence of other phenotypes not revealed in the current sample. It would also be of interest to investigate whether these subtypes exist in other neurological populations with high rates of depression, such as stroke, which might suggest a common mechanism underlying behavioural disturbances across superficially diverse neurological diseases.

To date, symptomatic diversity has likely hindered the progress of research into the causal mechanisms and treatment of patients with both depression and epilepsy. To rectify this, the functioning of different neurocognitive and affective brain networks in the context of depression and epilepsy could be investigated using task-based functioning
neuroimaging paradigms in patients with different subtypes of depressive disorder relative to euthymic patients and controls. Confirmation of their role would give more nuanced insights into what anatomical, neurochemical, and functional systems could be targeted by pharmacotherapy or psychotherapy. For instance, dampening of CCN activation in unipolar depression has been shown to dysregulate the mesostriatal dopamine system (Hamilton et al., 2011), potentially providing insights into region-specific neurotransmitter systems that may be targeted by future medical treatments.

Another priority for future investigation is whether there are differential health outcomes conferred by different phenotypes of depression in epilepsy. Given the conceptualisation of depression, seizures, and memory impairment as symptoms of a common underlying disease of neurocognitive networks, exploration is warranted regarding whether treatment – prophylactic or otherwise – of depressive symptoms could protect patients from negative health prognoses such as cognitive decline or worsening seizures.

7.3.5 Study Three conclusions

The ultimate goal of neurology might be to cure a disorder, but a critical first step is increasing the precision of diagnosis. The significance of the current study is the delineation of phenotypes for depression in epilepsy that are observed in other populations. The typology is strengthened by its interpretability, through its provision of evidence for what is clinically known: that there are meaningful differences in the presentation of people with epilepsy who are given the categorical diagnosis of depression. The results of the current study highlight the value of data-driven phenotyping to refine diagnoses of behavioural syndromes in neurological populations. In the immediate future, these typologies will hopefully improve the recognition and management of depression in the busy neurology clinic. Looking forward, it is anticipated that meaningful phenotypes can give clearer insights into the pathogenesis of depression in epilepsy and ultimately, guide the development of individually-tailored treatments.
Chapter 8. General Discussion

This thesis is a collection of prospective behavioural studies delineating the correlates of autobiographic memory impairment in focal epilepsy, including its links to depression. Study One suggests that FLE can selectively disrupt brain networks important for autobiographic memory and mood. Study Two showed that the predictors of autobiographic memory network dysfunction differ between patients with early onset and late onset epilepsy: poor autobiographic memory was linked to disease chronicity and reduced working memory in patients with seizures during the critical neurodevelopmental phase of childhood/adolescence, while impoverished recall in late onset epilepsy was largely related to depressive symptoms. The final study disclosed a binary taxonomy of depression in epilepsy, comprising a frequent Cognitive phenotype characterised by reduced autobiographic memory and distorted cognitive processing, and a less common Somatic subtype distinguished by anhedonia, sleep and appetite changes, anxiety, and frequent seizures.

Together, the findings indicate that poor autobiographic memory function in epilepsy is multidetermined, encompassing different epileptological, cognitive, psychiatric, and neurodevelopmental factors in different individuals (see Figure 8.1). Contrary to the ubiquity of autobiographic memory impairments in depressed patients from psychiatric cohorts, the current study revealed that disruption to autobiographic memory networks only contributes to depression in certain epilepsy syndromes (i.e., late onset epilepsy, Cognitive depression). Mood and memory are otherwise dissociable. Moreover, syndromes that show links between autobiographic memory and depressive symptoms in epilepsy are not strongly associated with markers of chronic or severe disease, discounting the hypothesis that seizure-related disruption to cognitive networks leads to depression in epilepsy.
The current thesis highlights the usefulness of epilepsy as a model of network disease. In particular, given that it typically alters the functioning and healthy development of neurocognitive networks without destroying the underlying anatomical substrate, epilepsy allows researchers to more precisely study the role of discrete, overlapping, or widely distributed brain networks that support cognition and other behavioural functions.

8.1 Extension of the neurocognitive network model of depression to focal epilepsy

Despite ongoing debate regarding the differential presentations of mood disturbance in people with epilepsy (Mula, 2014), there has been no integration of depressive symptomology with other indices of brain function and subsequently, no systems-level model of depression in epilepsy. With some adaptation, the neurocognitive model of depression to emerge in Chapter 3 seems commensurate with network disease, i.e., focal epilepsy. In particular, behavioural indicators of AMN, CCN, and AN disruption...
idiosyncratic to two subtypes of depressive disorder suggest that the symptoms of depression in epilepsy are underpinned by the same dysregulation of neurocognitive networks implicated in depression more broadly. Depression in epilepsy, however, requires a more nuanced neurocognitive model than that described for unipolar depression in Chapter 3: namely, different profiles of depressive symptoms index altered functioning in different brain networks. This may not be unique to epilepsy; future behavioural studies or functional neuroimaging in phenotypes of unipolar depression may well reveal a similar story.

Altered functioning of neurocognitive networks in depression has been attributed to the release of inflammatory cytokines during injury, illness, or psychological stress, causing dysregulation of synaptic plasticity in neural pathways implicated in depression (Piser, 2010). Possible extensions to epilepsy are clear. The release of inflammatory cytokines in response to epileptiform discharges (see Section 4.2.4.3.2) is associated with altered neuronal plasticity at the site of the seizure focus, potentially leading to maladaptive connectivity within proximal neurocognitive networks (Korczyn et al., 2013). A fundamental task in establishing the role of cognitive networks in the pathogenesis of depression in epilepsy will be to carefully ascertain in vivo how relationships between mood and neurocognitive networks change with the introduction of network disease. This includes examination of whether changes to mood-related neurocognitive networks precede the onset of seizures (i.e., a primary mechanism), and whether network dysfunction can be a secondary effect of the seizures.

### 8.2 Primary effects of epilepsy on cognition and behaviour

*Or “Cognitive reframing for epilepsy researchers”*

An unexpected finding in the current thesis was that depressive symptoms and disorder were not strongly associated with markers of seizure severity or chronicity. This fails to support the assumption that more frequent and severe seizure-related activity would damage the cognitive networks and lead to depressive symptoms. There is some evidence for the first part of this assumption, notably the link between autobiographic memory impairments and seizure chronicity in early onset epilepsy, however there was no evidence that this increases the risk of mood disturbance. An alternative interpretation is that autobiographic memory impairment, depressive symptoms, and seizures can arise
independently from the effects of underlying network disease (i.e., epilepsy), with some secondary interaction effects (see Figure 8.2). According to this model, the network disease (epilepsy) can entrain and alter unique cognitive and affective networks in the individual, giving rise to dissociable neuropsychological and behavioural syndromes as well as seizures.

Figure 8.2. Primary effects of epilepsy disease on cognition and mood versus the secondary effects of seizures on behavioural phenomenon.

The model illustrated by Figure 8.2 supports the growing notion that the epilepsies may involve the abnormal synergistic engagement of large-scale cognitive networks, leading to the cognitive deficits commonly seen in patients, as well as in relatives without seizures (Berkovic & Jackson, 2014). This stems from work by Berg (2011) as well as Wilson and Baxendale (2014), who assert that the behavioural features commonly associated with focal epilepsy may be primary manifestations of the disease, rather than secondary “comorbidities” resulting from the effects of seizures, overt pathology, or antiepileptic medication. In this model, seizures and behavioural disturbances are dissociable phenomenon arising from a single disease (epilepsy). While the cardinal feature of epilepsy remains the physiological occurrence of seizures, the impact of the disease on overlapping neurocognitive networks should not be discounted, and may explain why in some patients cognitive or behavioural disturbances are more severe and debilitating than the seizures. It also accounts for a growing body of evidence suggesting
that cognitive and behavioural symptoms can first emerge before the onset of seizures (Pulliainen et al., 2000; Taylor et al., 2010) thereby providing a subtle but independent marker of network disease.

Consideration that behavioural disorders may be a fundamental outworking of network disease in epilepsy heralds a paradigm shift towards a deeper understanding of the disease based on molecular biology. As outlined at the end of Chapter 3, ultimately this will involve revisiting the epilepsy classification system to include new knowledge on how the signs and symptoms of different epilepsy phenotypes are tied to intrinsic neurobiological mechanisms, such as neurocognitive networks (Mirnezami et al., 2012).

### 8.3 Phenotyping in epilepsy

The current thesis illustrates the clinical and research value in grouping individuals with focal epilepsy according to behavioural features that co-occur with high frequency. In particular, it highlights that diverse factors can underpin the same outcome (here, impoverished autobiographic memory) in patients with differing presenting features. The validity of the phenotypes described herein will ultimately be confirmed or disproven through the identification of idiosyncratic biological markers at the network, cellular, or genetic level (O’Brien, 2000). For instance, a recent paper by Busch et al (2014) noted that genetic anomalies underlie many epilepsy syndromes with phenotypic patterns of cognitive impairment, which will likely be polygenic. Using neuropsychological profiling in this way enriches our understanding of differing epilepsy syndromes by linking observable patterns of cognitive or behavioural impairment to underlying genetic or structural-metabolic mechanisms. This broadly analogous to what has been successfully achieved medically with the ILAE’s overhaul of the epilepsy classification system described in Chapter 4.

The validity of the current phenotypes will also be tested by their ability to predict meaningful patient outcomes in a sensitive and specific manner. This encompasses neurological outcomes such as seizure intractability, suitability for certain medications, and the likelihood of seizure freedom after epilepsy surgery, as well as neuropsychological outcomes such as cognitive decline or vulnerability to psychiatric illness. This, in turn, would allow complications and impairments to be anticipated and proactively treated in an early stage of the disease and in a more targeted manner. Inherent
in this idea is that behavioural phenotypes and their outcomes are not immutable, nihilistic concepts; rather, the clinical picture can be changed through the use of intervention strategies likely developed through interdisciplinary collaborations.

**8.4 Directions for future research**

The findings from each of the studies in the current thesis gave rise to numerous suggestions for future research. Detailed suggestions have already been outlined in the preceding chapters, and are included here in summary form:

- Use of phenotyping methodology in epilepsy research, to improve precision in how patients are grouped in behavioural, genetic, or neuroimaging studies. This should help prevent the effects of smaller subgroups of individuals from being “washed out” in larger samples
- Development of task based fMRI paradigms to assess the functioning of the AMN, CCN, and AN in vivo, in patients with differing phenotypes of epilepsy relative to healthy controls
  - Patterns of de/activation related to out-of-scanner cognitive phenotypes
  - Longitudinal studies to assess whether improved or prophylactic treatment of depression in epilepsy is associated with normalisation of neuroimaging patterns and cognitive functioning
- Longitudinal studies investigating the differential medical, psychological, and cognitive outcomes conferred by various phenotypes in epilepsy
- Longitudinal studies to assess whether improved or prophylactic treatment of depression in epilepsy is associated with improved cognitive and medical outcomes
- Identification, development, and randomised control trial-validation of next-generation psychological and pharmacological treatments that target the abnormal brain systems implicated by different phenotypes of epilepsy
  - e.g., neuropsychological therapies for Cognitive depression that aim to improve autobiographical recall (or medications to normalise AMN function), to enable more effective engagement in traditional cognitive behavioural therapies
In sum, longitudinal, multidisciplinary programmes of behavioural and neuroimaging research could verify the neurobiological hypotheses raised by the current thesis, as well as better understand the prognostic indicators and optimal treatment allocations embedded in various phenotypes or subgroupings of focal epilepsy.

8.5 Conclusion

At first glance, it may seem somewhat capricious that some people living with focal epilepsy consider the cognitive and mood disorders that commonly accompany their disease to be more significant than the rather more dramatic problem of seizures. Recognising the behavioural heterogeneity in patients with seizures, however, reveals interesting and clinically recognisable subgroups that index involvement of different neurobiological systems and developmental mechanisms. This individual-centred approach closely aligns with current goal in medical science for ‘precision medicine’, which strives to predict and prevent negative health outcomes by tailoring patient treatments to an individual’s unique presentation. This approach relies on a holistic view of illness that links the behavioural phenomena accompanying epilepsy to their underlying neurobiological mechanisms. This approach, embodied in the current thesis, holds the promise of discovering innovative ways of treating depression and memory disturbance in people with epilepsy, and ultimately improving their quality of life.
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Appendices

Appendix Table A. Symptoms defining somatic and cognitive subtypes of depression across studies

Appendix Table B. Overview of the 43 studies sourced from literature search

Appendix A: Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient edition, mood module

Appendix B: Neurological Disorders Depression Inventory for Epilepsy

Appendix C: Patient Health Questionnaire – Generalised Anxiety Disorder, 7-item

Appendix D: Autobiographic Memory Interview

Appendix E: Wechsler Memory Scale, 4th edition

Appendix F. Case vignettes of patient cognition & mood from Study One

12 First two pages only displayed for copyright reasons
<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Somatic Subtypes</th>
<th>Cognitive Subtypes</th>
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<tbody>
<tr>
<td>Blazer et al. (1988)</td>
<td>406 community-based adults endorsing depressive symptoms</td>
<td>Prominent vegetative features</td>
<td>Psychometric cognitive difficulties, dysthymia</td>
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<tr>
<td>de Jonge et al (2007)</td>
<td>863 outpatients with stable coronary heart disease</td>
<td>Sleeping problems, fatigue, appetite problems, psychomotor agitation/retardation</td>
<td>Anhedonia, depressed mood, negative feelings about self, concentration problems, suicidal ideation</td>
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<tr>
<td>Stewart et al (2007)</td>
<td>324 older community-based adults</td>
<td>Anhedonia, fatigue, sleep/appetite disturbance, loss of energy, irritability, agitation, loss of interest in sex</td>
<td>Sadness, pessimism, indecisiveness, past failure, worthlessness, self-dislike, guilt, suicidality, punishment feelings</td>
</tr>
<tr>
<td>Schiffer et al (2009)</td>
<td>366 consecutive outpatients with chronic heart failure</td>
<td>As above (Associated with increased mortality)</td>
<td>(as in de Jonge et al., 2007)</td>
</tr>
<tr>
<td>Deverts et al (2010)</td>
<td>2,544 community-based adults aged 33-45 years</td>
<td>Poor appetite, sleep disturbance (Associated with increased neuroinflammation i.e., circulating C-reactive protein)</td>
<td>Depressed affect e.g., sadness and loneliness</td>
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<td>Cognitive Subtypes</td>
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<tr>
<td>Marijnissen et al (2011)</td>
<td>1,284 community-based adults</td>
<td>Insomnia, fatigue, loss of appetite, weight loss, somatic preoccupation, diminished libido (Associated with increased waist circumference, waist-to-hip ratio, and body mass index)</td>
<td>Pessimism, a sense of failure, guilt, self-dislike, self-accusation, body image change, suicidality (Associated with increased body mass index)</td>
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<tr>
<td>Roest et al (2011)</td>
<td>913 patients with unstable angina pectoris or myocardial infarction</td>
<td>Insomnia, fatigue, loss of appetite, weight loss, somatic preoccupation, loss of libido, irritability, dissatisfaction (Associated with increased mortality)</td>
<td>Sadness, pessimism, sense of failure, dissatisfaction, guilt, punishment, sense of self-dislike, self-accusations, suicidality, crying, social withdrawal, indecisiveness, body image change</td>
</tr>
<tr>
<td>Bekke-Hansen et al (2012)</td>
<td>2,442 depressed and/or socially isolated patients with acute myocardial infarction</td>
<td>Work difficulties, insomnia, fatigability, loss of appetite, somatic preoccupation, decreased libido (Associated with increased mortality)</td>
<td>Sadness, pessimism, sense of failure, dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidality, crying, irritability, social withdrawal, indecisiveness, body image change</td>
</tr>
<tr>
<td>Stewart et al (2012)</td>
<td>2,171 middle-aged community-based adults</td>
<td>Poor appetite, sleep disturbance</td>
<td>Depressed affect e.g., sadness and loneliness (Predicted 5-year incidence of coronary artery calcification)</td>
</tr>
<tr>
<td>Hawkins et al (2014)</td>
<td>2,537 healthy primary care patients aged 60 years or older</td>
<td>Poor appetite, sleep disturbance (Predictive of nonfatal acute myocardial infarction or coronary artery disease-related death)</td>
<td>Depressed affect e.g., sadness and loneliness</td>
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<td>Beauregard et al., (1998)</td>
<td>7 patients with unipolar depression (two medicated); 7 healthy controls</td>
<td>Viewing of an emotionally laden film clip (sad valence) in fMRI, contrasted with viewing of an emotionally neutral clip</td>
<td>AN; AMN</td>
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<tr>
<td>Bench et al (1992)</td>
<td>33 patients with primary depression (10 with associated severe cognitive impairment); 23 age-matched controls</td>
<td>PET 15Oxygen, resting-state.</td>
<td>CCN</td>
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<tr>
<td>Davey et al (2012)</td>
<td>18 patients with MDD; 19 healthy controls</td>
<td>fMRI, event-related design. Functional connectivity changes with the subgenual ACC measured during brain activation/deactivation associated with a cognitive control task</td>
<td>AN; CCN</td>
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<tr>
<td>de Kwaasteniet et al (2013)</td>
<td>18 patients with MDD, 24 healthy controls</td>
<td>Multimodal neuroimaging to assess the relation between frontolimbic structural and functional connectivity abnormalities in depression. Integrity of the uncinate fasciculus was assessed, which connects the subgenual ACC to the MTL with diffusion tensor imaging. Functional connectivity between these brain regions was assessed with fMRI.</td>
<td>AN; AMN</td>
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<tr>
<td>Delaveau et al (2011)</td>
<td>126 cases with depression</td>
<td>A quantitative Activation Likelihood Estimation (ALE) meta-analysis was performed across nine emotional activation fMRI and PET studies before and after antidepressant drug treatment, using the Activation Likelihood Estimation technique.</td>
<td>AMN; CCN; AN</td>
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<td>Desseilles et al (2009)</td>
<td>14 nonmedicated patients with a first episode of unipolar MDD and 14 matched controls.</td>
<td>fMRI. Participants performed two tasks each with two different levels of attentional load at fixation (easy or difficult), while irrelevant coloured stimuli were presented in the periphery. Whether MDD alters attentional (&quot;top-down&quot;) effects on the neural filtering of irrelevant, nonemotional visual stimuli.</td>
<td>AN; AMN</td>
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<tr>
<td>Epstein et al (2011)</td>
<td>10 unmedicated patients with MDD; 12 healthy controls</td>
<td>fMRI, functional connectivity. Principal component analysis was used to examine differences in functional connectivity during a positive word viewing task.</td>
<td>AMN; AN</td>
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<tr>
<td>Fang et al (2012)</td>
<td>22 first-episode, treatment-naive adults with MDD; 26 matched healthy controls.</td>
<td>Diffusion MRI. Using machine learning approaches, depressed patients were differentiated from healthy controls based on whole-brain anatomical connectivity patterns, and the most discriminating features that represent between-group differences were identified.</td>
<td>AN; AMN</td>
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<tr>
<td>Foland-Ross et al (2013)</td>
<td>14 individuals with MDD (8 with comorbid anxiety disorders; 3 treated with psychotropic medication); 15 nondepressed healthy controls.</td>
<td>fMRI. Brain activation changes evaluated during an emotionally-valenced verbal working memory task. Second-level analysis of relationships between activation patterns and levels of self-reported rumination.</td>
<td>AN; CCN</td>
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<tr>
<td>Grimm et al (2009)</td>
<td>19 patients in an acute MDE (free of psychotropic medication for at least 1 week prior to scanning); 29 healthy controls.</td>
<td>fMRI. Negative BOLD responses (NBRs) measured during emotional stimulation (pictures selected from the International Affective Picture System with positive or negative valence) alternating with a fixation condition and an expectancy condition.</td>
<td>AN; AMN</td>
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<tr>
<td>Grimm et al</td>
<td>25 patients with MDD and 25 healthy controls</td>
<td>fMRI. Neural activity in regions of the AMN was assessed during self-related emotional judgement and passive picture viewing.</td>
<td>AMN</td>
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<td>Harvey et al</td>
<td>10 individuals with MDD; 10 healthy controls</td>
<td>fMRI. Task-related changes measured during the n-back task.</td>
<td>CCN</td>
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<td>Hasler et al</td>
<td>15 unmedicated patients with MDD in full remission; 13 healthy controls</td>
<td>Randomised, double-blind, placebo-controlled, crossover, single-site experimental trial of catecholamine depletion. Outcome measures of this intervention included quantitative PET of regional cerebral glucose utilisation, and behavioural assessments of mood.</td>
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<tr>
<td>Kanske et al (2012)</td>
<td>Twenty-three remitted patients with previous episodes of MDD; 25 healthy controls, matched for age, sex, handedness, and education</td>
<td>fMRI. Neural responses to emotional images (negative, positive, neutral) from the International Affective Picture System. Participants viewed the pictures (view condition) or down-regulated the emotional response by either reappraising the meaning of the stimuli (reappraisal condition) or by distraction from the images by solving an arithmetic task (distraction condition).</td>
<td>AN; AMN</td>
</tr>
<tr>
<td>Lemogne et al (2009)</td>
<td>15 depressed patients; 15 healthy controls</td>
<td>fMRI; assessed neural correlates of excessive self-focus. Participants presented with personality traits and asked them to judge whether each trait described them ('self' condition) or a generally desirable trait ('general' condition)</td>
<td>CCN</td>
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<tr>
<td>Authors</td>
<td>N</td>
<td>Description</td>
<td>Networks Described</td>
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<tr>
<td>Linden et al</td>
<td>8 each of medically-refractory patients with depression, experimental condition &amp; control</td>
<td>fMRI; patients learned to upregulate brain areas involved in the generation of positive emotions (vlPFC and insula) during 4 neurofeedback sessions. The control group underwent same training procedure but without neurofeedback</td>
<td>AN</td>
</tr>
<tr>
<td>Liu et al</td>
<td>Twenty adults with MDD; 20 gender-, age-, and education-matched healthy controls</td>
<td>Resting-state functional connectivity of the cerebellum using seed-based fMRI.</td>
<td>CCN; AMN</td>
</tr>
<tr>
<td>Ma et al</td>
<td>Twenty-four medication-free patients with MDD; 29 matched controls</td>
<td>Resting-state fMRI</td>
<td>AMN</td>
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<tr>
<td>Authors</td>
<td>N</td>
<td>Description</td>
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<tr>
<td>Marchand et al (2012)</td>
<td>22 unmedicated male patients with recurrent unipolar depression</td>
<td>fMRI, functional connectivity of striatal-cortical midline structures. Association between functional connectivity and current depression severity, suicidal ideation, or a history of self-harm.</td>
<td>AN; CCN</td>
</tr>
<tr>
<td>Matsuo et al (2007)</td>
<td>15 untreated individuals with recurrent MDD; 15 healthy controls matched for age, sex and race</td>
<td>fMRI; measured prefrontal cortex function during working memory processing. The n-back task (0-back, 1-back and 2-back) was used to elicit working memory architecture.</td>
<td>CCN</td>
</tr>
<tr>
<td>Matthews et al (2008)</td>
<td>15 young, unmedicated subjects with current MDD; 16 healthy controls</td>
<td>fMRI; activation design with functional connectivity. Neural activation measured during performance of a emotional face-matching task. Amygdala activity and strength of amygdala-cingulate functional coupling contrasted between the groups and related to current symptom severity.</td>
<td>AN; CCN</td>
</tr>
</tbody>
</table>
Mayberg et al (1997)  
18 hospitalised patients with unipolar depression; 15 non-depressed healthy controls  
PET; measured relationship between pre-treatment regional cerebral glucose metabolism and eventual antidepressant drug response  
AMN  
rACC metabolism uniquely differentiated eventual treatment responders from non-responders. Hypometabolism characterized non-responders when compared with controls, in contrast to responders who were hypermetabolic. Metabolism in no other region discriminated the two groups, nor did associated demographic, clinical or behavioural measures, including motor speed, cognitive performance, depression severity or illness chronicity.

Milak et al (2005)  
43 drug-free (excluding benzodiazepines) patients who met criteria for MDD  
Examined associations between Hamilton Depression Rating Scale component clusters (psychic depression, loss of motivated behaviour, psychosis, anxiety, sleep disturbance) and resting glucose cerebral metabolism assessed by [(18)F]-FDG PET.  
AN  
Total Hamilton Depression Rating Scale score correlated positively with activity in bilateral limbic, thalamic, and basal ganglia structures. Psychic depression correlated positively with metabolism in the cingulate gyrus, thalamus, and basal ganglia. Sleep disturbance correlated positively with metabolism in limbic structures and basal ganglia. Loss of motivated behaviour was negatively associated with parietal and superior frontal cortical areas.
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Description</th>
<th>Networks Described</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller et al (2013)</td>
<td>21 patients with major depression (20/21 medicated) and 21 healthy subjects matched for gender, age and education</td>
<td>fMRI; activation study. Participants rated the expression of happy, neutral and fearful faces while concurrently being exposed to emotional or neutral sounds.</td>
<td>AN; AMN</td>
<td>Results demonstrated group differences in left inferior frontal gyrus and inferior parietal cortex when comparing incongruent to congruent happy facial conditions, mainly due to a failure of patients to deactivate these regions in response to congruent stimulus pairs. Moreover, healthy subjects decreased activation in right posterior superior temporal gyrus/sulcus and midcingulate cortex when an emotional stimulus was paired with a neutral rather than another emotional one. In contrast, patients did not show such deactivation when neutral stimuli were integrated.</td>
</tr>
<tr>
<td>Naismith et al (2010)</td>
<td>19 patients with MDD, most of whom were receiving antidepressant medication; 20 control participants</td>
<td>fMRI; block design paradigm. A motor sequencing task that included implicit learning was contrasted with a random sequence (baseline) condition.</td>
<td>AN; CCN</td>
<td>While both groups activated the striatum, there was no significant difference between patients and controls in striatal activation. Instead, control subjects showed significantly greater activity in the middle frontal gyrus during implicit learning whereas the patients exhibited greater activity in the superior temporal gyrus and cerebellum.</td>
</tr>
<tr>
<td>Authors</td>
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<td>Description</td>
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<tr>
<td>Nugent et al (2011)</td>
<td>10 medically healthy female subjects with MDD and 7 healthy controls</td>
<td>H(2)(15)O-PET and electrocardiographic were recorded during the performance of mildly stressful tasks (a handgrip motor task and an n-back task). Indices of heart rate variability were calculated and correlated with rCBF to assess neural correlates of autonomic control.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peng et al (2012)</td>
<td>Sixteen patients with first-episode, medication-naïve MDD; 16 matched health controls</td>
<td>Resting-state fMRI functional connectivity; The pregenual ACC was used as seed region to construct the cortical section of the 'mood regulating circuit', and the thalamus was used as seed region to construct the limbic section.</td>
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<td></td>
<td></td>
<td>Differences in the rCBF and heart rate variability correlations between depressed and healthy subjects were evident in both the medial of PFC and frontal pole. In addition, these areas appeared to be involved in different facets of autonomic control with regard to sympathetic or parasympathetic dominance of cardiac control.</td>
<td></td>
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<td></td>
<td></td>
<td>Depressed patients exhibited significantly greater functional connectivity between pregenual ACC, left parahippocampal gyrus, left parietal lobe, and left frontal lobe</td>
<td></td>
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<tr>
<td>Authors</td>
<td>N</td>
<td>Description</td>
<td>Networks Described</td>
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</tr>
<tr>
<td>Ritchey et al (2011)</td>
<td>22 unmedicated patients with MDD; 14 healthy controls</td>
<td>fMRI; examined neural responses to positive, negative, and neutral pictures. After the initial scan, MDD patients were treated with CBT and scanned again after treatment.</td>
<td>AN; CCN; AMN</td>
<td>Prior to treatment and relative to controls, patients exhibited overall reduced activity in the vmPFC, diminished emotion discrimination in the amygdala, caudate, and hippocampus, and enhanced responses to negative stimuli in the left anterior temporal lobe and right dIPFC. CBT-related symptom improvement in depressed patients was predicted by increased activity at baseline in vmPFC as well as the valence effects in the anterior temporal lobe and dIPFC. Pre- to post-treatment, depressed patients exhibited overall increases in vmPFC activation, enhanced arousal responses in the amygdala, caudate, and hippocampus, and reversal of valence effects.</td>
</tr>
<tr>
<td>Schlosser et al (2008)</td>
<td>16 drug-free patients with MDD; 16 healthy controls</td>
<td>Dynamic causal modelling of a fronto-cingulate network was undertaken to re-analyse data from a preceding fMRI activation study that employed an in-scanner version of the Stroop Color-Word Test (Wagner et al., 2006)</td>
<td>AMN; CCN</td>
<td>In both groups, a significant reciprocal interregional connectivity was found in a cognitive control network including PFC and rACC. There was significant higher dorsal to rACC connectivity in depressive patients relative to controls. Additionally, enhanced task-related input from the dorsal to rostral ACC was evident in patients with depression. The correlation between interference scores and intrinsic connections from dACC to dIPFC was significant for both groups together, but no significant group differences in correlations could be detected.</td>
</tr>
<tr>
<td>Authors</td>
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<tr>
<td>Schoning et al</td>
<td>28 well-characterised,</td>
<td>fMRI; activation paradigm to challenge working-memory function comprised a</td>
<td>CCN</td>
<td>In the absence of significant behavioural differences, comparable overall patterns of brain activation were observed across patients and</td>
</tr>
<tr>
<td>(2009)</td>
<td>euthymic, unipolar</td>
<td>verbal n-back task (0-, 1-, and 2-back)</td>
<td></td>
<td>controls. As expected, both groups showed stronger activation of the typical working-memory network with increasing memory load. However,</td>
</tr>
<tr>
<td></td>
<td>depression patients; 28</td>
<td></td>
<td></td>
<td>significant hyperactivation of the cingulate cortex was observed in euthymic patients.</td>
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<tr>
<td></td>
<td>healthy control subjects</td>
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<td></td>
<td>matched according to age,</td>
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<td></td>
<td>sex, and educational level.</td>
<td></td>
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<tr>
<td>Seidel et al</td>
<td>15 depressed patients; 15</td>
<td>fMRI; neural activation measured while participants are confronted with</td>
<td>AN; AMN</td>
<td>Behaviourally, controls showed a self-serving bias, whereas patients demonstrated a balanced attributional pattern. There were significant</td>
</tr>
<tr>
<td>(2012)</td>
<td>healthy controls</td>
<td>positive and negative social events and asked to make causal attributions</td>
<td></td>
<td>group differences in a frontotemporal network comprising temporal pole, dmPFC, vlPFC. Higher activation of this network was associated with non</td>
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<td></td>
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<td>(internal vs. external). Healthy self-serving attribution bias defined as</td>
<td></td>
<td>self-serving attributions in controls but self-serving attributions in patients. Reduced coupling between a dmPFC seed region and</td>
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<td></td>
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<td>internal attribution of positive life events and external attribution of</td>
<td></td>
<td>limbic (amygdala, insula, caudate) areas was observed during self-serving attributions in patients compared to controls.</td>
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<tr>
<td></td>
<td></td>
<td>negative events.</td>
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<tr>
<td>Authors</td>
<td>N</td>
<td>Description</td>
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<tr>
<td>Sheline et al (2010)</td>
<td>18 unmedicated patients with MDD; 17 demographically similar controls</td>
<td>Resting-state functional connectivity using fMRI</td>
<td>AN; CCN; AMN</td>
<td>Compared with controls, in depressed subjects each of these three networks had increased connectivity to the same bilateral dmPFC region, an area that we term the dorsal nexus. The dorsal nexus demonstrated dramatically increased depression-associated fMRI connectivity with large portions of each of the three networks.</td>
</tr>
<tr>
<td>Tao et al (2011)</td>
<td>15 treatment-naive patients with first-episode MDD, 24 treatment-resistant MDD patients; 37 matched controls</td>
<td>Resting-state fMRI; A canonical template of connectivity in 90 different brain regions was constructed from healthy controls, with each network corresponding to a different functional system.</td>
<td>AN</td>
<td>Both groups of depressed patients: uncoupling of circuit involving superior frontal gyrus, insula and putamen. Other changes in circuits related to risk and action responses, reward and emotion, attention and memory processing. Voxel-based morphometry revealed no evidence for altered gray or white matter densities in the regions showing altered functional connectivity.</td>
</tr>
<tr>
<td>van Eijndhoven et al (2011)</td>
<td>20 patients with a first depressive episode, 20 patients recovered from a first episode; 20 healthy controls</td>
<td>fMRI; activation study examining the neural correlates of episodic memory formation for neutral stimuli</td>
<td>AN; CCN; AMN</td>
<td>Both patient groups showed stronger subsequent memory effects in the amygdala when compared to controls, in the absence of any differences in hippocampal activity between groups. Patients with a first episode of depression showed increased activity related to episodic memory formation in a fronto-limbic network including left inferior frontal gyrus, right caudate nucleus, left posterior cingulate cortex and left precuneus.</td>
</tr>
<tr>
<td>Authors</td>
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<td>Description</td>
<td>Networks Described</td>
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<tr>
<td>Vasic et al</td>
<td>14 inpatients with MDD treated with antidepressant medication; 14 controls</td>
<td>Event-related fMRI using a verbal working memory paradigm. By means of independent component analyses, two components of interest were identified that showed either a positive or a negative temporal correlation with the delay period of the cognitive activation task.</td>
<td>CCN</td>
<td>Decreased task-related functional connectivity in depressed patients in a pattern comprising inferior parietal, superior prefrontal and frontopolar regions. Within this network, depressed patients additionally revealed a pattern of increased functional connectivity in the left dLPFC and the cerebellum compared to healthy controls. In a second, temporally anticorrelated network, patients exhibited lower connectivity in the ACC, vLPFC, and superior PFC.</td>
</tr>
<tr>
<td>Veer et al</td>
<td>19 medication-free patients with a recent diagnosis of MDD (within 6 months before inclusion) and no comorbidity; 19 matched controls</td>
<td>Resting-state fMRI data; Independent component analysis. Thirteen networks identified in the entire sample. Next, individual representations of the networks were created using a dual regression method.</td>
<td>CCN; AN; visual processing networks</td>
<td>Abnormal functional connectivity was found within three resting-state networks in depression: (1) decreased bilateral amygdala and left anterior insula connectivity in an affective network, (2) reduced connectivity of the left frontal pole in a network associated with attention and working memory, and (3) decreased bilateral lingual gyrus connectivity within ventromedial visual regions. None of these effects were associated with symptom severity or gray matter density.</td>
</tr>
<tr>
<td>Authors</td>
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<td>Description</td>
<td>Networks Described</td>
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<tr>
<td>Walsh et al (2007)</td>
<td>20 medication-free individuals in an acute episode of MDD; 20 healthy individuals</td>
<td>fMRI; n-back tasks. Scans were acquired at weeks 0 (baseline), 2, and 8. Patients received treatment with fluoxetine after the baseline scan.</td>
<td>CCN</td>
<td>There were no significant differences in performance accuracy between groups. Main effect of group was observed in the load-response activity in frontal and posterior cortical regions within the CCN in which patients showed a greater response relative to controls. Group by time effects were revealed in the load-response activity in the caudate and thalamus. Marker of treatment response: lower baseline Activation in dorsal ACC, left middle frontal, and lateral temporal cortices was associated with improved clinical outcome.</td>
</tr>
<tr>
<td>Wang et al (2012)</td>
<td>18 first-episode, treatment-naive patients with MDD; 18 healthy controls</td>
<td>Resting-state fMRI; approaches of amplitude of low-frequency fluctuation (ALFF) and fractional ALFF were applied to examine the amplitude of low-frequency oscillations in unipolar depression.</td>
<td>AN; CCN; AMN</td>
<td>Compared with controls, depressed patients showed increased ALFF in the right fusiform gyrus and the right anterior and posterior lobes of the cerebellum but decreased ALFF in the left inferior temporal gyrus, bilateral inferior parietal lobule, and right lingual gyrus. fALFF in patients significantly increased in the right precentral and temporal gyri, bilateral fusiform gyrus, and bilateral cerebellum but was decreased in the left dorsolateral PFC, bilateral medial orbitofrontal cortex, bilateral middle temporal gyrus, left inferior temporal gyrus, and right inferior parietal lobule. After taking gray matter volume as a covariate, results remained.</td>
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<td>Authors</td>
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<tr>
<td>Zeng et al (2012)</td>
<td>24 depressed patients; 29 demographically matched healthy volunteers.</td>
<td>Whole-brain resting-state functional connectivity. Multivariate pattern analysis was employed. Permutation tests were used to assess classifier performance.</td>
<td>AMN, AN, visual processing networks</td>
<td>94.3% (P&lt;0.0001) of subjects correctly classified, including 100% identification of all patients. The majority of discriminating functional connections were located in the AMN, affective network, visual cortical areas and cerebellum. Amygdala, anterior cingulate cortex, parahippocampal gyrus and hippocampus also exhibit high discriminative power in classification.</td>
</tr>
<tr>
<td>Zhang et al (2011)</td>
<td>30 medication-naive, first-episode MDD patients; 63 healthy controls</td>
<td>Resting-state fMRI; whole-brain functional networks were constructed by thresholding partial correlation matrices of 90 brain regions, and their topological properties (e.g., small-world, efficiency, and nodal centrality) were analysed using graph theory-based approaches.</td>
<td>AN; AMN</td>
<td>Both depressed and control groups showed small-world architecture in functional networks. However, depressed patients showed altered quantitative values in the global properties, characterised by lower path length and higher global efficiency, implying a shift toward randomisation. The depressed patients exhibited increased nodal centralities, predominately in the caudate nucleus and AMN regions, including hippocampus, inferior parietal, medial frontal, and parietal regions, and reduced nodal centralities in the occipital, frontal (orbital part), and temporal regions. Altered nodal centralities in the left hippocampus and caudate were correlated with disease duration and severity.</td>
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<td>Authors</td>
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<td>Description</td>
<td>Networks Described</td>
<td>Findings</td>
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<tr>
<td>Zhong et al (2011)</td>
<td>29 medication-free patients with MDD, 26 never-depressed subjects with cognitive vulnerability to depression; 31 demographically matched healthy controls</td>
<td>fMRI; neural activation was measured during performance of an emotional matching/salience task.</td>
<td>CCN, AN</td>
<td>The MDD subjects showed elevated left amygdala responses and reduced left dlPFC activation levels. Similarly, nondepressed patients with a cognitive vulnerability had greater activity in the amygdala bilaterally and lesser activation in the dlPFC bilaterally relative to controls.</td>
</tr>
<tr>
<td>Zwanzger et al (2012)</td>
<td>Nine patients with remitted MDD (most responded to electroconvulsive therapy)</td>
<td>fMRI; A longitudinal follow-up examining neuronal activation over time, including full remission in a subgroup of patients (average follow-up 53.3 +/- 2.6 years)</td>
<td>Sensory processing networks</td>
<td>Results showed that although clinically remitted, patients still exhibited an increased activity of the secondary auditory cortex and multimodal recruitment of the left cuneus, an area of the visual system. However, activity of secondary visual network decreased over time. A positive correlation was observed between the number of hospital admissions during follow-up and activity of the secondary visual area at baseline.</td>
</tr>
</tbody>
</table>

ACC = anterior cingulate cortex; AMN = autobiographic memory network; AN = affective network; BA = Brodmann’s area; CBT = cognitive behaviour therapy; CCN = cognitive control network; dACC = dorsal anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomesial prefrontal cortex; fMRI = functional magnetic resonance imaging; MDD = major depressive disorder; MDE = major depressive episode; MFG = middle frontal gyrus; mPFC = mesial prefrontal cortex; MRI = magnetic resonance imaging; MTL = mesial temporal lobe; oPFC = orbitofrontal prefrontal cortex; PET = positron emission tomography; PFC = prefrontal cortex; rCBF = regional cerebral blood flow; vIPFC = ventrolateral prefrontal cortex; vmPFC = ventromesial prefrontal cortex
Appendix A: Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient edition, mood module
### SCID-I (for DSM-IV-TR)

**A. MOOD EPISODES**

**IN THIS SECTION, MAJOR DEPRESSIVE, MANIC, HYPOMANIC, EPISODES, CYSTHYMIC DISORDERS, MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION, SUBSTANCE-INDUCED MOOD DISORDER, AND EPISODE SPECIFIERS ARE EVALUATED. MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDERS ARE DIAGNOSED IN MODULE D.**

### CURRENT MAJOR DEPRESSIVE EPISODE

**How am I going to ask you some more questions about your mood.**

**In the last month...**

- Was the mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)? Note in children or adolescents, can be irritable mood.

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)</td>
<td>✔</td>
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</tr>
</tbody>
</table>

### NOTE: WHEN RATING THE FOLLOWING ITEMS, CODE "2" IF CLEARLY DUE TO A GENERAL MEDICAL CONDITION, OR TO MOOD-CONGRUENT DELUSIONS OR HALLUCINATIONS.

#### Mood Episodes 1

- **(3)** significant weight loss when not dieting, or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. Note: in children, consider failure to make expected weight gains.

- **(4)** insomnia or hypersomnia nearly every day.

- **(5)** psychomotor agitation or retardation nearly every day.

- **(6)** fatigue or loss of energy nearly every day.
Appendix B: Neurological Disorders
Depression Inventory for Epilepsy
# Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)

For the statements below, please circle the number that best describes you over the last two weeks including today.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Always or Often</th>
<th>Sometimes</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everything is a struggle</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Frustrated</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nothing I do is right</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Feel guilty</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty finding pleasure</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>I'd be better off dead</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix C: Patient Health Questionnaire – Generalised Anxiety Disorder, 7-item
### Patient Health Questionnaire-Generalized Anxiety Disorder-7 (PHQ-GAD-7)

<table>
<thead>
<tr>
<th></th>
<th>Nearly every day</th>
<th>More than half the days</th>
<th>Several days</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling nervous, anxious or on edge</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not being able to stop or control worrying</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Worrying too much about different things</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trouble relaxing</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Being so restless that it is hard to sit still</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Being easily annoyed or irritable</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Feeling afraid as if something awful might happen</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix D: Autobiographic Memory Interview
AMI
The Autobiographical Memory Interview

Scoring sheet

Note
Please follow the instructions provided in the Manual when using this scoring sheet.
For all autobiographical recollections questions please refer to pages 6 and 7, and Appendix 1 of the Manual for scoring details and examples.

Subject's details

Name

Age

Date of birth

Date of test

Reason for referral

Harcourt Assessment
The Psychological Corporation
Appendix E: Wechsler Memory Scale, 4th edition
Appendix F. Case Vignettes Of Patient Cognition & Mood, Study One
**Patient 1, “Holly” (Impaired Cognition)**

*Cognitive profile.* In the context of average range intelligence, indices of cognitive control and all aspects of auditory-verbal and visual learning were entirely normal. Against this background, Holly’s episodic autobiographic memory was clearly impaired. For example, when asked to recall an encounter with someone during her 20s she replied “I remember [my cousins] running around at Christmas-time together”, but was unable to provide any further detail or a specific time or place. Similarly, when asked to recall an incident from a family wedding she was unable to recount a specific event and instead responded “I just remember the dress I wore because it is still hanging in my wardrobe”. Consistent with her vague recall of personal life events, Holly spontaneously commented that her “time perception is really off, I think things happened [in my life] recently that actually occurred ages ago”. Holly’s semantic autobiographic memory was intact.

*Mood.* Clinical neuropsychiatric assessment did not reveal any overt psychiatric features. Commensurate with this, Holly’s responses on the SCID showed no past or current mood disturbance and the NDDI-E did not indicate any current mood symptomatology.

**Patient 2, “Ryan” (Impaired Cognition)**

*Cognitive profile.* In the context of average intellectual capacity, performances on tasks of cognitive control were somewhat variable; while visual symbol span was normal, orthographic lexical retrieval was reduced. Neuropsychological assessment showed some disturbance of visual memory with immediate recall falling in the moderately impaired range, and delayed recall in the low average range. Auditory-verbal memory was within normal limits. Against this background, Ryan’s episodic autobiographic memory was clearly impaired. For example, when asked to recall an incident from his first job, he replied “I was surprised by how laid-back the supervisors were”. When prompted for more information, he was unable to recount a more specific episode from this period. For many time periods he was unable to respond e.g., “I can’t remember anything specific, sorry” or “don’t know”. He also commented that “I only know [events have happened] because I was told about them, I don’t have any recollection”. In contrast, Ryan’s semantic autobiographic memory was preserved.
Mood. Neuropsychiatric assessment found no evidence of depression and clinically, it was felt that Ryan was optimistic given the significant functional disability imposed by his seizures. This was commensurate with the SCID and NDDI-E, neither of which suggested any past or current mood disturbance.

Patient 3, “Diana” (Impaired Cognition)

Cognitive profile. In the context of low average intelligence, cognitive control was in the low average range. Both immediate and delayed recall of auditory and visual memory fell in the low average to borderline range. Clinical neuropsychological assessment found that Diana had a memory impairment consistent with a lesion in the basal frontal region that appeared to affect verbal memory. Against this background, both the episodic and semantic components of Diana’s autobiographic memory were impaired. For example, when asked to recall a specific event from her wedding she responded “the photographer had an accident and the film was ruined. Only some [photographs] were salvageable”. Similarly, when asked to recall an episode from when her children were younger she responded “[child’s name] had juvenile arthritis and he had to have hydrotherapy and wear a night brace for a while”. She was unable to provide more precise details of these or other episodes when prompted. She was also unable to provide personal semantic details, such as the name of the suburb in which the Austin hospital is located.

Mood. Clinical psychiatric evaluation showed that Diana was not depressed, but it was noted she was frustrated with the restrictions that seizures imposed on her life. The SCID showed no evidence of any current or past mood disturbance. Somewhat incongruently her NDDI-E score suggested that she may be at risk of major depression, but inspection of her responses showed that they largely reflected her high levels of everyday frustration, rather than dysphoria or anhedonia.
**Patient 4, “Tiffany” (Impaired Cognition)**

*Cognitive profile.* In the context of average range intelligence, cognitive control was in the low average range. Indices of auditory-verbal and visuospatial memory were also below age-expected levels. Clinical neuropsychological assessment disclosed that Tiffany had a classical frontal lobe syndrome, taking the form of reduced ability to sustain activity or regulate goal-directed behaviour. Her working memory was especially poor. Against this background, both the episodic and semantic components of Tiffany’s autobiographic memory were impaired. For example, when asked to recall a specific episodic memory from her first job, she responded “*I was pretty rude to the customers, they didn’t keep me on*”, and when asked to recount an episode from a recent trip to hospital with her child she replied “[child’s name] got to watch TV after the surgery”. She was unable to provide more specific details from these periods when prompted. Like Ryan, for many life periods Tiffany was unable to recount any incident, and responded “*don’t know*”. She was also unable to provide many semantic facts, such as the details of a 30th birthday party she had been to “*a couple of years ago*”, including whose party it was.

*Mood.* Tiffany impressed as an optimistic and resilient woman. Consistent with this, the SCID did not reveal any current or past mood disorder, and her NDDI-E score did not indicate clinically significant endorsement of depressive symptoms.

**Patient 5, “Esther” (Impaired Cognition)**

*Cognitive profile.* In the context of low average intelligence, cognitive control was reduced. All aspects of auditory-verbal learning were impaired, and Esther’s performance on the delay trial of visuospatial memory was also below age-expected levels. Clinical neuropsychological assessment was suggestive of right frontal lobe impairment. Against this background, her episodic autobiographic memory was impaired. For example, when asked to recall an incident from her high school days, she replied “*I was like a teacher to the other kids*”, however she was unable to provide any examples of this. On other occasions she was able to recall an event but was unable to locate it in time or place e.g., when asked to recall an episode from a family wedding she responded “*we told the best
man to say something for us in the speech but they left it out”. Esther’s semantic autobiographic memory was intact.

**Mood.** Esther reported ongoing anxiety symptoms and suicidal ideation that she attributed to her extremely poor quality of life, in which because of the violence of her hypermotor seizures she was not only housebound, but also either bed-bound or forced to wear a posey vest for her own safety. Her depressive symptoms were being treated pharmacologically with 20mg escitalopram daily. The SCID was consistent with this, revealing a significant psychiatric profile comprising a current major depressive episode (MDE), past MDE, and Major Depressive Disorder (MDD; recurrent and currently severe).

**Patient 6, “Belinda” (Impaired Mood)**

*Cognitive profile.* Belinda’s intellectual functioning was estimated to fall in the average range. All indices of cognitive control fell within normal limits. Isolated deficits on the immediate recall trials of Verbal Paired Associates and Design were evident, however clinically these impressed as secondary to mild bradyphrenia. Consistent with this interpretation, her immediate learning fell within normal limits on the RAVLT and delayed recall was preserved across both auditory-verbal and visual aspects of memory. Against this background, both episodic and semantic aspects of autobiographic memory were preserved. For example, when asked to recall an incident from primary school, she responded “In around 1977 we went to the [name of local shopping centre] dressed in elephant trunks [made] of stockings full of newspaper. We sang an elephant song on the stage”.

*Mood.* Clinical neuropsychiatric evaluation revealed no specific psychiatric diagnosis but psychosocially Belinda’s marital situation was extremely disharmonious and individual counselling for depressed mood was recommended, but declined. On the SCID she endorsed feeling dysphoric and overwhelmed, decreased appetite, and anergia. Although these symptoms caused her distress and some functional impairment, they did not fulfil criteria for any depressive disorder as they lasted a few hours a day, more days than not, for the past 12-24 months. The level of depressive symptoms Belinda endorsed on the NDDI-E was high, but fell just below the cut-off score suggestive of major
depression. Together, these findings gave the clinical impression that Belinda was experiencing functionally significant, subthreshold depression.

**Patient 7, “Geoff” (Impaired Mood)**

*Cognitive profile.* Geoff’s neuropsychological profile showed that in the context of average range intelligence, he exhibited reduced cognitive control. Auditory-verbal and visuospatial memory were preserved. Against this background, all aspects of autobiographic memory fell within the normal range. For example, when asked to provide an incident from primary school, Geoff responded “I broke my arm playing football at school and came [to this hospital] and they put my arm in plaster. We had been playing over volcanic rocks and I got slung around. [Prompted:] I would have been about 10”.

*Mood.* Clinical neuropsychiatric assessment revealed that Geoff had a history of previous alcohol abuse as well as multiple current psychosocial stressors, including the recent death of his wife, the removal of his children from his custody, and an inability to work. There was evidence of severe depression and suicidality and active treatment for depression was commenced. Consistent with this, the SCID revealed a current Depressive Disorder Not Otherwise Specified (DDNOS; Minor Depressive Disorder), past MDE, and MDD (recurrent, currently severe). He also endorsed a high level of current symptoms on the NDDI-E.

**Patient 8, “Caroline” (Impaired Mood)**

*Cognitive profile.* In the context of average intellectual ability, both immediate and delayed recall of auditory-verbal information was intact. Delayed visual recall was also within normal limits. There were no measures of cognitive control available. All aspects of Caroline’s autobiographic memory were preserved. For example, when asked to recall an incident from a recent holiday, she responded “In September 2009, [name of child] and I went to Coogee Beach to enjoy the view and I was struck by the beautiful landscapes. Very pretty. Then we visited the university and went to an art exhibition. [The university] had lovely architecture, with stained glass in the windows”.

*Mood.* Caroline had a complex psychiatric and psychosocial history, beginning with psychological and emotional abuse in childhood and episodes of anorexia nervosa.
and depression occurring sporadically throughout her life. At the time of the assessment she was prescribed antidepressant pharmacotherapy (sertraline, 300mg daily). This history was reflected in the SCID, which showed a current DDNOS (minor depressive disorder), past MDE, and MDD (recurrent, in partial remission). The level of depressive symptomatology endorsed on the NDDI-E indicated that Caroline was at risk of major depression.

**Patient 9, “Luke” (Impaired Mood)**

*Cognitive profile.* Luke’s neuropsychological profile showed that in the context of average range intelligence, both immediate and delayed recall of auditory-verbal information was intact. Delayed visual recall was also within normal limits, and there was no dissolution of cognitive control. All aspects of Luke’s autobiographic memory were preserved. For example, when asked to recall an incident from his first job, he responded: “On my first day I started with [name of colleague] and we were given two tests to do and they gave us half an hour to do them. I had only done one in that time so when the boss came in I pretended that he had told me it was half an hour per test so he gave me another 15 minutes”.

*Mood.* Luke impressed as calm and friendly, although somewhat tired due to his frequent nocturnal seizures. Psychiatric assessment and the SCID revealed Major Depressive Disorder comprising one previous Major Depressive Episode of mild severity, occurring some years ago and now in full remission. Consistent with his euthymic mood state at present, he endorsed a low level of current symptoms on the NDDI-E.
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Title: Neurocognitive and psychiatric markers of network disease in epilepsy

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