Childhood maltreatment and structural neuroanatomy as risk factors for
adolescent onset depression.

Anna Barrett
Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy
19th December 2012
Melbourne School of Psychological Sciences
The University of Melbourne
Abstract

This thesis concerns three broad subjects – childhood maltreatment, structural neuroanatomical features in early adolescence, and depressive symptoms in mid-adolescence – with the aim of examining predictive relationships between them.

The core focus of the thesis was on investigating relationships between the volumes of key brain structures implicated in emotion regulation, and adolescent onset depression. The measurement of brain structures in a psychiatrically healthy sample of children aged 11-12 years, and the use of these measurements to predict onset of depressive symptoms 2-3 years later, allowed for contribution to theoretical debate about the timing of structural alterations previously associated with depression – specifically, whether observed alterations formed risk factors for depression, or whether they were outcomes of disease-related processes. The evidence of premorbid structural alterations demonstrated by this thesis suggests that there are vulnerability biomarkers for depression, and may assist in better understanding the mechanisms of depressive illness as well as identifying individuals at risk.

The secondary focus of the thesis was on retrospectively examining relationships between maltreatment in childhood and structural neuroanatomical features in adolescence, with the aim of identifying effects of childhood adverse experience on brain development. Previous studies have largely utilised adult populations with maltreatment-related psychiatric illness, and therefore have not been able to conclude whether structural alterations following childhood maltreatment only occur in those individuals who later develop psychopathology, or whether these changes occur before the onset of any psychopathology. This thesis investigated whether structural changes were associated with childhood maltreatment in a healthy sample of young adolescents, allowing the separation of early experiential effects from later psychopathological processes.

This research also explored whether the volumes of selected brain structures mediated relationships between childhood maltreatment and adolescent onset depression, however no such relationships were detected. As this was an exploratory measure secondary to the key themes of the thesis, and interpretations were constrained by issues of sample size, it is not dealt with in detail.

The most robust aspect of this research design was the examination of neurostructural risk factors for depression, and this formed the central content of the thesis. There is also a large extant body of research and literature on depression and brain development, from which to gain a strong theoretical grounding on the role of each brain structure examined in terms of the
cognitive and affective processes it is thought to subserve. For this reason, material on the epidemiology and neurobiological models of depression form the first three chapters. An exploration of the emerging body of literature on the relationships between childhood maltreatment and brain development is contained subsequently.

Chapter 1 provides an introduction to the epidemiology and selected etiological influences on adolescent depression. Chapter 2 gives an overview of the current understanding of brain development in adolescence, and describes some of the key theoretical models linking brain development to adolescent onset depression. Key structures highlighted in these models were selected for investigation within this thesis, and detailed examination of the evidence and resultant hypotheses for each of five selected structures' relationships with depression is contained in Chapter 3. The focus then turns to childhood maltreatment as a second major contributor to adolescent onset depression; Chapter 4 summarises research on the prevalence and types of childhood maltreatment and the relationships between childhood maltreatment and adverse outcomes including the development of depression. Chapter 5 reviews literature from the emerging field of developmental traumatology, drawing inferences from the body of work examining neuroendocrinological sequelae of childhood maltreatment and bringing together preliminary findings from a range of sources to form hypotheses regarding potential relationships between childhood maltreatment and the brain structures discussed in previous chapters. Chapter 6 gives detail on the design and methodology of the thesis, and Chapter 7 explains the data analysis used and reports on the results. Interpretation of findings, discussion of strengths and limitations of the research, and implications for future work are contained in Chapter 8.
Declaration

This is to certify that:

(i) the thesis comprises only my original work toward 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 less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Anna Barrett
Preface

The data used in this thesis come from a larger research project, the Orygen Adolescent Development Study (ADS) and the data collection and processing described in the method section was shared between myself and colleagues working on the ADS. The initial recruitment and screening of participants was conducted by research staff and students prior to the commencement of this thesis. My contribution to data collection included assisting with neuroimaging data collection and administering cognitive assessments at Time 1, and administering diagnostic interviews and questionnaire measures at Time 2. I undertook region of interest delineation in collaboration with several colleagues. All literature review, data analysis, and interpretation was carried out myself, for use in this thesis.

Some of the data used in this thesis have also been analysed and published elsewhere, as cited below:


Some of the material on gender and depression within this thesis was also included in a review chapter:

Acknowledgements

To my supervisors, Professor Nicholas Allen and Associate Professor Murat Yücel:

Murat, thank you for sharing your expertise and advice – your guidance was invaluable in helping me come to grips with what initially felt like very alien territory. Nick, I can’t thank you enough. Your acumen, rigour, humour, pragmatism, compassion, objectivity, insight and optimism, and the way you balance all of these in your professional practice are extraordinary and unique, and the patience, faith, kindness and support you have offered me over the years are more than I could possibly have expected from a supervisor.

Special thanks to past and present staff of Melbourne Neuropsychiatry Centre, Orygen Research Centre, and the many members of the ADS team for so generously sharing your work, data, ideas, and support, most especially Dr Sarah Whittle and Dr Julian Simmons. Thanks also to Dr Paul Dudgeon and Prof Vicki Anderson for your support as members of my advisory panel.

To the young people and their families who participated, thank you for allowing us into your homes and lives. The contents of this thesis represent only a fraction of what I took away from the experience of meeting you and hearing your stories. It was a privilege to get to know all the young people who shared their perspectives during such an important time in your lives and I wish you all the very best for the future.

Finally, thank you Mum, Dad and Dave, and Andy, Daniel, Gini, Jessie, Joseph, Lola, Michele, Morgana, Parisi, Simon, Simone, Tam, Tetsuya, Richard, and Victoria for your unfailing patience, love, encouragement and support over so many years.
Table of contents

Abstract .............................................................................................................................. ii
Declaration ......................................................................................................................... iv
Preface ............................................................................................................................... v
Acknowledgements .......................................................................................................... vi
Table of contents .............................................................................................................. vii
List of tables .................................................................................................................... xviii
List of figures ................................................................................................................... xxi
List of appendices .......................................................................................................... xxiv
Abbreviations .................................................................................................................. xxv

Chapter 1: Depression in adolescence ............................................................................. 1
  1.1 Adolescent depression: Clinical presentations, prevalence, course and outcomes .... 1
  1.2 Puberty and depression ............................................................................................... 3
    1.2.1 Neuroendocrinology of puberty ........................................................................ 3
  1.3 Female gender as a risk factor for depression ........................................................... 5
  1.4 Family environment and familial depression ............................................................. 10
  1.5 Temperament ............................................................................................................. 11
  1.6 Socioeconomic status ............................................................................................... 12
  1.7 Summary .................................................................................................................. 13

Chapter 2: Depression and brain development ............................................................... 14
  2.1 Adolescent brain development ................................................................................ 14
    2.1.1 Cortical grey matter ....................................................................................... 14
    2.1.2 Cortical white matter .................................................................................... 15
    2.1.3 Corpus callosum ............................................................................................. 16
    2.1.4 Subcortical structures .................................................................................... 17
    2.1.5 Summary ......................................................................................................... 18
  2.2 Brain development, emotional experience and cognitive and affective regulation .... 19
2.2.1 Maturational disparity ................................................................. 20
2.3 Neurodevelopmental models of affect and depression .......................... 21
  2.3.1 A focus on positive affect and reward ........................................ 22
  2.3.2 Prefrontal vulnerability theory .................................................... 23
  2.3.3 The social re-orienting of adolescence ......................................... 24
2.4 Summary ....................................................................................... 25
Chapter 3: Depression and neuroanatomy ................................................. 26
  3.1 Hippocampus ............................................................................... 26
    3.1.1 Emotional processing ............................................................... 26
    3.1.2 The hippocampus and depression .............................................. 27
    3.1.3 The hypothalamic-pituitary-adrenal axis .................................... 28
    3.1.4 Hippocampal volume reductions: Antecedents or consequences of depression? ................................................................. 29
      3.1.4.1 Consequences: Neurotoxicity .............................................. 29
      3.1.4.2 Consequences: Suppression of hippocampal neurogenesis ......................... 30
      3.1.4.3 Antecedents: Risk for poorer prognosis ................................ 31
      3.1.4.4 Antecedents: Vulnerability for onset ...................................... 32
    3.1.5 Summary and predictions ......................................................... 33
  3.2 Amygdala .................................................................................... 34
    3.2.1 Sensory processing ................................................................. 34
    3.2.2 Emotional learning and memory .............................................. 35
    3.2.3 Social processing ................................................................. 35
    3.2.4 The amygdala and depression ................................................. 36
    3.2.5 Summary and predictions ......................................................... 41
  3.3 Anterior cingulate cortex ............................................................. 41
    3.3.1 Executive functions .................................................................. 44
      3.3.1.1 Focussed attention ............................................................. 44
      3.3.1.2 Error-detection .................................................................. 45
      3.3.1.3 Conflict monitoring ......................................................... 46
3.3.2 Affect

3.3.3 Reward processing

3.3.4 Social processing

3.3.5 Development of affect regulation

3.3.6 Valence and laterality

3.3.7 The anterior cingulate cortex and depression
   3.3.7.1 Ventral anterior cingulate cortex
   3.3.7.2 Dorsal anterior cingulate cortex
   3.3.7.3 Rostral anterior cingulate cortex

3.3.8 Summary and predictions
   3.3.8.1 Ventral anterior cingulate cortex
   3.3.8.2 Dorsal anterior cingulate cortex
   3.3.8.3 Rostral anterior cingulate cortex

3.4 Orbitofrontal cortex
   3.4.1 Social processing
   3.4.2 Reward processing
   3.4.3 Laterality
   3.4.4 Medial/lateral parcellation
   3.4.5 The orbitofrontal cortex and depression
   3.4.6 Summary and predictions

3.5 Corpus callosum
   3.5.1 The corpus callosum and depression
   3.5.2 Summary and predictions

3.6 Restatement of hypotheses
   3.6.1 Hippocampus
   3.6.2 Amygdala
   3.6.3 Anterior cingulate cortex
      3.6.3.1 Ventral anterior cingulate cortex
3.6.3.2 Dorsal anterior cingulate cortex ................................................................. 65
3.6.3.3 Rostral anterior cingulate cortex ............................................................... 66
3.6.4 Orbitofrontal cortex ......................................................................................... 66
3.6.5 Corpus callosum .............................................................................................. 66
3.7 Conclusion ............................................................................................................. 66

Chapter 4: Childhood maltreatment and depression .................................................. 67

4.1 Types and prevalence of childhood maltreatment ................................................ 67

4.2 Predictors of childhood maltreatment .................................................................. 70

4.2.1 Gender ............................................................................................................. 70
4.2.2 Age .................................................................................................................. 70
4.2.3 Disability ......................................................................................................... 71
4.2.4 Familial and neighbourhood socioeconomic disadvantage ............................... 71
4.2.5 Parental substance use and mental illness ....................................................... 72
4.2.6 Family structure ............................................................................................. 73

4.3 Adverse sequelae of childhood maltreatment ..................................................... 74

4.3.1 Socio-economic and health outcomes ........................................................... 74
4.3.2 Psychopathology ............................................................................................ 75
4.3.3 Childhood maltreatment and depression ....................................................... 76

4.3.3.1 Stress-sensitization ..................................................................................... 78

4.4 Conclusion and hypotheses .................................................................................. 79

Chapter 5: The neurobiology of childhood maltreatment ......................................... 80

5.1 Studying the psychobiology of childhood neglect ............................................ 82

5.2 Stress-response systems ..................................................................................... 83

5.2.1 The catecholamine/sympathetic nervous system ........................................ 83
5.2.2 The hypothalamic-pituitary-adrenal axis ...................................................... 84

5.3 Stress and reward systems .................................................................................. 87

5.4 Maltreatment and the developing brain ............................................................. 88

5.5 Structural neuroanatomical correlates of childhood maltreatment ..................... 89
6.3 Structural magnetic resonance imaging ................................................................. 108
  6.3.1 Image analysis ................................................................................................. 109
  6.3.2 Whole brain volume ....................................................................................... 110
  6.3.3 Amygdala ....................................................................................................... 111
  6.3.4 Hippocampus .................................................................................................. 113
  6.3.5 Anterior cingulate cortex ................................................................................ 114
  6.3.6 Orbitofrontal cortex ....................................................................................... 118
  6.3.7 Corpus callosum ............................................................................................. 120
    6.3.7.1 Area ........................................................................................................... 120
    6.3.7.2 Length ....................................................................................................... 121
  6.4 Recruitment ......................................................................................................... 122
    6.4.1 Target population selection .......................................................................... 122
    6.4.2 Screening for affective temperament ......................................................... 122
    6.4.3 Final sample selection ................................................................................. 124
  6.5 Procedure ........................................................................................................... 125
    6.5.1 Temperament screening .............................................................................. 125
    6.5.2 Time 1 home assessment ............................................................................ 126
    6.5.3 Time 1 MRI and cognitive assessment ....................................................... 126
    6.5.4 Time 2 home assessment ............................................................................ 127
    6.5.5 Magnetic resonance imaging: Acquisition, preprocessing and region of interest delineation .......................................................... 127
      6.5.5.1 Image acquisition .................................................................................... 127
      6.5.5.2 Image preprocessing ............................................................................... 127
      6.5.5.3 Morphometric analysis ........................................................................... 128
      6.5.5.4 Region of interest tracing reliabilities ................................................... 128
  6.6 Summary of research structure and measures ..................................................... 129
  Chapter 7: Results .................................................................................................... 130
  7.1 Data analysis introduction .................................................................................. 130
7.4.5.5 KSADS-PL depressive disorders and parental education ........................................... 146
7.4.6 Childhood Trauma Questionnaire ............................................................................... 146
  7.4.6.1 Factor structure ....................................................................................................... 146
  7.4.6.2 Internal consistency ............................................................................................... 147
  7.4.6.3 CTQ and gender ................................................................................................... 147
  7.4.6.4 CTQ and FSIQ ...................................................................................................... 148
  7.4.6.5 CTQ and parent education ..................................................................................... 148
  7.4.6.6 CTQ and age ........................................................................................................ 148
7.4.7 Neuroanatomical regions of interest ......................................................................... 148
  7.4.7.1 Regions of interest and gender ............................................................................. 148
  7.4.7.2 Regions of interest and age .................................................................................. 149
  7.4.7.3 Regions of interest and handedness ...................................................................... 149
  7.4.7.4 Regions of interest and FSIQ ............................................................................... 149
  7.4.7.5 Regions of interest and parent education ............................................................. 150
7.5 Regression models .......................................................................................................... 150
7.6 Research Question 1: Are childhood experiences of neglect or abuse predictive of adolescent onset depression? ................................................................. 150
  7.6.1 CES-D ....................................................................................................................... 150
    7.6.1.1 CTQ Neglect and CES-D .................................................................................... 151
    7.6.1.2 CTQ Abuse and CES-D ..................................................................................... 151
  7.6.2 KSADS-PL depressive disorders ............................................................................. 156
    7.6.2.1 CTQ Neglect and KSADS-PL depressive disorders ......................................... 156
    7.6.2.2 Abuse ................................................................................................................ 157
7.7 Research Question 2: Are childhood neglect and abuse reflected in adolescent neuroanatomy? ............................................................................................................. 158
  7.7.1 CTQ Neglect ............................................................................................................ 158
    7.7.1.1 Left dorsal paracingulate volume and CTQ Neglect .......................................... 158
    7.7.1.2 Right rostral cingulate volume and CTQ Neglect .............................................. 159
7.7.1.3 Corpus callosum midlength and CTQ Neglect ................................................. 161
7.7.2 CTQ Abuse ............................................................................................................. 162
  7.7.2.1 Left amygdala volume and CTQ abuse ......................................................... 162
  7.7.2.2 Left rostral cingulate volume and CTQ Abuse ............................................ 163
  7.7.2.3 Left dorsal cingulate volume and CTQ Abuse ............................................. 165
  7.7.2.4 Corpus callosum midlength and CTQ Abuse ............................................... 166
7.8 Research Question 3: What neuroanatomical correlates of depressive symptomatology can be observed prior to onset? ................................................................................. 167
  7.8.1 CES-D Total ........................................................................................................... 167
    7.8.1.1 Right rostral cingulate volume and CES-D Total ........................................ 167
  7.8.2 CES-D Depressed Affect ...................................................................................... 168
    7.8.2.1 Right hippocampus volume and CES-D Depressed Affect ....................... 169
    7.8.2.2 Left ventral cingulate volume and CES-D Depressed Affect ..................... 170
  7.8.3 CES-D Somatic ..................................................................................................... 172
    7.8.3.1 Left ventral cingulate volume and CES-D Somatic ..................................... 172
    7.8.3.2 Right orbitofrontal cortex volume and CES-D Somatic ............................ 174
  7.8.4 CES-D Wellbeing ................................................................................................. 176
    7.8.4.1 Right hippocampus volume and CES-D Wellbeing .................................. 176
    7.8.4.2 Left dorsal paracingulate volume and CES-D Wellbeing ......................... 177
    7.8.4.3 Left dorsal cingulate volume and CES-D Wellbeing ................................. 179
    7.8.4.4 Right rostral cingulate volume and CES-D Wellbeing ............................ 180
    7.8.4.5 Corpus callosum midlength and CES-D Wellbeing ................................. 181
  7.8.5 CES-D Interpersonal ............................................................................................ 182
  7.8.6 KSADS-PL depressive disorders ....................................................................... 182
    7.8.6.1 Whole brain volume and KSADS-PL depressive disorders .................... 183
    7.8.6.2 Right rostral paracingulate volume and KSADS-PL depressive disorders .. 184
    7.8.6.3 Right ventral paracingulate volume and KSADS-PL depressive disorders .. 184
7.9 Summary of Research Question 2 and 3 findings ................................................. 186
7.10 Research Question 4: Do neuroanatomical features mediate relationships between early life adversity and adolescent onset depression? .................................................................................................................. 187

7.10.1 Mediation models .................................................................................................................. 187

7.10.1.1 CTQ Abuse, corpus callosum midlength, and CES-D Wellbeing ......................... 189

7.10.1.2 CTQ Neglect, corpus callosum midlength, and CES-D Wellbeing .................. 190

7.10.1.3 CTQ Neglect, right rostral cingulate volume, and CES-D Wellbeing ............. 191

Chapter 8: Discussion .................................................................................................................. 193

8.1 Prevalence of neglect and abuse............................................................................................... 193

8.2 Prevalence of depressive symptoms ......................................................................................... 193

8.3 Research Question 1: Are childhood experiences of neglect or abuse predictive of adolescent onset depression? ............................................................................................................... 195

8.4 Research Question 2: Are childhood neglect and abuse reflected in adolescent neuroanatomy? ........................................................................................................................................... 197

8.4.1 Hippocampus ......................................................................................................................... 198

8.4.2 Amygdala......................................................................................................................................... 200

8.4.3 Anterior cingulate cortex ........................................................................................................... 203

8.4.4 Orbitofrontal cortex .................................................................................................................. 204

8.4.5 Corpus callosum......................................................................................................................... 205

8.5 Research Question 3: What neuroanatomical correlates of depressive symptomatology can be observed prior to onset? ........................................................................................................... 208

8.5.1 Hippocampus .......................................................................................................................... 209

8.5.2 Amygdala......................................................................................................................................... 212

8.5.3 Anterior cingulate cortex ........................................................................................................... 214

8.5.3.1 Ventral anterior cingulate cortex ...................................................................................... 214

8.5.3.2 Dorsal anterior cingulate cortex ...................................................................................... 217

8.5.3.3 Rostral anterior cingulate cortex .................................................................................... 218

8.5.4 Orbitofrontal cortex .................................................................................................................. 221

8.5.4.1 The orbitofrontal cortex’s role in emotion regulation ...................................................... 222
8.5.4.2 The orbitofrontal cortex and reward .................................................. 223
8.5.5 Corpus callosum ................................................................. 224
8.5.6 Relevance to neurobiological models of affect regulation .................. 226

8.6 Research Question 4: Do neuroanatomical features mediate relationships between early life adversity and adolescent onset depression? .................................................. 227

8.7 Strengths and limitations ............................................................................. 229
  8.7.1 Design ....................................................................................... 229
  8.7.2 Sample selection ............................................................................. 229
  8.7.3 Interpreting gender interactions for depressive symptoms .................. 230
  8.7.4 Measurement of maltreatment .......................................................... 230
  8.7.5 Potential confounds of the relationship between maltreatment and brain structure .... 231
  8.7.6 Measurement of depressive symptoms .............................................. 232

8.8 Foci for future research .............................................................................. 232
  8.8.1 Puberty ....................................................................................... 233
    8.8.1.1 Pubertal development and the diathesis for affective disorder in girls .......... 233
    8.8.1.2 Pubertal timing ....................................................................... 233
    8.8.1.3 Interpersonal stressors: a mediator between pubertal processes and depression in females ........................................................................................................... 234
  8.8.2 Developmental timing of maltreatment .................................................. 236
  8.8.3 Differential effects of different types of maltreatment .......................... 237
  8.8.4 Comorbidity and parental mental health .............................................. 238
  8.8.5 Measurement of stress hormones ....................................................... 238
  8.8.6 Next steps in interpreting structural volumetric findings .................... 239

8.9 Conclusion .................................................................................................. 240

References ........................................................................................................ 242
List of tables

Table 1 Internal consistencies for lower (a) and higher order (b) EATQ-R factors derived from screening sample (n=2453) .................................................................................................................................................. 123
Table 2 Independent samples t-test comparing CES-D scale scores between participants who did and did not opt in for MRI scanning........................................................................................................................................ 124
Table 3 Intra- and inter-rater reliabilities for manual tracings of neuroanatomical regions of interest .......................................................................................................................................................... 128
Table 4 Summary of research methods and measures .......................................................................................................................................................................................... 129
Table 5 Missing data rates ........................................................................................................................................................................................................ 132
Table 6 KSADS-PL depressive disorder diagnoses at Time 2 ........................................................................................................................................ 133
Table 7 Significant scheffe post-hoc contrasts indicating relationships between parent education and child FSIQ ........................................................................................................................................ 136
Table 8 Four-factor structure of CES-D at Time 2 .......................................................................................................................................................... 137
Table 9 Internal consistency of Time 1 and 2 CES-D subscales ........................................................................................................................................ 138
Table 10 Descriptive statistics and repeated measures t-test results for Time 1 and Time 2 CES-D scales .......................................................................................................................................................... 138
Table 11 Unstandardised residuals from regression of Time 2 onto Time 1 CES-D scale scores .......................................................................................................................................................... 139
Table 12 Descriptive statistics and independent samples t-test results comparing CES-d scale scores between males and females ........................................................................................................................................ 139
Table 13 Descriptive statistics and repeated measures t-test results comparing Time 1 and Time 2 CES-D scale scores: Males ........................................................................................................................................ 140
Table 14 Descriptive statistics and repeated measures t-test results comparing Time 1 and Time 2 CES-D scale scores: Females ........................................................................................................................................ 140
Table 15 Descriptive statistics and independent samples t-test results comparing male and female CES-D scale residual scores ........................................................................................................................................ 141
Table 16 Games-Howell post-hoc comparisons indicating relationships between parent education and child CES-D Scale scores ........................................................................................................................................ 142
Table 17 Pearson correlations between age at MRI and time between interviews and Time 1 and 2 CES-D scale scores ........................................................................................................................................ 143
Table 18 Pearson correlations between time between interviews and CES-D scale residual scores ........................................................................................................................................................................ 143
Table 19 Pearson correlations between CES-D scale scores and residuals and WISC-IV (Short Form) Full Scale IQ ................................................................. 144
Table 20 Time 1 and Time 2 CES-D scale scores for those with and without a KSADS-PL depressive disorder diagnosis at Time 2 ........................................... 145
Table 21 Results of independent samples t-tests comparing Time 2 CES-D Scale and residual scores for those with and without KSADS-PL depressive disorders diagnosis at Time 2 .......... 145
Table 22 Internal consistency of established CTQ subscales in the current sample ........................................ 146
Table 23 Two-factor structure for the Childhood Trauma Questionnaire ......................................................... 147
Table 24 Descriptive statistics and results of independent samples t-tests comparing CTQ Neglect and Abuse scores for males and females ......................................................... 148
Table 25 Significant Pearson correlations between neuroanatomical regions of interest and age 149
Table 26 Structure of CES-D by CTQ linear regression models ................................................................. 151
Table 27 Result of regressions predicting Time 2 CES-D with covariates, an independent variable of CTQ Neglect, and an interaction term of Neglect and gender .................................................. 154
Table 28 Result of regressions predicting Time 2 CES-D with covariates, an independent variable of CTQ Abuse, and an interaction term of Abuse and gender .................................................. 155
Table 29 Structure of KSADS-PL depressive disorders by CTQ logistic regression models .... 156
Table 30 Results of logistic regression predicting KSADS-PL depressive disorder diagnosis from CTQ Neglect ........................................................................................................ 157
Table 31 Results of logistic regression predicting KSADS-PL depressive disorder diagnosis from CTQ Abuse.................................................................................................................. 157
Table 32 Structure of region of interest by CTQ linear regression models .................................................. 158
Table 33 Results of linear regression predicting left dorsal paracingulate from CTQ Neglect................................. 159
Table 34 Results of linear regression predicting right rostral cingulate volume from CTQ Neglect ............................................................................................................................... 160
Table 35 Results of linear regression predicting corpus callosum midlength from CTQ Neglect ......................................................................................................................... 161
Table 36 Results of regression predicting left amygdala volume from CTQ Abuse .............................................. 162
Table 37 Results of linear regression predicting left rostral cingulate volume from CTQ Abuse 164
Table 38 Results of linear regression predicting left dorsal cingulate volume from CTQ Abuse 165
Table 39 Results of linear regression predicting corpus callosum midlength from CTQ Abuse 166
Table 40 Structure of CES-D by region of interest linear regressions .................................................................. 167
Table 41 Results of linear regression predicting CES-D Total symptom change from right rostral cingulate volume ........................................................................................................ 168
Table 42 Results of linear regression predicting CES-D Depressed Affect symptom change from right hippocampus volume.......................................................... 169
Table 43 Results of linear regression predicting CES-D Depressed Affect symptom change from left ventral cingulate volume ................................................................. 171
Table 44 Results of linear regression predicting CES-D Somatic symptom change from left ventral cingulate volume ................................................................. 172
Table 45 Additional results of linear regression predicting CES-D Somatic symptom change from left ventral cingulate volume, divided by gender................................. 173
Table 46 Results of linear regression predicting CES-D Somatic symptoms at Time 1 from left ventral cingulate volume ................................................................. 174
Table 47 Results of linear regressions predicting CES-D Somatic symptom change from right orbitofrontal cortex and right lateral orbitofrontal cortex volumes................................. 175
Table 48 Results of linear regression predicting CES-D Wellbeing symptom change from right hippocampus volume ................................................................. 176
Table 49 Results of linear regression predicting CES-D Wellbeing symptom change from left dorsal paracingulate volume ................................................................. 178
Table 50 Results of linear regression predicting CES-D Wellbeing Symptom change from left dorsal cingulate volume ................................................................. 179
Table 51 Results of linear regression predicting CES-D Wellbeing symptom change from right rostral cingulate ................................................................. 180
Table 52 Results of linear regression predicting CES-D Wellbeing symptom change from corpus callosum midlength................................................................. 181
Table 53 Structure of region of interest by KSADS-PL depressive disorder logistic regression models................................................................. 183
Table 54 Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from whole brain volume ................................................................. 183
Table 55 Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from right rostral paracingulate volume ................................................................. 184
Table 56 Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from right ventral paracingulate volume ................................................................. 185
Table 57 Summary of predictive relationships between CTQ neglect/abuse and neuroanatomical regions of interest, and between neuroanatomical regions of interest and CES-D and KSADS-PL measures of depression ................................................................. 186
List of figures

Figure 1. Age and prevalence of unipolar depression in the Great Smoky Mountains Study. 6
Figure 2. Age and depression scale scores from the Childhood Depression Inventory and the Short Mood and Feelings Questionnaire. 7
Figure 3. Proportion of individuals in each age group scoring at or above the mean for 26- to 30-year-olds on indices of cognitive capacity and psychosocial maturity. 21
Figure 4. Divisions within the anterior cingulate cortex. 43
Figure 5. Substantiated child protection notifications in Australia, 2009-2010 by maltreatment type. 69
Figure 6. Representative tracings of the left (yellow) and right (blue) amygdala at the anterior (a) and posterior boundaries (c), as well as differentiation between amygdala and hippocampus (left: red, right: green). 112
Figure 7. Representative tracings of the left (red) and right (green) hippocampi at posterior (a) and anterior (b) aspects. 114
Figure 8. Representative tracings of dorsal paracingulate (cyan), dorsal cingulated (blue), rostral paracingulate (green), rostral cingulate (red), ventral paracingulate (yellow) and ventral cingulated (pink) regions in cases with (a) and without (b) a paracingulate sulcus. 117
Figure 9. Representative tracing of the left medial (cyan) and lateral (yellow) and right medial (pink) and lateral (blue) orbitofrontal cortices. 119
Figure 10. Sagittal view of lateral orbitofrontal cortex tracing. 120
Figure 11. a) Midslice corpus callosum image; b) Callosal area; c) Callosal midlength, measured via midspline connecting endpoints and traversing midpoints of dorsal-ventral line segments. 121
Figure 12. Sampling frame for temperament screening, Time 1 and Time 2 assessments. 125
Figure 13. Summary of variables, research questions, and statistical techniques used in data analysis. 130
Figure 14. Distribution of scores on the Edinburgh Handedness Inventory. 134
Figure 15. Highest level of education attained by either parent. 135
Figure 16. WISC-IV (short form) Full Scale IQ by highest level of parent education. 136
Figure 17. CES-D scale residual means for males and females. 141
Figure 18. Interaction between gender and CTQ Abuse in predicting CES-D Total symptom change. 152
Figure 19. Interaction between gender and CTQ Abuse in predicting CES-D Somatic symptom change. 153
Figure 20. Interaction between gender and CTQ Neglect in predicting left dorsal paracingulate volume. ................................................................. 159
Figure 21. Interaction between gender and CTQ Neglect in predicting right rostral cingulate volume. ........................................................................ 160
Figure 22. Interaction between gender and CTQ Neglect in predicting corpus callosum midlength................................................................. 161
Figure 23. Interaction between gender and CTQ Abuse in predicting left amygdala volume..... 163
Figure 24. Interaction between gender and CTQ Abuse in predicting left rostral cingulate volume. ........................................................................ 164
Figure 25. Interaction between gender and CTQ Abuse in predicting left dorsal cingulate volume. ........................................................................ 165
Figure 26. Interaction between gender and CTQ Abuse in predicting corpus callosum midlength. ........................................................................ 166
Figure 27. Right rostral cingulate volume and CES-D Total residual score for males and females. ........................................................................ 168
Figure 28. Interaction between gender and right hippocampus volume in predicting CES-D Depressed Affect symptom change. ........................................................................ 170
Figure 29. Interaction between gender and left ventral cingulate volume in predicting CES-D Depressed Affect symptom change. ........................................................................ 171
Figure 30. Left ventral cingulate volume predicting CES-D Somatic symptom change, divided by gender. ........................................................................ 173
Figure 31. Interaction between gender and right orbitofrontal cortex volume in predicting CES-D Somatic symptom change. ........................................................................ 175
Figure 32. Interaction between gender and right hippocampus volume in predicting CES-D Wellbeing symptom change ........................................................................ 177
Figure 33. Interaction between gender and left dorsal paracingulate volume in predicting CES-D Wellbeing symptom change........................................................................ 178
Figure 34. Main effect of left dorsal cingulate ACC volume in predicting CES-D Wellbeing symptom change. ........................................................................ 179
Figure 35. Main effect of right rostral cingulate volume in predicting CES-D Wellbeing symptom change........................................................................ 181
Figure 36. Main effect of corpus callosum midlength in predicting CES-D Wellbeing symptom change ........................................................................ 182
Figure 37. A simple mediation model. ........................................................................ 187
Figure 38. Structure of mediation models to be tested................................................................. 188

Figure 39. Model testing whether corpus callosum midlength mediated the relationship between CTQ Abuse and CES-D Wellbeing................................................................. 190

Figure 40. Model testing whether corpus callosum midlength mediated the relationship between CTQ Neglect and CES-D Wellbeing................................................................. 191

Figure 41. Model testing whether corpus callosum midlength mediated the relationship between CTQ Neglect and CES-D Wellbeing................................................................. 192

Figure 42. Comparative regression analysis of fetal corpus callosal length data.......................... 207

Figure 43. Localization of activity in several studies that activated rostral ACC vs dorsal ACC. 220
List of appendices

Appendix 1
  Sample of communications with participants and families........................................338
Appendix 2. Independent samples t-test comparing those with present and absent data from T1 CES-D on T2 Questionnaire measures.................................................................347
Appendix 3. CES-D distribution and transformations ....................................................348
Appendix 4. CTQ distribution and transformations .......................................................349
Appendix 5. ROI distributions and transformations .....................................................350
Appendix 6. CES-D and parent education .....................................................................351
Appendix 7. CTQ Four Factor Structure ......................................................................353
Appendix 8. Descriptive statistics for raw ROI volumes ..............................................354
Appendix 9a. Region of interest correlations .................................................................355
Appendix 9b. Region of interest correlations summary ................................................357
Appendix 10. Independent sample t-tests for gender differences on raw, uncorrected region of interest volumes ..................................................................................358
Appendix 11. Correlations between regions of interest and age ................................359
Appendix 12. Correlations between ROIs and handedness .........................................360
Appendix 13. Correlations between ROIs and FSIQ ....................................................361
Appendix 14. Mediation analyses ..................................................................................362
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADS</td>
<td>Adolescent Development Study</td>
</tr>
<tr>
<td>AIFS</td>
<td>Australian Institute of Family Studies</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BA</td>
<td>Brodmann Area</td>
</tr>
<tr>
<td>BAS</td>
<td>Behavioural activation system</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>BET</td>
<td>Brain Extraction Tool</td>
</tr>
<tr>
<td>BIS</td>
<td>Behavioural inhibition system</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-oxygen-level-dependent</td>
</tr>
<tr>
<td>BRI</td>
<td>Brain Research Institute</td>
</tr>
<tr>
<td>CAH</td>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>CES-D</td>
<td>Centre for Epidemiologic Studies – Depression scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Corticotropin-releasing factor</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin releasing hormone</td>
</tr>
<tr>
<td>CTQ</td>
<td>Childhood Trauma Questionnaire</td>
</tr>
<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
</tr>
<tr>
<td>DHEAS</td>
<td>Dehydroepiandrosterone sulfate</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
<tr>
<td>EATQ-R</td>
<td>Early Adolescent Temperament Questionnaire – Revised</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EHI</td>
<td>Edinburgh Handedness Inventory</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ERN</td>
<td>Error-related negativity</td>
</tr>
<tr>
<td>ERP</td>
<td>Event-related potential</td>
</tr>
<tr>
<td>FAST</td>
<td>FMRIB’s Automated Segmentation Tool</td>
</tr>
<tr>
<td>FLIRT</td>
<td>FMRIB’s Image Registration Tool</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FMRIB</td>
<td>Functional Magnetic Resonance Imaging of the Brain</td>
</tr>
<tr>
<td>FSIQ</td>
<td>Full scale intelligence quotient</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GAF</td>
<td>Global Assessment of Functioning</td>
</tr>
<tr>
<td>GnRH</td>
<td>Gonadotropin releasing hormone</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>KSADS-PL</td>
<td>Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MNC</td>
<td>Melbourne Neuropsychiatry Centre</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl-D-aspartate</td>
</tr>
<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
</tr>
<tr>
<td>ORC</td>
<td>Orygen Research Centre</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>ROI</td>
<td>Neuroanatomical region of interest</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin re-uptake inhibitor</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel based morphometry</td>
</tr>
<tr>
<td>VENs</td>
<td>von Economo neurons</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WISC-IV</td>
<td>Wechsler Intelligence Scale for Children – Fourth edition</td>
</tr>
</tbody>
</table>
Chapter 1: Depression in adolescence

1.1 Adolescent depression: Clinical presentations, prevalence, course and outcomes

Depression in adolescence is characterised by many of the same symptoms as in adulthood; sleep changes, appetite changes, loss of interest and energy, inability to experience pleasure, hopelessness, sadness, and particularly in younger people, irritability (Hankin, 2006; National Institute of Mental Health, 2003). A case level major depressive episode is defined as a period of at least two weeks in which the individual experiences a constellation of depressive symptoms, sometimes including psychotic symptoms. Adolescents may also experience mild, self-limited bouts of depression, clearly linked to a stressor, which are usually termed adjustment disorders with depressed mood. Alternatively, chronic depressive symptoms of milder intensity for a period of a year or more are classified as dysthymic disorder, over which major depressive episodes may be superimposed. Finally, many adolescents will experience sub-syndromal depression – milder experiences of depressive symptoms that may subsequently escalate into a case level disorder (American Psychiatric Association, 2000).

Often, depression is not experienced in isolation from other psychiatric symptoms. In children, anxiety is a common precursor of adolescent depression, and many depressive experiences include anxious elements, or are comorbid with case level anxiety disorders (e.g. Brady & Kendall, 1992). Likewise, substance use problems exhibit a bidirectional causal relationship with depression; substance use may precipitate depressive illness, which in itself is a risk factor for substance abuse. Attention deficit and conduct disorders are also highly frequent comorbidities with depression in children and adolescents (Zalsman, Brent & Weersing, 2006).

There is no sharp distinction between ordinary sadness and clinical depression (Hankin, Fraley, Lahey & Waldman, 2005); however, neither are the depressive symptoms experienced by many adolescents merely part of the normative emotional changes associated with that life stage. Depression in adolescence can be particularly difficult to define and detect precisely because of those normative changes. The phrasing of current categorical depressive diagnoses assumes a baseline for the individual – symptoms are described as loss of previous interest and pleasure in normally rewarding activities, and a depressive episode is a phase of emotional functioning considered to be out of the ordinary for that individual (American Psychiatric Association, 2000). During adolescence, the individual’s experience of what is interesting and pleasurable is changing, and emotional functioning and self-concept are evolving (e.g. Cole et al., 2001; Dahl,
It is also because of these formative changes in motivations, emotional experience and self-concept that depression may be particularly toxic at this time. When a child, at the entrance to their adult life, finds it punishing, tiresome and pleasureless, they are at risk of forming lifelong biological, behavioural and attributional tendencies based not on an understanding that they are suffering an escapable illness, but on the expectation that this is what life now holds for them.

The average duration of depressive episodes has been estimated at between 3 and 6 months in community samples and between 5 and 8 months in referred samples (Kovacs, 1996; Birmaher, Arbelaez & Brent, 2002). For adolescents who experience a first episode of depression, the risk of persistent or recurrent depression is high, estimated at 30% and 70% within 1 to 5 years (Lewinsohn et al., 1998; Birmaher et al., 2000; Emslie, Rush, Weinberg, Kowatch, Carmody & Mayes, 1998; McCauley, Myers, Mitchell, Calderon, Schloredt & Treder, 1993; Kovacs et al., 1984b; Kovacs, Feinberg, Crouse-Novak, Paulauskas & Finkelstein 1984a). Comorbidity with anxiety and substance abuse, as well as presence of “double depression” (the combined experience of dysthymic disorder and a major depressive episode) are associated with longer episode duration, as are familial environments characterised by discord and parental depression (Birmaher et al., 2000; Warner, Weissman, Fendrich, Wickramaratne & Moreau, 1992; Kaminski & Garber, 2002).

Episodes of depression in adolescence are more commonly associated with life stresses than are subsequent episodes experienced in adulthood (Brown & Harris, 1989; Post, 1992; Lewinsohn, Allen, Seeley & Gotlib, 1999; Kendler, Thornton & Gardner, 2000; Monroe & Harkness, 2005). It appears that after the initial experience of depression, the individual is more vulnerable to subsequent episodes, the incidence of which is less and less tied to external factors and the gaps between which become shorter and shorter (Harrington et al., 1997; Weissman et al., 1999). It is clear from this disquieting picture that the prevention of adolescent onset depression has consequences for quality of life and years lost to disability that extend far beyond the adolescent period.

Recurrence of depressive episodes predicts a suite of negative outcomes for adolescents, including poor social and familial relationships, drug and alcohol abuse, suboptimal educational/occupational achievement, behavioural problems, suicidal behaviour, and health issues such as obesity (Zalsman et al., 2006). The prevalence, chronicity and severity of consequences for adolescent onset depression make it one of the most serious health issues for adolescence and warrant investigation into risk factors, with a view to prevention efforts in the
future. Understanding biological and environmental risk factors for adolescent onset depression will make a significant impact on a major public health issue and assist with early detection and intervention.

According to the World Health Organisation (WHO), depression is now the leading cause of years of life lost to disability in women and men, globally. Depression also makes the largest contribution to the burden of disease in middle- and high-income countries, and the eighth largest contribution in low-income countries, where burden of infectious diseases is higher (WHO, 2008). Indeed, in developed countries, adult depression affects a larger proportion of the total life course than any other chronic condition (Kessler, Avenevoli, Ries & Merikangas, 2001; Mathers, Vos, Stevenson & Begg, 2000).

Epidemiological data points to puberty as a developmental stage at which the risk for onset of depression is greatly elevated (Angold & Costello, 2006). Depression in adolescence is common, with point prevalence rates ranging from 1.5% to 8% and a lifetime prevalence of up to 24% by the end of adolescence (Lewinsohn, Rohde & Seeley, 1998; Costello, Mustillo, Erkanli, Keeler & Angold, 2003; Reinherz, Giaconia, Pakiz, Silverman, Frost & Lefkowitz, 1993; Costello et al., 1996; Fleming & Offord, 1990; Whitaker et al., 1990). Case level depression most commonly emerges in the late teens and early adulthood (Lewinsohn, Duncan, Stanton & Hautzinger, 1986); a pattern which has been observed cross nationally (Cooper & Sartorius, 1996; Hwu, Yeh & Chang, 1989; Weissman et al., 1996). Rates of depression have also increased markedly over the last few decades, although there is debate as to whether reports of dramatic increases in adolescent depression are due to artefact (Cross-National Collaborative Group, 1992; Costello, Erkanli & Angold, 2006).

The main foci of this thesis are on relationships between childhood experiences of abuse and neglect, structural neuroanatomy in early adolescence, and the emergence of adolescent depression. However, before concentrating on these topics, it is useful to describe briefly some of the other known predictors of adolescent depression.

1.2 Puberty and depression

1.2.1 Neuroendocrinology of puberty

Puberty refers to hypothalamic-pituitary-gonadal axis activation, culminating in gonadal maturation, and should be differentiated from the definition of adolescence, which incorporates psychosocial and cognitive aspects of maturation (Sisk & Foster, 2004). While pubertal timing is
under strong genetic influence, a parsimonious trigger mechanism for onset of pubertal processes is yet to be defined – relationships have been found between pubertal timing and genetic, physiological (especially body weight) and social (stress, family environment) factors (Anderson, Dallal & Must, 2003; Kaplowitz, Slora, Wasserman, Pedlow & Herman-Giddens, 2001; Ge, Natsuki, Neiderhiiser & Reiss, 2007; Mustanski, Viken, Kaprio, Pulkkinen & Rose, 2004; Ellis, McFadyen-Ketchum, Dodge, Pettit & Bates, 1999).

The neuroendocrine processes of puberty are thought to begin with the de-inhibition of the arcuate nucleus of the hypothalamus, which when active secretes gonadotropin releasing hormone (GnRH) pulses. Contributors to the de-inhibition of the arcuate nucleus are not fully understood, however the GABA-ergic, kisspeptin-GPR54 (Messager et al., 2005; Smith, Clifton & Steiner, 2006; Dungan, Clifton & Steiner, 2006), Neurokinin B (Topaloglu et al., 2008) and neuropeptide Y (El Majdoubi, Sahu, Ramaswamy & Plant, 2000) systems are implicated. GnRH pulses prompt secretion of luteinizing hormone from the anterior pituitary gland and follicle stimulating hormone, beginning as night-time sleep entrained pulses at puberty onset and progressing to 24-hour secretion by the end of puberty (Boyar, Finkelstein, Roffwarg, Kapen, Weitzman & Hellman, 1972).

At around 6-8 years, adrenarche – a process which occurs in parallel with but is distinct from hypothalamic-pituitary-gonadal axis activation – occurs. Adrenarche refers to an increase in androgens such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) from the zona reticulosa of the adrenal cortex. No trigger for adrenarche has been identified, however permissive action of leptin (related to adiposity; Plant, 2001; Mann & Plant, 2002) and kisspeptin-GPR54 systems (Smith et al., 2006) is speculated. As well as the physiological changes of pubic hair growth, change in sweat composition and odour, and oiliness of the skin and hair, adrenarche is thought to contribute to declining GABA-ergic activity. This results in increased glutamate concentration, which in turn prompts the onset of night-time GnRH secretion (Parent, Matagne & Bourguignon, 2005).

In boys, the increased luteinizing hormone prompted by GnRH pulses stimulates the Leydig cells of the testes resulting in a rise in circulating testosterone, some of which is converted to oestradiol, the actions of which include growth spurt and bone maturation (Bordini & Rosenfield, 2011).

In girls, luteinizing hormone stimulates the theca cells of the ovaries resulting in testosterone (mostly converted to oestradiol in the ovaries’ granulosa cells) and progesterone production. As
well as growth spurt and bone maturation, resulting physiological changes include breast growth, increased fat composition, growth of the uterus, increased thickness of the endometrium and the vaginal mucosa, and widening of the lower pelvis (Bordini & Rosenfield, 2011).

As a unitary construct, puberty is notoriously difficult to define and measure. It is a multiphasic process without any fixed order of progression through many of its stages. There is huge inter-individual variation in age of onset, speed of progression, and intensity of physiological and morphological changes. While physiological, morphological, cognitive and emotional changes associated with puberty loosely co-occur, there are not one-to-one relationships between the putative causal factors and outcomes of pubertal processes. Likewise there is a range of temporally correlated changes to social environment, life roles, and expectations which are likely to have their own impacts (Angold & Costello, 2006; Sisk & Foster, 2004; Dahl, 2004).

Stage of puberty, measured via morphological development, has been found by several large studies to be related to level of depression in girls, even when age and pubertal timing are controlled for (Angold, Costello & Worthman, 1998; Patton et al., 1996). However it has been questioned whether changes in rates of depression at adolescence associated with pubertal stage are specifically related to the physiological changes of puberty, or whether changing sociocultural influences cued by the visible manifestations of puberty are the primary precipitators of depression. This problem has been clarified by the addition of hormonal variables into the model (Angold, Costello, Erkanli & Worthman, 1999), which eliminated the effect of morphological status, strongly implicating the effects of oestrogen in the development of depression in adolescent girls. Interestingly, such effects of hormonal level may be restricted to transitional stages – for example, while peripubertal testosterone and oestradiol levels have been associated with depression, post-pubertal levels have not (Angold & Costello, 2006).

1.3 Female gender as a risk factor for depression

One of the most striking features of depression in adolescence is the sudden sharp increase in onset observed at around 13-15 years, largely accounted for by increased incidence in females, which climbs to around double that in males at this time (Weissman et al., 1996; Blazer, Kessler, McGonagle & Swartz, 1994; Kessler, McGonagle, Nelson, Hughes, Swartz & Blazer, 1994; Wells, Bushnell, Hornblow, Joyce & Oakley-Browne, 1989; Wittchen, Essau, von Zerssen, Krieg & Zaudig, 1992; Hankin, Abramson, Moffitt, Silva, McGee & Angell, 1998; Angold et al., 1998; Cairney, 1998). Although studies have generally found little gender difference in depression in prepubescent children, by 15 years of age females are twice as likely as males to have experienced
a major depressive episode (e.g., Hankin et al., 1998; Anderson, Williams, McGee & Silva 1987; Angold & Rutter, 1992; Nolen-Hoeksema, Girgus & Seligman, 1991; Cohen et al., 1993; Angold et al., 1998). Females are nearly twice as likely as males to experience case-level depression diagnoses (McGrath, Keita, Strickland & Russo, 1990; Kessler et al., 1994; Nolen-Hoeksema, 1990; Weissman & Klerman, 1977), and this finding holds true across a variety of cultures and racial/ethnic groups (Gater, Tansella, Korten, Tiemens, Mavreas & Olatawura, 1998). Furthermore, studies of non-clinical depressed mood states have shown that women experience more symptoms during episodes of depressed mood than do men (Wilhelm, Parker & Asghari, 1998).

This pattern is evident both in case level depression diagnosis, and in dimensional measures of depressive symptomatology. Figure 1 is reproduced from Angold and Costello (2006) and shows data from the Great Smoky Mountains Study (totalling 7,746 observations from 1,420 participants) on DSM-IV case level depression in adolescent boys and girls.

![Figure 1. Age and prevalence of unipolar depression in the Great Smoky Mountains Study (Angold & Costello, 2006).](image-url)
Figure 2 (also from Angold and Costello, 2006) shows the results of meta-analyses of samples using depression scale scores from the Childhood Depression Inventory (totalling over 43,000 observations; Twenge & Nolen-Hoeksema, 2002) and the Short Mood and Feelings Questionnaire (over 8,500 observations; Angold, Erkanli, Silberg, Eaves & Costello, 2002).

![Graph](image)

**Figure 2.** Age and depression scale scores from the Childhood Depression Inventory and the Short Mood and Feelings Questionnaire (reproduced from Angold and Costello, 2006).

The striking rise in prevalence of both case level depression and depressive symptomatology in early adolescence is well illustrated in these figures. It is also evident that while there is some rise in incidence of depression in adolescent boys, this stabilises in late adolescence and is far less dramatic and sustained than the increase in depression for adolescent girls.

Interestingly, the other life stage associated with a similarly sharp spike in depression onset is post-partum, suggesting that biological processes associated with pubertal development and childbirth contribute to depressive aetiology in women. However, the preponderance of female
depression is attributed solely to a greater rate of onset; men and women have been found to have similar course of illness and similar relapse and recovery rates after depression onset (Kessler, 2000).

Two major reporting artefacts have been cited as potentially contributing to the reported gender gap in depression; a help-seeking artefact, and a recall artefact. The help-seeking artefact refers to a perceived reticence in males to seek treatment or advice for depressive symptoms, which could explain the preponderance of females reporting for treatment. However, in a comparison of data from two worldwide multicentre studies conducted by the Cross National Collaborative Group and the WHO worldwide epidemiological survey for WHO, Kuehner (2003) found that the rates of depression identified in community samples were in accord with those reported from primary care settings. The recall artefact postulates that women’s recall is biased in favour of past negative affective states, and thus women report a higher rate of lifetime depression. Kuehner (1999) conducted a controlled test of this by comparing men and women’s reports of depressive symptomatology during a depressive episode, and their recall of these symptoms six months later. He found no recall artefact: there was no disparity between males and females in the differential between the reported severity of symptoms at times one and two.

A third suggested artefact is that the higher rate of sexual abuse and rape experienced by girls and young women accounts for subsequent depression rates, although it is worth noting that is this does not constitute an artefact per se, but rather a potential etiological explanation for the gender difference in mood disorders. Kessler (2000) did find that after rape and sexual trauma were controlled for in a population database, the gender difference in a first episode of depression was halved. However, when traumatic experiences more likely to be experienced by men were also controlled for, the female preponderance was restored. Findings such as these suggest that the increased prevalence of depression in females is not due to artefact.

There are several theories on the reasons behind the gender gap in depression. Some have interpreted this pattern as reflecting sociocultural pressures on women. The gender intensification hypothesis (Hill & Lynch, 1983; Wichstrom, 1999) suggests that exacerbated gender socialisation pressures cause gender role orientations to intensify over the adolescent years. For women, these socialisation experiences are suggested to promote assumptions that emphasise collectivity and a lower sense of self-esteem amongst girls, which in turn contribute to the increase in depressive symptoms in women. Intensified gender typing, according to this theory, leads to deficits in efficacy and instrumentality, reflected in low levels of traditionally masculine personality characteristics, which may place adolescent girls at higher risk for
depression through greater exposure to experiences that promote learned helplessness (Obeidallah, McHale & Silbereisen, 1996).

Aside from the difficulties designing research which would allow strong causal inferences to be drawn regarding socialisation and the emergence of the gender gap in mood disorders, there is also some literature that is inconsistent with this hypothesis. Studies documenting the trajectories of children’s own gender role concepts have shown that the rigidity of children’s gender stereotypes tends to lessen as adolescence approaches. These studies have also found that boys are likely to labour under more rigid self-imposed sex-types than girls (Banerjee & Lintern, 2000). The emergence of the gender gap at adolescence has been cited as support for gender intensification theories; however the onset of the gender difference in depression is not predicted by age as such, but rather by pubertal status of the individual (Angold et al., 1999). This suggests that biological factors have at least an interacting role with sociocultural ones in contributing to the female preponderance of depression.

In addition to sociocultural interpretations, biological factors have been proposed as causal factors behind the gender gap in adolescent onset depression, including that the maturation of the female hypothalamic-pituitary-gonadal system during puberty may have a direct relationship with the emergence of depression (Angold & Costello, 2006). At puberty, females’ hormonal levels begin to fluctuate cyclically over a broader spectrum than males’. Oestrogen in particular is recognised as playing an important role in mediating females’ sensitivity to stress. Oestradiol apparently acts as an anxiolytic, and thus the cyclical withdrawal of oestrogen that occurs shortly prior to menstruation may be analogous to the physiologic effects of anxiolytic withdrawal, creating a greater sensitivity in menarcheal and adult females to the anxiogenic and depressogenic effects of negative life events.

The precipitants of early episodes of depression are usually social events. The breakup of a romantic relationship is particularly potent for young people, with almost half of all adolescents with a first episode of depression having had a relationship breakup in the preceding year (Monroe, Rohde, Seeley & Lewinsohn, 1999). Rejection by peers also has particular salience for adolescent depression and other interpersonal failures and social disappointments are commonly identified as precipitants (Vernberg, 1990; Hecht, Inderbitzen & Bukowski, 1998; Prinstein & Aikins, 2004). It has been suggested that increased affiliative proclivities amongst females, in combination with the alteration in gonadal steroids associated with puberty, render them more vulnerable to the depressogenic consequences of interpersonal failures during adolescence (Cyranowski, Frank, Young & Shear, 2000; Brooks-Gunn & Warren, 1989).
Female gender is perhaps the most outstanding risk factor for developing depression during adolescence, however there are several other well-established risk factors for both girls and boys, which are discussed below.

1.4 Family environment and familial depression

One of the strongest predictors of adolescent depression is parental depression. Heritable factors are particularly implicated in adolescent onset depression, which has been found to have a greater genetic component than prepubertal depression (Scourfield, Rice, Thapar, Harold, Martin & McGuffin, 2003). Heritable depression appears to be cotransmitted with anxiety symptoms – the genetic propensity for anxiety may in fact predispose children to depression by creating a diathesis for increased sensitivity to negative life events known to predict depression onset in adolescents (Thapar & McGuffin, 1997; Eaves, Silberg & Erkanli, 2003; Zalsman et al., 2006).

At early adolescence, family interactions are still a social environment of primary importance for young people (Sheeber, Allen, Davis & Sorensen, 2000). Notably, it appears that family relations are more reliable predictors of adolescent depressive symptomatology than are peer relations (Barrera & Garrison-Jones, 1992; Stice, Ragan & Randall, 2004). There are strong relationships between family interactions and both internalising and externalising spectrum psychopathologies. Key variables associated with internalizing symptomatology include elevated levels of harsh and conflictual interactions and low levels of warmth and support (Sheeber & Sorensen, 1998). Family environments of clinically and sub-clinically depressed adolescents are likely to involve high levels of harsh and conflictual interactions as well as low levels of support. Such family variables also predict increases in depressive symptomatology over time (Sheeber, Hops, Alpert, Davis & Andrews, 1997). Parenting variables emerging as important predictors of emotion dysregulation include punitive responses to adolescent emotional behaviour as well as parents’ own emotional dysregulation. Adolescents’ involvement in marital conflict may also predict increases in aggressive and depressive behaviour, beyond that predicted by the conflict itself (Davis, Hops, Alpert & Sheeber, 1998; Davis, Sheeber, Hops & Tildesley, 2000; Eisenberg, Cumberland & Spinrad, 1998; Gross & Munoz, 1995; Lindahl, Clements & Markman, 1998).

Parental depression may also influence adolescent depression through socialization of adolescent affective behaviour, for example modelling of depressive behaviours, social styles and cognitive distortions, all of which the child may have an elevated sensitivity to (Hammen, Shih, Altman & Brennan, 2003; Diego, Sanders & Field, 2001; Frye & Garber, 2005; Scourfield et al., 2003; Hammen, Burge & Stansbury, 1990). Parents’ reinforcing responses to adolescent dysphoric
behaviour (i.e., conditional increases in nurturant responses and decreases in aggressive behaviour) are associated with both elevated levels of depressive symptomatology and longer duration of dysphoric behaviour (Sheeber et al., 1998; Sheeber, Hops & Davis, 2001). Parental socialization of adolescent emotion, construed broadly to reflect parents’ own emotional expression as well as their responses to their children’s emotional behaviour, has been related to both adolescent depressive symptomatology and adolescent emotion regulation (Yap, Allen & Ladouceur, 2008; Yap, Allen & Sheeber, 2007). Relationships between the familial environment and depression are further explored in Chapter 4.

1.5 Temperament
Temperament is a constitutionally-based individual difference that is likely to influence the interactions of affective reactivity and regulation, and therefore has the potential to contribute to vulnerability for psychopathology (Rothbart, Ahadi & Evans, 2000). Significant and stable relationships have repeatedly been established between mental disorders and higher-order personality/temperament dimensions, and childhood temperament can act as a risk factor for a range of adverse developmental outcomes (Pickering & Gray, 1999; Clark, 2005). For example, Krueger (1999) found that temperamental traits of negative emotionality, constraint, agency and communion in 18 year old participants were better predictors of mental disorder at 21 years than was mental disorder at 18 years. High negative emotionality (or neuroticism) was particularly predictive of affective disorders. High negative affect has been established as a risk factor for subsyndromal and case level mood and anxiety disorder in both adolescence and adulthood in a range of studies (Caspi, Henry, McGee, Moffitt & Silva, 1995; Clark, Watson & Mineka, 1994; Klein, Dougherty, Laptook & Olino, 2008; Lonigan, Phillips & Hooe, 2003; Krueger, 1999).

Response styles characterised by low levels of flexibility in response to changes in the environment and a tendency to withdraw from novel stimuli, and to experience negatively valenced moods have been associated with depression in adolescence (e.g., Muris, Meesters & Spinder, 2003; Muris, Merckelbach, Schmidt, Gadet & Bogie, 2001; Windle, 1992; Windle & Mason, 2004; Leve, Kim & Pears, 2005). For example, Betts, Gullone and Allen (2009) found that adolescents with higher self-rated depressive symptomatology scored lower on temperamental approach, flexibility, and positive mood quality.

Effortful control (the ability to inhibit a dominant response in order to perform a subdominant response) has most frequently been associated with externalising disorders, however there is also evidence of an association with depressive symptoms (Compas, Connor-Smith & Jaser, 2004;
Muris, van der Pennen, Sigmond & Mayer, 2008). Kendler, Gardner and Prescott (2002; 2006) noted that, in addition to the development of depression associated with high negative emotionality, there was another pathway characterised by externalising symptoms in early adolescence (and low effortful control), which in turn predicted subsequent onset of depression. It has been suggested that this association may work through an inability of young people with low effortful control to engage in coping behaviours such as distraction or disengagement from sources of emotional distress (Compas et al., 2004). Additionally, the conduct problems often associated with low effortful control tend to have adverse consequences within themselves that may be depressogenic (Burke, Loeber, Lahey & Rathouz, 2005). As temperament in childhood is thought to confer vulnerability to psychopathology in adolescence and adulthood, temperament dimensions were used in an initial screening of the participants for this project, with the aim of creating a risk-enriched sample (see Chapter 6 for more detail).

1.6 Socioeconomic status

It is a well established finding that adolescents living in low socioeconomic status (SES) contexts are at greater risk for depression symptoms than those living in higher SES families (e.g., Kaplan, Hong & Weinhold, 1984; Graham & Easterbrooks, 2000; Siegel, 2002). Goodman, Slap and Huang (2003) examined the impacts of SES on adolescent mental and physical health at the population level, using data from the National Longitudinal Study of Adolescent Health. They analysed parental education and household income, as well as body mass index and scores on the Center for Epidemiologic Studies – Depression scale (CES-D) for over 15,000 adolescents, and found that low household income and low parental education were associated with approximately one third of the depression observed in the sample. The risk for depression attributable to low SES was not restricted to the lowest quintile, but rather followed a linear pattern. They also noted that low parental education accounted for more of the risk than low household income. The authors speculated that the particular effect of education may be related to differences in coping styles and interpersonal skills. Others have suggested that SES is likely to have its most consistent impact on depression in children through parenting practices, which have been found to be more problematic among parents of lower socioeconomic status (Kim & Ge, 2000; McLoyd, 1998).

Interestingly, in a sample of 2014 early adolescents, MacPhee and Andrews (2006) found that SES only predicted depressive symptoms for females, and that the relationship between SES and depression was mediated by parental nurturance. This suggests that females from low SES
backgrounds are placed at particular risk for depression when they experience low levels of warmth and nurturance from parents. This may also tie in with earlier research which reported that negative parenting practices result in greater vulnerability to depression in girls than in boys (Ge, Lorenz, Conger, Elder & Simons, 1994; Liu, 2003). Based on the evidence that lower SES, and particularly lower parental education, is a risk factor for depression, parental education was used as a covariate within the design of this research (see Chapter 6).

1.7 Summary
This chapter has discussed the prevalence, clinical presentations, and risk factors for adolescent depression, with a special focus on pubertal neuroendocrinological processes both as an overall influence on affective experience, and as a particular risk factor for the development of depression in girls. The following chapter will examine the neurodevelopmental processes that accompany puberty and adolescence, and will discuss how developmental processes in physical, cognitive, affective and psychosocial domains may interact to buffer or expose adolescents to risk for depression.
Chapter 2: Depression and brain development

Having discussed the epidemiology and established risk factors for adolescent depression in the previous chapter, this chapter will focus on the aspects of adolescent emotional, cognitive and neurobiological development thought to relate to risk for depression. The putative relationships between individual brain structures and adolescent onset depression and evidence regarding each structure is discussed in more detail in Chapter 3. The following chapter discusses neurobiological models of adolescent psychopathology that attempt to link neuroanatomical, functional and psychological findings to give integrated accounts of the development of depression in the maturational context of adolescence, beginning with a description of normative structural changes in the adolescent brain.

2.1 Adolescent brain development

The following section describes patterns of grey and white matter development in cortical and subcortical regions in childhood and adolescence, including sexually dimorphic patterns of development. As this thesis studies the structural aspects of adolescent brain development, a description of normative adolescent structural neurodevelopment is given below.

The brain maturation that occurs across the second decade of life is hypothesised to involve myelination, increase in axonal calibre, and cortical synapse elimination (Andersen, 2003; Huttenlocher, 1984; Huttenlocher & Dabholkar, 1997; Paus, 2009). Myelination increases the efficiency of communication between functionally distributed structures, while synaptic pruning contributes to refinement and specialisation in the neural circuitry that strengthens remaining connections and reduces competition from suboptimal associations. Thus both processes contribute to a steady improvement of communication between distributed systems. Brain maturation appears to follow a broad posterior to anterior and inferior to superior temporal pattern. This is the case for myelination (Barkovich, 2000) and for grey matter loss (Wilke, Krageloh-Mann & Holland, 2007).

2.1.1 Cortical grey matter

Brain maturation during adolescence is broadly characterised by reductions in grey matter, attributable to synaptic pruning. It has been repeatedly observed that grey matter development follows an inverted U-shaped trajectory throughout childhood and adolescence (Giedd et al. 1999a; Sowell, Trauner, Gamst & Jernigan, 2002; Wilke et al., 2007). This is thought to reflect
prolific synaptic arborisation in early childhood, and a more attenuated pattern of grey matter increase in later childhood, followed by a second wave of synaptogenesis (particularly in the prefrontal cortex) at the onset of puberty (Blakemore & Choudhury, 2006).

Lenroot and colleagues (2007) examined normal brain development in 829 structural magnetic resonance imaging (MRI) scans from a sample of 387 healthy children 4-22 years of age. Total grey matter peaked at 8.5 years in females and 10.5 years in males. Grey matter cortical volume changed in different ways and rates in different cortices. In the frontal lobe, grey matter reached its peak volume at 9.5 years for females and 10.5 years for males, then began to decline after adolescence. Parietal lobe grey matter also increased prior to adolescence, with a peak at 7.5 years for females and 9 years for males before declining. Temporal lobe grey matter reached its peak volume at 10 years for males and 11 years for females, and demonstrated less subsequent reduction than frontal and parietal lobes. The trajectory for occipital lobe grey matter was less clear. In an earlier study using a smaller sample, Giedd and colleagues (1999a) demonstrated a linear increase in occipital grey matter with age, without a decline or plateau within the age range studied. However in the study by Lenroot and colleagues (2007), there appeared to be a mild but steady decline in occipital grey matter volume with increasing age.

Regional gender differences in grey matter include increased anterior cingulate gyrus (Paus et al., 1996a), and dorsolateral prefrontal cortex (Schlaepfer, Harris, Tien, Peng, Lee & Pearlson, 1995) grey matter volumes for females as compared to males, and increased paracingulate cortex grey matter in males (Paus et al., 1996). Lenroot and colleagues (2007) also noted that females showed greater grey matter to white matter ratios in the frontal lobes particularly, while Good, Johnsrude, Ashburner, Henson, Friston and Frackowiak, (2001) noted greater grey matter for females in frontal areas as compared to males.

2.1.2 Cortical white matter

Lenroot and colleagues (2007) found that total white matter increased with age across all cortical areas in childhood and adolescence. The rate of increase was greater for males than females in the frontal, temporal, parietal and occipital lobes, but not in the corpus callosum. This is consistent with several other findings of an absolute and relative increase in cortical white matter throughout childhood and adolescence, resulting in a higher ratio of white to gray matter than in earlier childhood. The ratio of white to grey matter diverges between males and females in adolescence, with males having more white matter relative to grey matter (Paus, Collins, Evans, Leonard, Pike & Zijdenbos, 2001). Giedd and colleagues (2001) reported a greater increase in cortical white matter for males than females, a finding also noted by DeBellis and colleagues.
(2001) in a sample aged 6 to 17 years. Changes in white matter density (as distinct from volume) have also been noted, particularly decreased density for boys in the posterior limb of the internal capsule (the putative cortico-spinal tract) and in the left arcuate fasciculus, connecting anterior and posterior language areas (Perrin et al., 2009; Schmithorst, Holland & Dardzinski, 2008). Decreases in white matter density are suggested to be associated with rising levels of testosterone during adolescence (Perrin et al., 2009).

Paus and colleagues have argued that decreases in white matter density for males during adolescence, observed via diffusion tensor imaging and magnetisation-transfer imaging, suggest that the increase in white matter volume observed during this period cannot be accounted for by increasing myelination alone, but rather through a combination of myelination and relative increase in axonal diameter (Perrin et al., 2009; Perrin et al., 2008). Both myelination and axonal diameter affect conduction velocity; it has also been suggested that axonal calibre is affected by androgens and has effects on processes linked to cell metabolism and neurotransmission (Paus, 2009).

2.1.3 Corpus callosum

The corpus callosum has been observed to grow in area from birth through to the mid-twenties (Pujol, Vendrell, Junque, Marti-Vilalta & Capdevila, 1993; Lenroot et al., 2007). While myelination follows a posterior to anterior time sequence after birth, childhood and adolescent growth in the area of the corpus callosum appears to occur largely in the posterior section, particularly the splenium (Giedd et al., 1999b; Thompson, Giedd, Woods, MacDonald, Evans & Toga, 2000). Sexual dimorphism of the corpus callosum has been noted in some studies, in particular that females’ corpora callosa are larger in relation to total brain size, and demonstrate larger splenium sizes than males (e.g., De Lacoste-Utamsing & Holloway, 1982; De Lacoste-Utamsing, Holloway & Woodward, 1986; Allen, Richey & Chai, 1991; Yoshi, Barker, Apicella, Chang, Sheldon & Duara, 1986), whereas males demonstrate larger genu sizes than females (Dubb, A. Gur, Avants & Gee, 2003). It has been suggested that females’ larger splenium sizes may be related to enhanced bihemispheric representation of language function in females whereas the larger male genu may be related to enhanced motor coordination in men (Dubb et al., 2003; Saykin et al., 1995). However, null findings are also frequently reported, and methodological differences in measurement and image pre-processing have further complicated the issue (Giedd et al., 1996a; Giedd et al., 1996b; Bermudez & Zatorre, 2001).

Contrary to the overall trend for greater white matter growth in males than females during adolescence, no gender differences are apparent in corpus callosum growth during this period,
which takes the form of a linear increase in volume throughout adolescence (Giedd et al., 1999b, Lenroot et al., 2007). Dubb and colleagues (2003) noted some gender differences in corpus callosum age-related changes, (splenial expansion in females and genu contraction in males), however these occurred largely in the third decade of life.

2.1.4 Subcortical structures

There is not a homogenous pattern of structural development for subcortical areas. In a large cross-sectional study of subcortical brain development using 171 participants aged 8-30, Østby, Tamnes, Fjell, Westlye, Due-Tønnessen and Walhovd (2009) found differential developmental trajectories for several subcortical structures. Basal ganglia grey matter was reported to exhibit a weak negative relationship with age; this finding has been replicated elsewhere, particularly in the head of the caudate and in males (Thompson et al., 2000; Durston, Hulshoff Pol, Casey, Giedd, Buitelaar & van Engeland, 2001). Although the overall pattern was for grey matter reduction with age (including reduction in cortical thickness and surface areas in all lobar regions), they found grey matter volume increases in the hippocampus and amygdala. In a cross-sectional study of children aged 5-18 years, Wilke and colleagues (2007) also detected a volumetric increase in medial temporal lobe structures.

Hippocampal increases have been observed (Giedd et al. 1996a; Toga, Thompson & Sowell, 2006) however null findings have also been reported (e.g., Bigler et al., 1997). Gogtay and colleagues’ (2006) analysis of 31 children and adolescents, scanned every 2 years between ages 4 and 25, addressed many of the methodological issues suggested to contribute to the discrepant findings regarding hippocampal development. They used a technique for spatiotemporal mapping of the hippocampal surface, which allowed measurement of localized growth or reduction in grey matter volumes for individuals over time. Age-related structural changes in the hippocampus were found to differ between posterior subregions, whose volume increased with age (particularly in the left hemisphere and for females), and anterior subregions, whose volume decreased with age (particularly in the right hemisphere and for males). These divergent patterns of development may reflect functionally distinct subregions of the hippocampus; it has been suggested that the posterior hippocampus subserves spatial learning and memory functions while the anterior region is more involved in emotional processing (particularly anxiety-related functions; Bannerman et al., 2004).

Gender differences have been reported in the relative size of subcortical structures. Relatively larger caudate volumes have been reported for females in several studies (see Durston and colleagues, 2001, for review). Larger amygdala complex sizes (relative to total cerebrum size)
have also been described in male children and adults (Good et al., 2001; Durston et al., 2001; Goldstein et al., 2001). Several studies have noted increased relative hippocampal size in females compared to males in adults (Filipek, Richelme, Kennedy & Caviness Jr, 1994; Murphy et al., 1996) and children (Caviness Jr, Kennedy, Richelme, Rademacher & Filipek, 1996). Durston and colleagues (2001) speculate that larger amygdala volumes in males and larger hippocampal volumes in females may be related to sex hormone differences, noting that the hippocampus contains predominantly oestrogen receptors, whereas the amygdala contains predominantly androgen receptors.

2.1.5 Summary

The development of cortical grey matter generally follows an inverted U-shaped trajectory throughout childhood and adolescence. Peak grey matter volume appears to be reached earlier for girls in most cortical areas. Giedd and colleagues (1999a) suggest that this may correspond with the earlier onset of puberty for girls. A greater increase in cortical white matter is observed in adolescence for males than females, and the corresponding reduction in grey matter occurs at a greater rate in males than females (Giedd et al., 1999a; DeBellis et al., 2001). The exception to this pattern is the corpus callosum, which increases in volume linearly for both genders, and may be proportionately larger in females than males. The net effect of these changes appears to be a greater ratio of grey to white matter in the female brain as compared to the male brain, particularly in the anterior cingulate cortex (Paus et al., 1996a; Good et al., 2001) and frontal areas (Schlaepfer et al., 1995).

Heterogeneous developmental trajectories have been observed for subcortical regions; for example basal ganglia structures have been noted to decrease in volume with age while the amygdala and hippocampus appear to increase in size through adolescence (Durston et al., 2001), although gender differences in these trajectories have been noted. Gender differences in timing and rate of grey and white matter alterations may be related to differential influences of sex steroids on neurodevelopment. For example, testosterone has been associated with myelogenesis (Melcangi et al., 1988; Martini & Melcangi, 1991), which may be relevant to the greater increase in white matter volume for males, while oestadiol may inhibit synaptic pruning in some brain regions (Naftolin, Garcia-Segura, Keefe, Leranth, Maclusky & Brawer, 1990) which may be relevant to decrease grey matter loss in females, and has been associated with hippocampal cell proliferation and synaptogenesis (Tanapat, Hastings, Reeves & Gould, 1999; Gould, Woolley, Frankfurt & McEwen, 1990; Woolley, Jurgen Wenzel & Schwartzkroin, 1996), which may contribute to the larger hippocampi observed in females.
While these dramatic neurodevelopmental processes are not apparent to the naked eye, they interact with and underpin the most obvious and characteristic observable alterations in children as they advance towards adolescence – puberty, cognition, and affective reactivity.

2.2 Brain development, emotional experience and cognitive and affective regulation

It has often been a source of consternation for those dealing with adolescents that, while their ability to think and reason rationally evidently improves greatly during adolescence, their behaviour is often characterized by emotionality, risk-taking, impulsivity, and novelty-seeking. The influence and importance of peers in particular can seem disproportionate and can eclipse other, more long-term motivations (Spear, 2000).

Cognitively, adolescence is characterised by improvements in information processing speed and capacity, logic and deductive reasoning, and general expertise, rendering adolescents capable of better long term planning, metacognition and abstract thought. For example, research has documented cognitive improvements such as voluntary initiation and suppression of eye movements (Luna et al., 2001), and selective attention and response inhibition during adolescence (Booth et al., 2003; Paus, 2005). These cognitive improvements correspond less to pubertal stage than to age and experience (Keating, 2004). Cold cognition reaches close to adult levels in mid-adolescence, however adolescent cognition cannot be accurately characterised without placing it in context, recognising key changes in affective experience and motivation that also occur during this developmental period.

Many adolescents experience an upswing in the intensity of emotional responses. Studies have found a significant association between pubertal stage and behavioural measures of affective reactivity such as sensation seeking and risk-taking (e.g., Martin et al., 2002). That pubertal stage, and not age, has been associated with affective reactivity implicates the biological changes associated with puberty, particularly the influx of gonadal steroids. The amygdala/hippocampus, ventral striatum, and hypothalamus, all implicated in affective processing, are densely innervated by gonadal steroid receptors (Sisk & Foster, 2004). Gonadal steroids have also been found to be linked with sensitivity to social status (Rowe, Maughan, Worthman, Costello & Angold, 2004), and to regulate neurotransmitter systems associated with affective and social response (Osterlund & Hurd, 2001; McEwen, 2001; Epperson, Wisner & Yamamoto, 1999).

One of the fundamental challenges of negotiating adolescence is the integration of newly developed cognitive mechanisms with increased emotional reactivity. Social situations are thought to be especially emotionally provocative for young adolescents, and therefore constitute
an important context within which to consider adolescent affect, behaviour and decision-making. Social and sexual stimuli become far more salient to the individual at adolescence, and primary social bonds begin to extend beyond the bonds of family. This is particularly relevant to understanding adolescent behaviour; while adolescents rapidly approach an adult-like understanding of the potential risks of various activities, they are still far more likely to undertake risky behaviours than adults, perhaps partially due to difficulties in consolidating this hypothetical cognitive understanding of risk with the social demands and motivations of risk-taking in context, and also due to a heightened intensity of reward experienced during social interactions (Cauffman & Steinberg, 2000; Steinberg & Cauffman, 1996).

2.2.1 Maturational disparity
As discussed above, entrance to adolescence is associated with cognitive, social, affective and neurodevelopmental changes. While these developmental processes occur within relative temporal proximity, they do not necessarily occur in synchrony, and are not driven by the same biological schedules (Dahl, 2004). Maturational disparity theories suggest that significant desynchrony between the development of some of these capacities at early adolescence forms a risk factor for future psychopathology (Steinberg, 2005).

In their 2009 statement on the legal system’s stance on adolescent maturity, Steinberg, Cauffman, Woolard, Graham and Banich demonstrated that separation exists between adolescents’ basic cognitive abilities, and other factors which affect decision-making in real-world contexts (which they termed psychosocial maturity). The construct of psychosocial maturity contained measurements of risk perception, sensation seeking, resistance to peer influence and future orientation. As shown in Figure 3, while cognitive abilities reach close to adult levels from around 16 years, psychosocial maturity follows a far more protracted course of development extending into the 20s.
Figure 3. Proportion of individuals in each age group scoring at or above the mean for 26- to 30-year-olds on indices of cognitive capacity and psychosocial maturity (reproduced from Steinberg et al., 2009).

This suggests that while adolescents may have the required cognitive and regulative abilities to avoid risky or impulsive behaviour under some conditions, under others their decision-making is more influenced by the social and emotional currents of the moment than by rational considerations of risk and consequence. This explains findings such as those of Gardner and Steinberg (2005) who measured the number of risky decisions made during a driving simulation in adolescents and adults. In one condition, the game was played alone, and levels of risky driving were comparable across the three age groups. However, when the game was played in the presence of peers, adolescents doubled the amount of risky decisions they made, whereas the presence of peers did not affect the driving behaviour of the adults.

2.3 Neurodevelopmental models of affect and depression

The maturation of self-regulatory skills required for good decision-making is thought to be associated with the brain remodelling described earlier. The regions which show some of the most protracted and radical remodelling are those associated with social cognition, response inhibition, monitoring, the capacity for abstract, reflective and hypothetical thinking, and affect regulation (Nelson, Leibenluft, McClure & Pine, 2005; Paus, 2005). Affect regulation represents the subset of processes involved in the adaptive modulation of affective experiences, particularly the strategic control of feelings in the service of a goal or purpose. Typically, this modulation involves inhibition, delay, or alteration of emotional expression and behaviour in ways that incorporate social rules, long-term goals, or avoid future negative consequences (Dahl, 2004;
Thompson & Fox, 1994). While affective states are thought to be driven largely by early-maturing subcortical areas, the development of successful affect regulation is thought to be partially dependent on the later maturation of frontal regions associated with inhibitory control and calibration of risk and reward (Steinberg, 2005; Drevets, 2001; Newman & Grace, 1999). Affect regulation involves not only modulating emotionally motivated behaviour, but also being able to modulate internal states adaptively. Thus affect dysregulation has been a causal descriptor for a spectrum of psychopathologies, both externalising and internalising.

2.3.1 A focus on positive affect and reward

Forbes and Dahl (2005) argue that the description of “affect dysregulation” is insufficient to characterise depression, and proposed that future models disentangle the alterations in positive and negative affect associated with depression and identify neurological substrates for the processes. They propose that although heightened negative affect is an easily recognised sign of depression, reduction in positive affect lies at its core, and also differentiates depression from other disorders such as anxiety (Clark & Watson, 1991). In the most fundamental terms, positive affect is defined as the emotional state elicited by reward (Rolls, 1999) and its absence is exemplified in the core depressive symptom of anhedonia. This idea has been borne out in research showing alterations in subjective, behavioural, and physiological responses to pleasant stimuli. For example, adults with depressive disorders have been found to show attenuated responses to pleasant or amusing stimuli (Rottenberg, Kasch, Gross & Gotlib, 2002; Sloan, Strauss, Quirk & Sajatovic, 1997; Sloan, Bradley, Dimoulas & Lang, 2002) and poorer memory for such stimuli (Sloan, Strauss & Wisner, 2001; Deldin, Deveney, Kim, Casas & Best, 2001).

The mesolimbic and mesocortical dopaminergic pathways, which connect the ventral tegmental area of the midbrain with the limbic system and cerebral cortex, are thought to subserve reward functions. The nucleus accumbens, striatum, orbitofrontal cortex, dorsolateral prefrontal cortex, and amygdala are particularly implicated in the processing of reward (Dalgleish, 2004; Rolls, 2000). The nucleus accumbens is heavily implicated in receiving dopaminergic inputs from the ventral tegmental area in response to both natural reinforcers and drugs of abuse (Carelli, 2002). The striatum is suspected to play a function in reward detection and production of reward-seeking behaviour (Schultz & Romo, 1988) and the orbitofrontal cortex is associated with the expectation of reward (Schoenbaum, Chiba & Gallagher, 1998). The amygdala is thought to play a role in associating stimuli with rewards, and in reward response (Baxter & Murray, 2002) while the dorsolateral prefrontal cortex putatively subserves varied functions such as the anticipation of reward, maintenance of goal-related information and initiation of reward-related behaviour.
Structural abnormalities in several areas thought to be associated with reward processing have been identified – many of these will be discussed further in the following chapter.

2.3.1 The triadic model

The role of positive affect in depression has also been conceptualised through motivation based models (e.g., Depue & Iacono, 1989), which characterise behaviour as governed by appetitive and aversive systems. Ernst, Pine and Hardin’s (2005) triadic model of motivated behaviour extends Gray’s (1972) model of neurobehavioural approach and avoidance systems to include a regulatory arm. The neural correlates of the approach system are suggested to include the dorsolateral prefrontal cortex, ventral striatum and dopaminergic action, while the amygdala, temporal pole and serotonergic action is implicated in the avoidance system (Davidson, 1998). The circuits of the prefrontal cortex are proposed as the regulatory arm, calibrating the relative influences of the approach and avoidance systems on behaviour.

The triadic model proposes that adolescence is characterised by a dominance of reward system activity, reflected in behavioural features of novelty seeking and impulsivity, high sensitivity to reward, including susceptibility to drugs of abuse (Chambers, Taylor & Potenza, 2003) and lowered sensitivity to risk (Steinberg, 2004; Ernst et al., 2005). The activity of several areas in the prefrontal cortex has been associated with executive functions concerning monitoring and modulating behavioural responses to valenced stimuli (e.g., Bush, Luu & Posner, 2000; Blair, 2004). The triadic model can be said to generate a maturational disparity theory for depression, in that it proposes that adolescent onset psychopathology can be described as an imbalance between the action of the approach and avoidance arms, which are yet to fall under the control of the late-developing regulatory arm.

2.3.2 Prefrontal vulnerability theory

An alternative theory as to the relevance of the maturing prefrontal areas is suggested by Davey, Yücel and Allen (2008) who propose that rather than the delayed development of the prefrontal cortex causing a lack of regulatory capacity, it is in fact the development of certain prefrontal capacities themselves which predispose adolescents to depression. They suggest that as the prefrontal cortex develops, the pursuit of more complex and distal rewards becomes possible. According to their theory, motivation and arousal are nested in a hierarchy such that higher-order (more abstract and distant) reward representations underpin the motivations for lower-order rewards. As the capacity for representation of higher-order rewards becomes more
sophisticated, these representations also become *requisite* for lower-order rewards to maintain their reinforcing properties. The depressogenic aspect of this, they suggest, is that the complex and distal rewards anticipated by the developing prefrontal cortex are more easily frustrated both by nature of their complexity, and their interpersonal quality during a developmental period when interpersonal relationships are notoriously volatile. Frustration of these distal rewards is then thought to lead to suppression of the motivating value of nested lower-order rewards, resulting in the clinical picture of reduced positive affect, motivation, and engagement with previously pleasurable activities.

2.3.3 The social re-orienting of adolescence

As mentioned earlier, the negotiation of social interactions at this life stage is particularly germane to the study of adolescent mood disorder onset (Monroe et al., 1999). A hypersensitivity to acceptance and rejection by others has been observed during adolescence (O’Brien & Bierman, 1988; Larson & Richards, 1994), and Cyranowski and colleagues (2000) reported that the majority of stressors preceding the onset of adolescent depression are of an interpersonal quality. Indeed, much of the rewarding stimuli discussed in the theories already mentioned is of an interpersonal nature – for example the higher order dimension of positive affectivity includes the components of affiliation (the rewards associated with interpersonal bonds) and agency (including rewards associated with social dominance and leadership; Depue and Collins, 1999). Nelson and colleagues (2005) have proposed a model of adolescent depression which, while conforming to a basic maturational disparity outline, emphasises what they term the “social reorienting of adolescence” and its neural underpinnings as a critical factor in the development of depression.

They outline the existence of three nodes of social information processing – the detection node, the affective node and the cognitive-regulatory node. The detection node is comprised of the inferior occipital cortex, inferior regions of the temporal cortex, the intraparietal sulcus, the fusiform face area, the superior temporal sulcus and the anterior portion of the temporal cortex in detection and evaluation of basic properties. The affective node includes the amygdala, ventral striatum, septum, bed nucleus of the stria terminalis, hypothalamus, and orbitofrontal cortex, and assigns emotional and motivational significance and prompts affective reactions to social stimuli. These processes are thought to be particularly sensitive to pubertal changes in hormonal milieu, and the affective and motivational value of social stimuli is amplified by the pubertal influx of gonadal steroids.
Maturing latest, and less tied to pubertal processes, the cognitive-regulatory node involves multiple areas in the prefrontal cortex and allows complex and subtle cognitive processes including theory-of-mind operations. This node also allows for the modulation of affective and behavioural response to social stimuli, particularly the inhibition of prepotent responses and the generation of goal-directed behaviours. Nelson and colleagues suggest that a mismatch between the functioning of the affective and cognitive-regulatory nodes may contribute to the development of psychopathology during adolescent development.

2.4 Summary
This chapter has outlined normative developmental changes in adolescent brain structure, and discussed models of neurodevelopment that have attempted to link neurodevelopmental processes with the emergence of depression in adolescence. These models identified several candidate brain structures putatively involved in capacities whose dysfunction are germane to the development of depression, such as social information processing, production and regulation of affect, and reward pursuit. The aim of the current research was to investigate the relationships of individual structure volumes with the development of depression; the theories reviewed above allowed the specification of appropriate structures for further investigation, and findings regarding each structure can provide further information with which to consider these theories in future. In particular, this research quantifies a measure of structural development (volume) very early in adolescence, and prior to the onset of depression. This will provide further information on whether the processes discussed above are impinged upon in the course of adolescence and perhaps in consequence of processes associated with the experience of depression and psychiatric distress, or whether abnormalities in implicated structures are observable early, prior to emergence of psychiatric issues. In the following chapter, five structures implicated in the abovementioned models are discussed in more detail, with an emphasis on structural neuroanatomical findings in depressed populations.
Chapter 3: Depression and neuroanatomy

The previous chapter discussed neurobehavioural models of motivation, affect and affect regulation. This chapter focuses specifically on five individual brain structures which featured frequently in the neurodevelopmental models reviewed: the amygdala, hippocampus, anterior cingulate cortex (ACC), orbitofrontal cortex, and corpus callosum. These structures were chosen as the foci of this research as they are implicated in the models discussed in Chapter 2 and are known to undergo significant development during the adolescent period (Lenroot et al., 2007; Giedd et al., 1999a; Paus et al., 1996a; Pujol et al., 1993; Østby et al., 2009). There are other regions also clearly implicated by the models discussed (most prominently the nucleus accumbens and dorsolateral prefrontal cortex) however these regions are difficult to delineate and measure reliably with the methods used in the present research and therefore are not discussed in detail here. In the following sections, each region of interest’s structural and functional characteristics are introduced, followed by a review of the evidence implicating the structure in the pathogenesis of depression, with a particular focus on structural neuroanatomical findings. Finally, hypotheses as to whether each region of interest’s volume is likely to predict adolescent onset depression are presented.

3.1 Hippocampus

The hippocampus is located under the medial temporal lobe, is closely connected to the entorhinal cortex and the amygdala, and has extensive connectivity with parietal, temporal and prefrontal neocortical regions, as well as afferents from all sensory modalities (Canto, Wouterlood & Witter, 2008; Witter, 1993). The most thoroughly researched roles of the hippocampus are in spatial processing (e.g., Hölscher, 2003) and memory formation (e.g., Tulving & Markowitsch, 1998), however it is also thought to have an important influence on emotion.

3.1.1 Emotional processing

Bannerman and colleagues (2004) described a cohesive theory of hippocampal function which posits the localisation of memory and spatial learning functions to the posterior (or dorsal, in non-primates) half of the hippocampus, and emotional processes to the anterior (or ventral, in non-primates) half. In support of this theory, they cite animal studies in which lesions to the
dorsal hippocampi resulted in impairment on spatial memory tests such as the Morris watermaze (e.g., E. I. Moser, M. B. Moser & Andersen, 1993), while lesions to the ventral hippocampi left spatial memory functions preserved, but resulted in perseverative behaviours (e.g., Jarrard & Isaacson, 1965), or failure to acquire appropriate fear responses such as freezing to conditioned stimuli (e.g., Richmond et al., 1999), both of which can be interpreted as failures of the behavioural inhibition system. In further indication of preferential involvement of the dorsal (or caudal in primates) hippocampus in spatial learning and memory, most of the major visuo-spatial inputs from primary sensory cortical areas to the hippocampus terminate in this region (M. B. Moser & E. I. Moser, 1998). The ventral (rostral in primates) hippocampus has widespread connections to diverse cortical and subcortical areas known to contribute to mood regulation, including the prefrontal cortex, amygdala, basal ganglia and hypothalamus (Rosene & Van Hoesen, 1987, pp 345-456; Gray & McNaughton, 1983; Soares & Mann, 1997). The particular role of hippocampal connections to the hypothalamus and its associated function in the regulation of the body’s stress response is reviewed later.

The hippocampus has generally been linked to negative affect, particularly anxiety, and is proposed to be central to the behavioural inhibition system (Gray & McNaughton, 1996). In encoding and retrieving emotional memory, the hippocampus is thought to operate in concert with the amygdala. However, while the amygdala is putatively involved in the generation of fear responses to discrete threatening objects or events, the hippocampus seems to be more implicated in memory for contextual and relational information, for example the conditioning of a fear response to background contextual information. This facilitates anticipatory emotional function based on context rather than discrete objects or events (Tucker, Derryberry & Luu, 2000). Thus the amygdala is said to be more involved in the generation and regulation of fear, while the hippocampus is more involved with anxiety.

3.1.2 The hippocampus and depression

While the majority of research into the emotional aspects of hippocampal functioning centres around anxiety, there is strong evidence for a specific association between depressive illness and hippocampal volume abnormalities. The most consistent finding has been for reduced hippocampal volume in adult sufferers of depression (e.g., Frodl et al., 2002b; Bremner, Narayan, Anderson, Staib, Miller & Charney, 2000; Sheline, Wang, Gado, Csernansky & Vannier, 1996; Sheline, Sanghavi, Mintun & Gado, 1999). There have also been reports that did not find significant alterations in hippocampal volume for depression patients, however these are far fewer in number (Ashtari et al., 1999; Axelson et al., 1993; Vakili et al., 2000; Posener et al.,
Comparatively less research focuses on hippocampal volume in paediatric depression, and findings have been less consistent than those for adults. Rosso, Cintron, Steingard, Renshaw, Young and Yurgelun-Todd (2005) found no difference in hippocampal volume between paediatric depression patients (mean age of onset 12.8 years, mean illness duration 24 months) and healthy controls, however MacMaster and colleagues (2008) found bilaterally reduced hippocampal volumes in a sample of depressed children and adolescents with family histories of major depression (mean age 14.08 years, mean illness duration 27.7 months). In a sample of adolescents with current major depressive disorder (MDD; mean age 16.67, mean illness duration 2.89 years), MacMaster and Kusumakar (2004) found smaller bilateral (especially left) hippocampi in depressed teens, and the effect was more prominent in males. Interestingly, hippocampus volume correlated negatively with age of onset but positively with illness duration. Caetano and colleagues (2007) found that a currently depressed sample with a mean age of 13.9 years (mean illness duration 27.4 months) showed reduced left hippocampal grey matter compared with healthy controls. None of these studies found the negative predictive relationship between illness duration and hippocampal volume reported in adult samples.

A prominent theory regarding the cause of smaller hippocampal volume in depression is that high levels of the stress hormone cortisol lead to neurotoxicity and hippocampal atrophy (Sapolsky, 2000). In order to understand the role of the hippocampus in neuroendocrinological stress responses including cortisol secretion, it is necessary first to outline the function of the hypothalamic-pituitary-adrenal (HPA) axis.

3.1.3 The hypothalamic-pituitary-adrenal axis

The HPA axis is comprised of the hypothalamus, and the pituitary and adrenal glands. Activity of the HPA axis is triggered by stress, and begins with the secretion of corticotropin releasing hormone (CRH) and vasopressin from the hypothalamus. These substances elicit the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which then stimulates the secretion of glucocorticoids (mainly cortisol in humans) from the adrenal cortices. Once released, glucocorticoids exert a negative feedback effect on the hypothalamus and pituitary to suppress further CRH and ACTH secretion (Herman & Cullinan, 1997; Herbert et al., 2006).

In the brain, cortisol acts at two types of receptor – mineralocorticoid receptors and glucocorticoid receptors – in a multitude of target tissues. The hippocampus, a structure with a high concentration of glucocorticoid receptors, plays a major part in the down-regulation of the HPA axis (Herman & Cullinan, 1997).
Dysregulation of the HPA axis is implicated in several psychiatric disorders, particularly in major depression (Pariante & Lightman, 2008). For example, a large proportion of depressed adults demonstrate higher plasma cortisol levels than healthy controls (Nemeroff & Vale, 2005). This excess of cortisol is thought to result from reduced feedback inhibition from endogenous glucocorticoids. In support of this, a synthetic agent (dexamethasone) which binds to glucocorticoid receptors thereby inhibiting the synthesis and secretion of ACTH and, consequently, the secretion of cortisol, tends not to exert this negative feedback effect in depressed individuals (Kunugi et al., 2006). The lack of a suppressive effect of dexamethasone in depressed patients may be explained by impaired glucocorticoid receptor signalling in these individuals (Ising, Kunzel, Binder, Nickel, Modell & Holsboer, 2005).

A flattening of the normal diurnal variation (raised in the morning and lowering in the afternoon) in cortisol is associated with depression and trait negative affect (Jacobs, Myin-Germeys, Derom, Delespaul, van Os & Nicolson, 2007; Polk, Cohen, Doyle, Skoner & Kirschbaum, 2005). As a major contributor to inhibitory control over glucocorticoid release (Herman & Cullinan, 1997), impaired function of the hippocampus may result in a failure of the negative feedback loop, and therefore greater HPA-axis activity, which then leads to higher circulating cortisol levels. In support of this theory, successful antidepressant treatment is thought to improve glucocorticoid receptor function, resulting in more effective negative feedback of the HPA axis (Pariante, 2006).

There is also an increasing weight of evidence to suggest that, rather than being solely an epiphenomenon of depression, HPA axis alterations may also precede and predispose toward psychopathology (Zipursky et al., 2011), and may be programmed by early life experiences (Pariante & Lightman, 2008) and genetic susceptibility to mood disorder (Krieg, Lauer, Schreiber, Modell & Holsboer, 2001).

3.1.4 Hippocampal volume reductions: Antecedents or consequences of depression?

3.1.4.1 Consequences: Neurotoxicity
There is substantial animal literature demonstrating that high levels of glucocorticoids associated with stress or HPA axis dysregulation can exert a neurotoxic effect on areas with high concentrations of glucocorticoid receptors, such as the hippocampus (e.g., Sapolsky, 1985; 1986). It has been suggested that exposure to stress hormones (which are present in higher concentrations in those with depression) cause damage to the hippocampus ranging from remodelling and atrophy of dendritic branching to frank neuronal death (McEwen, 2002; Sapolsky, 1996; Sapolsky, Uno, Rebert & Finch, 1990). The theory that stress processes
associated with depression are damaging to hippocampal tissue is supported in human research by the greater consistency of findings of hippocampal volume loss in recurrent and geriatric depression (e.g., Sheline et al., 1999; Steffens et al., 2000) as well as findings that depressive illness duration is negatively correlated with hippocampal volume (Sheline et al., 1996; MacQueen et al., 2003; Sheline, Gado & Kraemer, 2003; Caetano et al., 2006a). Particularly strong support comes from a prospective longitudinal finding that bilateral hippocampal grey matter density reductions were found in depressed individuals scanned once as inpatients, and then three years later. Reductions were noted between the first and second scans (as compared with healthy controls) and patients who relapsed during the follow-up period showed greater reductions at the second scan than stable remitted patients, suggesting that grey matter density decline in the hippocampus was dependent on active depression-related factors, such as stress (Frodl et al., 2008c).

None of the studies cited earlier on paediatric depression found the negative predictive relationship between illness duration and hippocampal volume reported in adult samples. This is interesting in light of the fact that hypercortisolemia is less reliably observed in depressed children and adolescents than in depressed adults (Kaufman & Ryan, 1999, pp. 810-822).

3.1.4.2 Consequences: Suppression of hippocampal neurogenesis

The hippocampus is one of a very few putative neurogenic regions in the human brain, the other best accepted neurogenic region being in the olfactory system. According to a review by Balu and Lucki (2009) neurogenesis in the adult hippocampus is regulated by factors including neurotrophins, antidepressants, stress, opioids, physical activity, learning, and hormones.

It has been suggested that stress processes associated with recurrent depression cause destruction of existing hippocampal cells. However it is also possible that volumetric alterations in the hippocampus are due to inhibition of hippocampal neurogenesis. In support of this theory, animal research using a range of paradigms has demonstrated a negative association between stress and cell proliferation and survival (Gould, McEwen, Tanapat, Galea & Fuchs, 1997; Gould, Tanapat, McEwen & Fuchs, 1998; Malberg & Duman, 2003; Tanapat, Hastings, Rydel, Galea & Gould, 2001; Mirescu & Gould, 2006; Czeh et al., 2002; Westenbroek, Den Boer, Veenhuis & Ter Horst, 2004).

Findings of volumetric alterations to the hippocampus in depression have been more consistent in males than females (e.g., Frodl, Meisenzahl & Zetzsche, 2002; Kronmüller et al., 2008; MacMaster & Kusumakar, 2004); this may relate to the effects of gonadal hormone
concentrations on cell proliferation and survival. Oestrogen is thought to possess neuroprotective qualities (Brann, Dhandapani, Wakade, Mahesh & Khan, 2007). For example, ovariectomy in rats (resulting in loss of circulating oestrogen) is associated with a significant decrease in the proliferation of granule cell precursors in the dentate gyrus. Further, the level of hippocampal cell proliferation in female rats has been found to be highest during proestrus, when oestrogen levels are high, and reduced during phases of the oestrous cycle when oestrogen levels are lower (Tanapat et al., 1999). There are findings to suggest that testosterone may aid neurogenesis, for example castrated male rats exposed to testosterone showed increased hippocampal neurogenesis (Spritzer & Galea, 2007). However there is also evidence to suggest that testosterone may reduce cell proliferation in the dentate gyrus in both male and female rats (Brannvall, Bogdanovic, Korhonen & Lindholm, 2005) and that testosterone increases vulnerability to neurotoxic processes (Yang et al., 2002). If, in broad terms, female gonadal hormones protect and promote neurogenesis, and male gonadal hormones do not protect, or in fact suppress cell proliferation, this may explain the greater hippocampal reductions noted in males than females with depression.

The putative effect of depressive disorders on hippocampal neurogenesis is supported by evidence that multiple types of antidepressants are associated with increased rates of cell proliferation (reviewed in Balu & Lucki, 2009). However, there is also evidence to suggest that volumetric reductions associated with depression are related to changes in glial cells, neuropil and dendritic complexity, rather than alterations to cell proliferation or cell death (Czeh & Lucassen, 2007; Santarelli et al., 2003; McEwen, 2005; Reif et al., 2006; Lucassen et al., 2001; Muller, Lucassen, Yassouridis, Hoogendijk, Holsboer & Swaab, 2001). This suggests that alterations to neurogenesis may not be a central pathophysiological process of depression, however may be an important compensatory aspect of the actions of antidepressant therapies, not to mention other treatments associated with both alleviation of depression and elevated neurogenesis, such as exercise (van Praag, Kempermann & Gage, 1999) and environmental enrichment (Meshi et al., 2006).

3.1.4.3 Antecedents: Risk for poorer prognosis

There is evidence that smaller hippocampal volumes are associated with poorer prognosis in depressed individuals, perhaps providing an alternative or complementary explanation for relationships found between illness duration and hippocampus size. Kronmüller and colleagues (2008) found that, for males only, smaller bilateral hippocampi during a major depressive episode predicted non-remission two years later. Frodl and colleagues (2004; 2008a) also found that
smaller bilateral hippocampal volume in depressed individuals was associated with poorer outcome for males and females at 1 and 3 year follow ups. While these studies could not measure whether the smaller hippocampal volumes preceded depression onset, this is compelling evidence that the relationship between depression and hippocampal volume may be bidirectional. However, it is not enough basis to conclude that hippocampal volume is a causative factor in the onset of depression. It is possible that while reduced hippocampal volume may not increase risk for depression, once depression is present the smaller hippocampus (potentially undergoing neurotoxic atrophy) is less able to down-regulate the HPA axis, contributing to a vicious cycle of impaired negative feedback. Several reports have noted that reduced hippocampal volume was specific to current acute depression, finding that currently depressed patients had smaller hippocampal volumes than formerly depressed patients in remission (Caetano et al., 2006a; Shah, Ebmeier, Glabus & Goodwin, 1998; Frodl et al., 2004). Once again, it is not possible to discern whether the difference in hippocampal volumes is due to recovery processes after remission, or whether the smaller hippocampi in non-remitted patients determined to some extent their poorer clinical outcome.

3.1.4.4 Antecedents: Vulnerability for onset

It has also been speculated that associations found between reduced hippocampus size and adolescent onset depression (e.g., MacMaster & Kusumakar, 2004; Caetano et al., 2007) implicate smaller hippocampal volume as preceding, and increasing vulnerability for, depression.

The presence of hippocampal volume reductions in some adolescent depression samples has been noted, but do not necessarily indicate that smaller hippocampal volume is a precursor to major depression. Negative relationships between hippocampal volume and illness duration have been reported in several studies, albeit with adult samples usually with recurrent depressive illness, which may support the theory that hypercortisolemia associated with depression has a neurotoxic effect on the hippocampus that is increasingly severe the longer the illness continues (e.g., Sheline et al., 1996; MacQueen et al., 2003; Sheline et al., 2003; Caetano et al., 2006a). No specific data have been reported that indicate how long the volume reduction hypothesised to be associated with depression takes to occur. It is possible that the approximately two years’ illness duration reported in adolescent depression studies cited above is sufficient time for hippocampal atrophy directly related to depressive illness to take place. The hippocampus does appear to exhibit structural responses to experience with surprising rapidity. While not directly comparable with humans, studies of repeated restraint stress in rats observed atrophy of apical dendrites of CA3 pyramidal neurons after 21 days (Conrad, Magarinos, LeDoux & McEwen, 1999;
Relatively rapid neuroplasticity has also been observed in humans. For example, Frodl and colleagues (2008a) found that hippocampus volume increased significantly over a period of three years for MDD patients who took antidepressant medication during that time.

More convincing evidence that smaller hippocampi may be a predisposing factor for depressive illness comes from studies of healthy, but at-risk individuals. Amico, Meisenzahl, Koutsouleris, Reiser, Möller and Frodl (2011) found that healthy adults with a family history of depression had smaller right hippocampi than those with no family history. Interestingly, they also had smaller right hippocampi than depressed patients – this was interpreted as reflecting the neuroplastic effects of antidepressants, which were being taken by most of the depressed sample. Likewise Rao, Chen, Bidesi, Shad, Thomas and Hammén (2010) found that healthy adolescents at risk for depression, as well as depressed adolescents, had smaller bilateral hippocampi than healthy adolescents without family history of depression. There is also evidence that smaller hippocampi are associated with internalizing tendencies (particularly withdrawal) in normally developing children and adolescents (Koolschijn, van Ijzendoorn, Bakermans-Kranenburg & Crone, 2012).

It remains unclear to what extent structural abnormalities in the hippocampus predate (and potentially predispose individuals towards) depressive illness, and to what extent stress-related neurotoxic processes or disruptions to hippocampal development or neurogenesis, associated with major depression cause hippocampal volume loss. The prospective longitudinal design of the current study allows new insight into this question.

3.1.5 Summary and predictions
There is a large body of evidence for a specific association between depressive illness and hippocampal volume abnormalities. A relationship appears to exist between reduced hippocampal volume and MDD in adults, particularly in males (e.g., Frodl et al., 2002b; Bremner et al., 2000; Sheline et al., 1996; Sheline et al., 1999). However there are multiple possible explanations for this observation. It is possible that hippocampal size predisposes individuals towards depression, and is programmed through early life experience (Pariante & Lightman, 2008), or is a neurobiological marker for genetic susceptibility to depression (Krieg et al., 2001). It is also possible that hippocampal size affects the course and prognosis of depressive illness once established (Kronmüller et al., 2008; Frodl et al., 2004; Frodl et al., 2008b). Finally, it has been theorised that hippocampal volume reductions are the outcome of depressive disease processes, in particular the neurotoxic effects of high glucocorticoid concentrations associated with HPA axis dysregulation (Sapolsky, 2000). Given the complexity of evidence and the
multiple theories discussed above, a single hypothesis was not formulated for the hippocampus. If in the present study, hippocampal volume prior to depression onset is observed to predict emergence of depressive symptoms, this will lend compelling support to the theory that hippocampal volume is a risk factor for depressive illness. If however hippocampal volume is not related to depression onset, this will suggest that reduced hippocampal volume associated with depression is largely epiphenomenal, potentially as a result of cortisol related neurotoxicity.

3.2 Amygdala
The amygdala is composed of several distinct subareas or nuclei located in the medial temporal lobe. The lateral nucleus is regarded as the entrance point to the amygdala, receiving inputs from visual, auditory, somatosensory, olfactory and taste systems. Animal studies have indicated that two routes provide the amygdala with sensory information: a rapid but crude input from the sensory thalamus and a slower, more detailed input from sensory cortices (LeDoux, 2000). The central nucleus is thought to be the source of output associated with emotional and behavioural responses. The medial region of the central nucleus projects to the brainstem, and prompts physiological and basic behavioural responses associated with emotional arousal (such as freezing in response to a threat), while the basal nucleus connects to striatal areas involved in goal directed behaviour, such as escaping from a threat (Phelps & LeDoux, 2005). Its major functional roles are conceptualised to be in the detection and processing of affectively significant stimuli, and in emotional learning and memory consolidation. While the majority of discussion around emotional functions of the amygdala focuses on negative emotions, particularly fear and threat-related learning, there is also evidence that the amygdala is involved in reward learning, and response to ambiguous and positive stimuli (e.g., Hamann, Ely, Hoffman & Kilts, 2002; Ball et al., 2009; Kensinger & Schacter, 2006).

3.2.1 Sensory processing
Research on animals and humans in a range of modalities has indicated that the amygdala affects attention and perception by influencing cortical sensory processing. Amygdalar activation in response to emotionally salient stimuli such as angry faces has been shown not to depend on conscious awareness or focus of attention on these stimuli. It has been suggested that the amygdala receives afferents from subcortical sensory regions (Phelps & LeDoux, 2005; although this contention has been debated – see Pessoa, McKenna, Gutierrez & Ungerleider, 2002) and influences allocation of further processing resources via efferents to cortical sensory areas. Animal studies have noted that the amygdala also contributes to cortical plasticity, such that
sensory systems become more attuned to detecting stimuli which signal emotionally salient events (Weinberger, 1995).

### 3.2.2 Emotional learning and memory

The amygdala’s role in emotional learning has primarily been studied using fear conditioning paradigms, in which a neutral stimulus is paired with an aversive event, eventually leading to an aversion response to the neutral stimulus alone. Synaptic plasticity in the lateral amygdala has been observed during fear conditioning learning trials, in which the neutral and aversive stimuli are presented concurrently. When the neutral stimulus is presented alone, these now potentiated synapses promote activation of the medial part of the central nucleus, outputs of which control conditioned fear responses (Li, Nair & Quirk, 2009; Kwon & Choi, 2009).

The amygdala is thought to enable implicit memory for fear conditioning, whereas the hippocampus is more concerned with declarative memory for fear associations. Thus, people with damage to the amygdala but intact hippocampi fail to show physiological indications of conditioned fear, however they can explicitly report the relationship between the conditioned and unconditioned stimuli. Conversely, those with damaged hippocampi and intact amygdalae exhibit normal physiological expressions of conditioned fear, but cannot consciously report the events of fear conditioning (Bechara, Tranel, H. Damasio, Adolphs, Rockland & A. R. Damasio, 1995).

Another role of the amygdala is to influence memory storage functions of other systems, both implicit and explicit, during memory formation and consolidation. Memory for an event is known to be stronger if the event was accompanied or followed by intense emotional experience. In brief, the amygdala ensures that emotionally arousing (and therefore potentially evolutionarily salient) events are preferentially remembered (McGaugh, 2002; 2004).

### 3.2.3 Social processing

The amygdala is also implicated in social information processing, in particular the processing of facial expression (Phelps & LeDoux, 2005). Adolphs, A. R. Damasio and colleagues have demonstrated subtle impairments in judgement of facial expressions in individuals with amygdala lesions, including under-attending to fearful faces, and judging faces as more trustworthy and approachable compared with controls (Adolphs, Tranel & A. R. Damasio, 1998; Adolphs, Gosselin, Buchanan, Tranel, Schyns & A. R. Damasio, 2005). A link between amygdala volume and social behaviour and network size has been demonstrated both in comparative studies of non-human primates, and in humans. Primate species that live in larger groups have been found
to have a comparatively larger corticobasolateral complex within the amygdala (Barton & Aggleton, 2000), while people with larger and more complex social networks were found to have larger amygdalae bilaterally (Bickart, Wright, Dautoff, Dickerson & Barrett, 2011).

3.2.4 The amygdala and depression

The evidence reviewed above suggests that the amygdala is involved in identifying and responding to emotionally salient stimuli, emotional processing and emotional memory. It follows then that the amygdala may be implicated in disorders of mood dysregulation, including depression. Functional imaging research supports this link, with altered patterns of amygdalar response to emotional stimuli observed in depressed compared with control subjects (Anand et al., 2005; Sheline, Barch, Donnelly, Ollinger, Snyder & Mintun, 2001; Siegle, Konecky, Thase & Carter, 2003; Thomas et al., 2001).

Increased resting blood flow and glucose metabolism in the amygdalae (particularly the left) has been observed in at least some subtypes of depression, including familial pure depressive disease and the melancholic subtype of MDD, and has been associated with increased plasma cortisol in depression (Drevets, Bogers & Raichle, 2002a). Resting amygdala activity has also been positively correlated with depression severity (Abercrombie et al., 1998; Drevets, Spitznagel & Raichle, 1995). It has been suggested that increased tonic activation of the amygdala in depression may contribute to a greater sensitivity in detection and retention of emotional aspects of the environment (Drevets, Videen, Price, Preskorn, Carmichael & Raichle, 1992).

As well as an increase in resting activity, increases in amygdala reactivity have been repeatedly observed in depressed individuals in response to negatively valenced stimuli such as sad faces (Drevets, Gautier, Lowry, Bogers, Greer & Kupfer, 2001; Fu et al., 2004; Neumeister et al., 2006), and fearful faces (Sheline et al., 2001). This finding has been linked to the consistent observation of mood-congruent processing biases in depression; depressed individuals tend to preferentially process and recall negatively valenced information more than non-depressed individuals (e.g., Nunn, Mathews & Trower, 1997; Gotlib, Kasch, Traill, Joormann, Arnow & Johnson, 2004). In support of this idea, greater functional connectivity has been observed in depressed individuals between the amygdala and hippocampus during encoding of negative stimuli (Hamilton & Gotlib, 2008). It is worth noting however that a recent study found heightened amygdala reactivity to positive social stimuli in depressed young people (Davey, Allen, Harrison & Yücel, 2011).
Functional amygdala alterations have also been linked to abnormal activation of cortical areas, particularly the ACC and orbitofrontal cortex. The voluntary down-regulation of negative emotions has been associated with increased activity in frontal and anterior cingulate regions and decreased activity in the amygdala (Lévesque et al., 2003; Ochsner, Bunge, Gross & Gabrieli, 2002; Ochsner et al., 2004; Phan, Fitzgerald, Nathan, Moore, Uhde & Tancer, 2005). This is thought to reflect top-down regulation by cortical regions over the activity of limbic regions. Decreased cortical regulation of limbic activity has been suggested as underpinning the persistent negative affect associated with depression (Anand et al., 2005). In support of this, Beauregard, Paquette and Levesque (2006) found that depressed participants attempting down-regulation of sadness showed less orbitofrontal cortex activity and greater right amygdala activity.

Histological research reported reductions in glial cell density in MDD subjects versus controls, particularly in the left amygdala (Bowley, Drevets, Ongür & Price, 2002). A later study indicated that this reduction was largely accounted for by reduction in density of oligodendrocytes; glial cells that support axon myelination (Hamidi, Drevets & Price, 2004).

Structural neuroimaging studies have found differences in amygdala volumes between depressed and control participants, however the directions of findings have been inconsistent. Hajek, Kopecek, Kozeny, Gunde, Alda and Höschl (2009) conducted a meta-analysis of volumetric MRI studies of the amygdala in unipolar and bipolar depression. They concluded that for bipolar depression, studies in children and adolescents indicated significantly reduced left amygdala volume, with a trend for right side reduction, whereas in adults, there was a trend for larger left amygdala volume. Eighteen studies using unipolar participants were included in the meta-analysis. Results were heterogeneous; four studies showed increased amygdala volumes in depressed subjects, nine showed decreased volumes, and nine studies reported no alterations. The meta-analysis found that overall, there was no difference in amygdala size between depressed and control subjects, in any age group. There was however evidence of larger left amygdala volume in unipolar inpatients specifically.

Two meta-analyses have indicated that some of the heterogeneity in these findings may be accounted for by effects of medication. Hamilton, Seimer and Gotlib (2008) found amygdala increases in medicated depression patients compared to healthy controls, but decreases in amygdala volume in unmedicated participants. In a recent meta-analysis of voxel-based morphometry studies of grey matter abnormalities in depression, Bora, Fornito, Pantelis and Yücel (2012) likewise found that reduced right amygdala volume was particular to participants who had a first episode of depression (the majority of whom had not received
pharmacotherapy). As in findings related to the hippocampus and orbitofrontal cortex, these findings too may support the theory that antidepressant treatment is associated with increases in brain-derived neurotrophic factor (BDNF), promoting cell proliferation and survival and protecting against the deleterious effects of glucocorticoid toxicity.

Kronenberg, Tebartz van Elst, Regen, Deuschle, Heuser and Colla (2009) found reduced bilateral amygdala volumes in unmedicated depressed adult inpatients, and also noted that number of previous depressive episodes was inversely related to amygdala size. The authors suggested two possible interpretations of this – one, that stress-related neurotoxicity may have progressively reduced amygdala size over the recurrent depressive episodes, or two that a smaller amygdala size was a risk factor for recurrent depression. They measured morning and afternoon salivary cortisol in depressed patients, but found no relationship with amygdala volume – although current measurements of salivary cortisol are not necessarily indicative of potential prior hypercortisolemia, the negative finding does cast some doubt on a neurotoxicity model of amygdalar reduction in depression.

Schuhmacher and colleagues (2012) compared adult participants with no depression with two currently depressed and medicated groups: those with a first episode of MDD, and those with recurrent MDD. They found that right amygdala volumes were reduced in first episode MDD as compared with controls, but no difference was noted between recurrent MDD and either controls or first episode patients. Depression severity in the first episode group was inversely correlated with right amygdala volume. They also found a complex association between cortisol and amygdala volume. While baseline cortisol level was not related to amygdala volume, bilateral amygdala volumes and cortisol were related in the context of pharmacotherapy for the recurrent depression group. In brief, larger bilateral amygdalae were associated with a more pronounced reduction in HPA activity during antidepressant treatment in recurrent depression (as measured by cortisol secretion in response to dexamethasone/CRH tests). The authors speculated that hippocampal atrophy and associated dysfunction during recurrent depression rendered the volume of the amygdala more important in HPA axis regulation in this group, and that the amygdala’s volume and regulatory capacity are both potentially enhanced by antidepressant treatment.

Frodl and colleagues (2008c) found that grey matter density in the left amygdalae of depressed adults declined between an initial scan taken from inpatients, and a follow-up scan taken three years later (in comparison with healthy controls). However, unlike declines in the hippocampus, the grey matter decline in the amygdala was no different between patients who had stably
remitted during the follow-up period, and those who had continued to experience depression. The authors suggested that grey matter decline in the amygdala was therefore independent of factors directly related to the depressive state – however there was considerable inhomogeneity in medication status over the follow-up period for these participants.

Lorenzetti, Allen, Whittle and Yücel (2010) found that left amygdala volumes were larger in currently healthy adults with a history of depression, compared with never depressed adults; this was in contrast with several previous null findings in remitted depression (Bremner et al., 2000; Frodl et al., 2008a; van Eijndhoven et al., 2009). There was no difference in amygdala volume between currently depressed and never depressed adults. They also found no effects of medication use in the prior 6 months, or comorbidity with anxiety disorders, on amygdala volume, however high scores on a measure of general distress were associated with smaller left amygdalae. Finally, Saleh and colleagues (2012) found that patients without a family history of depression had enlarged right amygdalae compared to both MDD patients with family history and controls without family history.

The following section outlines findings from those studies examining amygdala volume in depression using child and adolescent populations. Caetano and colleagues (2007) found no differences in amygdala size between 19 adolescents with major depression and controls, although they did note a trend for smaller right amygdala in MDD patients with comorbid anxiety disorders compared to those without. There was also an inverse relationship in the MDD group between score on the Children’s Depression Rating Scale and right amygdala volume. They interpreted these findings as being primarily due to the comorbid anxiety, and the possibility of emergence of bipolar disorder in members of the sample, citing evidence that bipolar children and adolescents consistently show reduced amygdala volumes (Blumberg and colleagues, 2003; DelBello, Zimmerman, Mills, Getz & Strakowski, 2004; Chen et al., 2004a).

Rosso and colleagues (2005) found bilateral amygdalar reduction in 20 children (mean age 15.35, $SEM = .34$) with major depression compared to controls. They also observed that there were no relationships between clinical features of depression such as severity and duration, and amygdala volume. However Munn and colleagues (2007) found no core, non-core or total amygdala volume differences between 29 depressed and 18 non-depressed young adult twin pairs, or between twins discordant for major depression. MacMillan and colleagues (2003) reported increased amygdala/hippocampus ratios in a sample of paediatric MDD patients, as well as a finding of larger amygdala volumes, which did not retain significance once intracranial volume was controlled.
MacMaster and colleagues (2008) reported no differences in amygdala volumes in a sample of 32 psychotropically naïve MDD patients aged 8-21 years. However, they did find right amygdalar enlargement in MDD patients with an illness duration of less than one year, compared to controls. No other clinical feature was related to amygdala volume, notably including comorbid anxiety which was present in two-thirds of their subjects. They suggested that enlarged amygdala may be a transitory feature of the acute phase of depression. This prospect is supported by van Eijndhoven and colleagues’ (2009) finding that bilateral amygdala enlargement distinguished currently depressed first episode MDD patients from recently recovered first episode patients and controls. This may also be reflected in the finding that the amygdala hyper-reactivity to negative stimuli characteristic of depressed patients normalized after successful pharmacotherapy, suggesting that this is was state- and not trait-marker for depression (Sheline et al., 2001).

The nature of any relationship between amygdala size and depression symptomatology is unclear. Siegle and colleagues (2003) found that core amygdala volume reduction in MDD was associated with functional magnetic resonance imaging (fMRI) hyperactivity on exposure to negative stimuli. Further studies combining structural and functional examination of the amygdala in depression are needed to explore this. Likewise, the causal mechanisms behind any alteration in amygdala volume have not been elucidated as yet. For example, it is unclear whether the stress-toxicity model and the BDNF hypothesis usually discussed with regard to the hippocampus may also apply to the amygdala (Frodl et al., 2003). The amygdala appears to contain a lower concentration of mineralocorticoid receptors relative to glucocorticoid receptors, compared with the hippocampus (Patel, Katz, Karssen & Lyons, 2008). As mineralocorticoid receptors are thought to exert a neuroprotective effect against exitotoxicity (Lai, Seckl & Macleod, 2005), this may place the amygdala at greater risk for stress-related damage.

Results regarding relationships between clinical characteristics such as depression duration or severity and amygdala size have been highly inconsistent, suggesting that size alteration may not be entirely secondary to the effects of the disease process. In combination with evidence that the amygdala undergoes maturational changes during childhood and adolescence (Durston et al., 2001) this could be interpreted as indicating that any amygdalar size alterations seen in depression are the results of aberrant brain development predisposing individuals to depression. Another possibility is that amygdala volume is an endophenotype of a genetic predisposition towards depression, although Munn and colleagues’ (2007) finding of no amygdalar differences between high risk and low risk groups does not support this. Furthermore, findings such as
those of MacMaster and colleagues (2008) and van Eijndhoven and colleagues (2009) suggest that there may be a transitory alteration in the size of the amygdala which is directly related to illness onset and severity. If this is the case, it is possible that many studies which include clinical characteristics in analysis lack the temporal specificity to capture this relationship. Further obscuring interpretations regarding amygdala volume and clinical course, it has been found that antidepressant and mood stabilising medications can result in significant alterations in amygdala size (Chang, Karchemskiy, Barnea-Goraly, Garrett, Simeonova & Reiss, 2005; Foland et al., 2008). For example, selective serotonin re-uptake inhibitor (SSRI) administration reduced amygdalar size in paediatric obsessive-compulsive disorder patients, and that the reduction was correlated with length and amount of administration (Szeszko et al., 2004). Likewise, Bowley and colleagues (2002) concluded that the glial cell density loss they observed in the left amygdalae of MDD sufferers was moderated by lithium and valproate treatment.

3.2.5 Summary and predictions
In summary, a clear picture of any relationship between amygdala volume and depression is yet to emerge. Increased, decreased, and unchanged amygdala volumes have all been observed to correspond with unipolar depression in adults (Hajek et al., 2009). There have been some indications that smaller amygdalae are associated with depression in adolescent samples (Rosso et al., 2005; Caetano et al., 2007), however these are complicated by the presence or possible development of anxiety and bipolar disorder and null findings have also been reported (MacMillan et al., 2003; MacMaster et al., 2008). Finally, there are some interesting but inconsistent findings suggesting that amygdala enlargement may be a transitory state characteristic of acute depressive illness (MacMaster et al., 2008; van Eijndhoven et al., 2009 but cf. Lorenzetti et al., 2010). It is hoped that the current prospective longitudinal study of a healthy group of adolescents will help to clarify whether amygdala size plays a predisposing role in risk for depression.

Based on the emerging, though inconsistent, indications that amygdala volume alteration may be a transitory effect directly related to current depression (MacMaster et al., 2008; van Eijndhoven et al., 2009) it was predicted that there would not be a relationship between amygdala size in early adolescence and depressive symptomatology in mid-adolescence.

3.3 Anterior cingulate cortex
The ACC has been conceptualised as providing an interface between affective, motivational, and higher cognitive processes (Allman, Hakeem, Erwin, Nimchinsky & Hof, 2001). It is a
functionally and structurally heterogeneous region located bilaterally on the medial walls of the frontal lobes, which follows the contour of the anterior corpus callosum. It is cytoarchitecturally and functionally distinct from the posterior cingulate cortex and the two regions are distinguished by different connectivity patterns (Bush et al., 2000).

Due to its location and parasagittal gyration, the ACC was previously thought to be an older part of the brain, in phylogenetic terms. However, Allman and colleagues (2001) have used the presence of von Economo neurons (VENs) to argue that the ACC is a relatively recent specialisation of the neocortex. The ACC is one of only two sites in the human brain known to contain VENs, large spindle-shaped neurons characterised by a single apical and basal dendrite extending from either pole (Nimchinsky, Gilissen, Allman, Perl, Erwin & Hof, 1999). VENs have only been found in species characterised by large absolute and proportional brain size, and well developed cognitive, social and communication capacities, including great apes, humpback whales, and African elephants (D. M. Pavlovic, A. M. Pavlovic & Lackovic, 2009). VENs are thought to enhance the capacity for long distance connections required in larger brains, and to be particularly implicated in social and emotional processing and tasks requiring cognitive flexibility (Allman et al., 2001). The relevance of these neurons to social and emotional processes is underscored by the receptors represented in VENs; vasopressin 1a, dopamine D3 and serotonin 2b (Allman, Watson, Tetreault & Hakeem, 2005).

Diverse functions of cognition, emotion, and motivated behaviour have been associated with the ACC, and have been broadly localised within the dorsal, rostral, and ventral (or subgenual) regions of the ACC (see Figure 4). The most basic functional differentiation generally made is that the dorsal ACC is specialised for cognitive tasks, whereas the rostral and ventral regions are specialised for affective processes (Bush et al., 2000). It is important to note however that while conceptual models specify separate, functionally distinct regions, there is overlap in the activity noted in these areas, and the areas themselves are highly anatomically interconnected (Allman et al., & Hof, 2001).
The ventral ACC (located inferior to the genu of the corpus callosum and therefore often termed the subgenual ACC) receives afferent connections from the orbitofrontal cortex and has outputs to the hypothalamus, periaqueductal grey, striatum, nucleus accumbens, thalamus, amygdala, and hippocampus (Price, 1999). It is theorised to be particularly associated with the experience of affect, via outputs to autonomic, endocrine and visceral effectors (Nauta, 1971).

The dorsal ACC has reciprocal connections with the lateral prefrontal cortex, parietal cortex, and motor/premotor areas, and has been posited as part of a distributed executive attention network (Posner & DiGirolamo, 1998; Bush et al., 2000). Such extensive connectivity is thought to reflect the dorsal ACC’s role in integration of higher cognitive processes and the conversion of cognitive processes into physical action (B. A. Vogt, Nimchinsky, L. J. Vogt & Hof, 1995).

The rostral ACC has connections with the orbitofrontal cortex, amygdala, hippocampus, and periaqueductal grey matter. The region has been particularly implicated in approach motivation and behaviour, including social (particularly affiliative) processes, and representation of reward.

*Figure 4. Divisions within the anterior cingulate cortex.*
values (D. M. Pavlovic et al., 2009). According to Mayberg and colleagues’ (1997) model, the rostral ACC also forms an intermediary to integrate the affective and cognitive functions of the ventral and dorsal ACC respectively.

The other major structural division that can be observed in the ACC is between the cingulate proper, lying directly adjacent to the corpus callosum, and the paracingulate region which lies parallel to the cingulate (Yücel, Wood, Fornito, Riffkin, Velakoulis & Pantelis, 2003). In discussing the dorsal, rostral and ventral subregions of the ACC it is possible to further divide them into cingulate and paracingulate sections, as will be done in the present research. This division will be discussed in more detail in the methodology section (Chapter 6); in most of the literature reviewed below the division is limited to dorsal, rostral and ventral.

The remainder of this section will be ordered according to functional capacities thought to be subserved by one or more subregions of the ACC, beginning with executive functions.

3.3.1 Executive functions

The ACC, particularly the dorsal region, has been implicated in a range of cognitive processes that can loosely be categorised as comprising elements of executive functioning (Allman et al., 2001). This is a notoriously difficult construct to define, and the intricacies of debate surrounding what is and is not executive function, as well as the composition and actions of distributed networks subserving its components, are not central to the current research. However, grouped under a suitably broad description such as that of Posner and Rothbart (1998), the concept of executive function as a suite of processes which facilitate “our voluntary ability to select among competing items, to correct error, and to regulate our emotions” (p. 1915) can provide some coherence in the discussion of the multiple, related cognitive functions associated with the dorsal ACC.

3.3.1.1 Focussed attention

Early research into the ACC noted relationships between activation and tasks requiring focussed attention. Functional neuroimaging of the ACC during word-generation tasks found that during concentrated and effortful tasks, activity was heightened in the ACC and corresponded with task difficulty. Once the same tasks became familiar, and less concentrated effort was required, the activity in this region lessened (Petersen, Fox, Posner, Mintun & Raichle, 1988; Raichle et al., 1994). Human electroencephalography (EEG) studies have also located activity within the ACC which corresponds to focused concentration, and which increases with task difficulty (Gevins, Smith, McEnvoy & Yu, 1997). This signal was weakened when the individual was in a
restless/anxious state, and restored when anxiety was psychopharmacologically relieved, (Mizuki, Suetsugi, Imai, Kai, Kajimura & Yamada, 1989; Suetsugi et al., 2000). This implies that activity of the ACC may regulate functioning along a continuum from focused concentration to restless or anxious fragmentation of attention, and more broadly that the ACC is particularly implicated in the allocation of attentional processes in line with motivational and affective information. Further implications of this are discussed under Development of Affect Regulation, below.

3.3.1.2 Error-detection
The error-related negativity (ERN) is a negative going event-related potential (ERP) component which is thought to originate in the ACC, (although the lateral prefrontal cortex may also play a role in its generation) and which occurs when an individual perceives that they have made an error (Dehaene, Posner & Tucker, 1994; Gehring & Knight, 2000; Holroyd, Nieuwenhuis, Mars & Coles, 2004; Luu, Flaisch & Tucker, 2000).

Gehring, Goss, Coles, Meyer and Donchin (1993) demonstrated a link between ERN and motivational value of correct or incorrect responses; greater amplitude ERNs were recorded in task conditions where accuracy was emphasised as of paramount importance to participants, compared to lower amplitude ERNs in conditions where speed was presented to participants as being more important than accuracy. Event-related fMRI research has found that activity in the ACC occurred in response to errors, but also in reaction to correct responses, where conditions included increased response competition. This was interpreted as indicating that the ACC may be concerned with monitoring situations in which errors are likely to occur, as well as or instead of the detection of errors themselves (Carter, Braver, Barch, Botvinick, Noll & Cohen, 1998).

Particularly interesting was Luu, Collins and Tucker's (2000) finding that individuals with high trait negative affectivity exhibited larger amplitude ERNs in response to early mistakes in a long experimental task, and longer reaction times in trials following mistakes, but the amplitude of their ERNs reduced to below those of control subjects as the task continued. This corresponded with self-reported dissatisfaction with their own performance, and disengagement with the task itself. This implicates the error-monitoring processes thought to be subserved by the ACC in the subjective experiences of distress in response to perceived errors, greater hesitancy and inhibition re-engaging with activities following discouraging experiences, and behavioural strategies of avoidance and withdrawal associated with trait negative affectivity and depression.
3.3.1.3 Conflict monitoring

It has also been argued that the dorsal ACC is not primarily involved in error monitoring, but is more generally involved in conflict monitoring (i.e., in situations eliciting conflict between response systems, or generating multiple potentially appropriate response options; Botvinick, Cohen & Carter, 2004). For example, ACC activation has been reported during tasks such as stem completion (Palmer, Rosen, Ojemann, Buckner, Kelley & Petersen, 2001) and verb generation (Barch, Braver, Sabb & Noll, 2000), and the strength of activation has been shown to correlate with the number of potential response options (Barch et al., 2000; Thompson-Schill, D’esposito, Aguirre & Farah, 1997). It has been suggested that response conflict indicates an unmet demand for cognitive control, and signals the necessity for altered allocation of cognitive resources (Botvinick, Braver, Barch, Carter & Cohen 2001). However, the two functions of conflict and error monitoring do not necessarily need to be viewed as mutually exclusive, and integrative accounts are increasingly being produced (e.g., Botvinick, 2007).

3.3.2 Affect

As discussed earlier, the ventral ACC is theorised to be particularly associated with the experience of affect (Nauta, 1971). For example, ventral activation has been noted when participants were asked to imagine situations provoking anger or sadness (J. V. Pardo, P. Pardo & Raichle, 1993; Dougherty et al., 1999; Liotti, Mayberg, Brannan, McGinnis, Jerabek & Fox, 2000). Electrical stimulation of the ventral ACC has been found to produce intense affective experience, both negative and positive (B. A. Vogt & Sikes, 2000; Bancaud & Talairach, 1992). Greater resting activation in the ventral ACC has also been found to correspond with greater trait negativity (Zald, Mattson & J. V. Pardo, 2002). Lesions to the ventral ACC have been reported to induce a range of alterations to emotional experience, prominently profound apathy and amotivation, in the absence of marked cognitive deficits (e.g., Bechara, Tranel, H. Damasio & A. R. Damasio, 1996; A. R. Damasio, Tranel & H. Damasio, 1990).

3.3.3 Reward processing

The ACC is a site of rich dopaminergic innervations from the ventral midbrain (Allman et al., 2001), a region which has been strongly linked to reward-related processing in primates (Schultz, 1998). Primate studies have also demonstrated that the ACC contains neurons which respond to reward signals, and neurons which respond when an expected reward is not received, and when a reward is unexpectedly received (i.e., when task contingencies change; Niki & Watanabe, 1979; Shima & Tanji, 1998). The ACC and orbitofrontal cortex are often discussed together in accounts of motivated behaviour, and are thought to be implicated in slightly different aspects of
reward and motivation; while the orbitofrontal cortex’s connections facilitate access to information regarding stimulus properties, the ACC has greater connectivity with spatial and motor systems. This may reflect a greater emphasis on reward associations with *objects* in the orbitofrontal cortex, and with *actions* in the ACC (Rushworth, Behrens, Rudebeck & Walton, 2007). Furthermore, results of an ablation study in macaques indicated that loss of ACC resulted in a failure of the animal to incorporate the reward history associated with an action in its response selection. In other words, the ACC was posited as important for integrating previous reinforcement history with voluntary behavioural choices (Kennerly, Walton, Behrens, Buckley & Rushworth, 2006).

Animal research (Weible, Rowland, Pang & Kentros, 2009) has also suggested that the ACC may be implicated in the production of exploratory behaviour in conditions of possible reward. Given the avolition and lack of approach in potentially rewarding situations associated with depressive illness, this suggests that the region is relevant to the current research.

The rostral ACC has been particularly implicated in reward processing. For example, increased rostral activation has been linked with the craving state experienced during substance addiction (Risinger et al., 2005) and with motivational components of male sexual arousal (Rauch et al., 1999; Redouté et al., 2000). This region has also been associated with social, particularly affiliative, processes (e.g., Bartels & Zeki, 2004; discussed below), and functional studies have shown links between rostral ACC activity and trait extraversion (Canli, Amin, Haas, Omura & Constable, 2004) and harm avoidance (Youn et al., 2002). This points towards the rostral ACC as being particularly implicated in approach motivation and behaviour.

As well as the production and experience of negative affective states, the ventral ACC is thought to be implicated in the reward experience associated with achieving desired outcomes. Accordingly, ventral activation has been linked with perceiving signals of good outcomes in gambling tasks (Rogers et al., 2004), the “rush” experienced after cocaine administration (Volkow et al., 2005; Brieter et al., 1997), and the autonomic components of male sexual arousal (Rauch et al., 1999; Redouté et al., 2000).

### 3.3.4 Social processing

Elements of social processing have been reportedly linked with several subregions of the ACC. For example, Cacioppo, Norris, Decety, Monteleone and Nusbaum (2009) found that individuals who reported high levels of loneliness demonstrated less activation in ventral striatal areas and ventral ACC when presented with pleasant pictures of people, compared with less lonely
subjects, indicating that perhaps social isolation is associated with experiencing a less pleasurable response to normal social reinforcers. Lesions to the ventral ACC have also been found to result in impairments in evaluating social signals, and consequently in using those signals to evaluate the appropriateness of one’s own behaviour (A. R. Damasio, Tranel & H. Damasio, 1990).

Dorsal areas of the ACC, which have been linked with the experience of physical pain, have also been shown to activate when people are shown pictures of others in pain, and in response to stimuli eliciting or representing hurt feelings, implicating this region in both psychological pain and empathy (Eisenberger, Lieberman & Williams, 2003). Dorsal ACC activation was also found by Rupp, James, Ketterson, Sengelaub, Janssen and Heiman (2009) to be associated with sexual decision-making in women, particularly in the consideration of potentially risky sexual practices.

There also appears to be a relationship between rostral ACC function and social affective processes; rostral activation has been associated with feelings of social exclusion (Somerville, Heatherton & Kelley, 2006), subjective distress experienced by mothers hearing infant cries (Lorberbaum et al., 2002), and positive feelings associated with viewing pictures of loved ones (Bartels & Zeki, 2004).

3.3.5 Development of affect regulation

The ability to regulate emotion depends in part on the maturation of cognitive capacities related to executive function, some of which are putatively subserved by the ACC (Kesek, Zelazo & Lewis, 2009). One such capacity is performance monitoring; the ability to recognise when an action is not having the desired effect, and therefore recruit further processing for generation of alternative behaviours (Zelazo & Cunningham, 2007). This is considered important for responding adaptively to conflict or frustration, particularly in emotionally demanding contexts. One putative marker of performance monitoring is the ERN (thought to originate in the ACC). Children tend not to exhibit the ERN, and the amplitude of this component increases with age. Several studies have noted that age related changes in the amplitude of the ERN appear to follow a time-frame which corresponds with pubertal development, and are associated with better task performance (Davies, Segalowitz & Gavin, 2004; Ladouceur, Dahl & Carter 2004).

Like other frontal areas, the ACC undergoes a protracted developmental process (Bush et al., 2000). A structural neuroimaging study of children and adolescents indicated that the volume of the right ACC (this included dorsal and some rostral ACC) was positively correlated with the ability to perform a task relying on inhibitory control (Casey et al., 1997). Given the significance of inhibitory control abilities in executive functioning and affect regulation, it is reasonable to
suggest that the development of the ACC in adolescence is pertinent to the development of affect regulation.

There is also evidence that the ACC is involved in exerting control over affective experience. Functional imaging studies have observed reciprocal suppression of the affective regions of the ACC during cognitive tasks, and likewise deactivation of the cognitive region during affective processing and experience (Drevets & Raichle, 1998; Bush, Whalen, Rosen, Jenike, McInerney & Rauch, 1998; Bush et al., 1999). As discussed in the amygdala section, down-regulation of negative affect is associated with activation in the ACC and deactivation in the amygdala, suggesting cortical inhibition of the amygdala (Mak, Wong, Han & Lee, 2009).

3.3.6 Valence and laterality
The ACC is notable for its extensive involvement with both positively and negatively valenced stimuli and behaviour, and its integration of positive and negative information. For example, the affective divisions of the ACC are implicated in the experience of intense distress, but also in pleasant experiences such as feelings of love for significant others, the rush associated with cocaine administration, and sexual arousal (B. A. Vogt & Sikes, 2000; Bancaud & Talairach, 1992; Rauch et al., 1999; Redouté et al., 2000). Furthermore, the ACC appears to integrate the positive and negative in response and action selection; for example, in motivated behavioural selection, there is evidence that the ACC incorporates learning from error monitoring and reward history (Kennerly et al., 2006). In light of the often observed associations between emotional valence and laterality (e.g., Wager, Phan, Liberzon & Taylor, 2003), the question arises as to whether the positive and negative aspects of processing subserved by the ACC co-occur within subregions, or are lateralised according to valence. Currently, given the complexity of the interactions between ACC subregions and other areas, the relative recency of interest in the ACC, and lack of an integrated understanding of ACC function, there is insufficient evidence to make predictions of laterality within ACC subregions and associated functions.

3.3.7 The anterior cingulate cortex and depression
Having reviewed evidence proposing that a range of functions are subserved within the ACC, the focus now turns to depression and to related functional and structural findings for each subdivision (ventral, dorsal, and rostral).

3.3.7.1 Ventral anterior cingulate cortex
The ventral ACC is the subregion most discussed in relation to depression, and it is understood to be so profoundly implicated in depressive pathophysiology as to be a target of deep-brain
stimulation in cases of treatment resistant depression (e.g., Johansen-Berg et al., 2008). Functional imaging has demonstrated increased activation in the ventral ACC during the experience of sadness in healthy people (Mayberg et al., 1999; A. R. Damasio et al., 2000; Liotti et al., 2000). Counterintuitively, resting activity in the ventral ACC was originally found to be reduced in depressed individuals (Buchsbaum et al., 1997; Drevets et al., 1997). However, once volumetric reductions (discussed further below; see also Hirayasu et al., 1999; Ongür, Drevets & Price, 1998) were accounted for by correcting for partial voluming effects, the proportionate ventral ACC activation has in fact been found to be greater in depressives (Drevets, 1999), which converges with Zald and colleagues’ (2002) finding that ventral ACC activity corresponded with greater trait negativity.

Depressed individuals have also demonstrated increased ventral ACC activation compared with controls during negative affective experimental tasks, for example viewing negatively valenced stimuli (Gotlib et al., 2005). Beauregard and colleagues (2006) asked depressed and non-depressed participants to attempt to down-regulate induced sadness. Depressed participants displayed greater activation in ventral ACC, which correlated with their reported level of difficulty in down-regulating their sad mood.

Given the links between ventral ACC function and social processing, in particular evaluations of social interactions and the consequences of social behaviour, dysfunction in the ventral ACC has also been suggested as a potential contributor to the content of depressive cognitive distortions such as heightened self-criticism, feelings of alienation, and heightened sensitivity to negative social signals and perceived criticism and rejection from others (A. R. Damasio et al., 2000; Coryell, Nopoulos, Drevets, Wilson & Andreasen, 2005).

Research has also implicated the ventral ACC in adolescent depression. Mannie, Norbury, Murphy, Inkster, Harmer and Cowen (2008) found that non-depressed children of depressed parents (mean age 19) showed altered activation patterns in the ventral ACC in response to an emotional Stroop task. The pattern of responses was consistent with an interpretation that increased familial risk of depression was associated with less efficient parallel monitoring of emotional and cognitive information. Yang and colleagues (2009) demonstrated that depressed adolescents (13-17 years) showed the same increase in task-related ventral ACC activity previously demonstrated in adults, which was positively correlated with depression severity and negatively correlated with Global Assessment of Functioning scores.
Ventral activation has also been found to index treatment response. Mayberg and colleagues (1999) found that recovery from depression was associated with decrease in ventral ACC activation. Successful antidepressant treatment has also been associated with reduction of ventral ACC activity (Buchsbaum et al., 1997, Drevets, Ongür & Price, 1998). Similarly, Kennedy and colleagues (2007) found that ventral ACC activation differentiated between responders and non-responders to cognitive behavioural therapy or venlafaxine treatments for depression.

While there is less structural than functional imaging research on the ACC’s role in depression, there is a fairly robust body of literature demonstrating volumetric reductions in the ventral ACC associated with depression. In a meta-analysis of 10 studies examining ventral ACC volumes and unipolar and bipolar depression, both left and right ventral volumes were found to be reduced compared with controls in unipolar (but not bipolar) depression (Hajek, Kozeny, Kopecek, Alda & Höschl, 2008). When participants in these studies were categorised into those with and without a family history, only those with a family history showed differences to controls, and these were limited to the left ventral ACC. These reductions were however noted for both bipolar and unipolar depression. That significant findings were constrained to those with a family history was interpreted as indicating that ventral ACC volumetric reduction may be associated with a genetic predisposition towards depressive illness, and therefore may be observed prior to illness onset.

In support of this theory, reduced ventral volume has been noted early in illness course and has been found not to correlate with length or severity of illness (Drevets et al., 1997; Hajek et al., 2008). For example, Botteron, Raichle, Drevets, Heath and Todd (2002) measured ventral prefrontal cortex volumes in young women (17-23 years) with early onset major depression (mean age of onset = 15.2 years, SD = 2.3) and middle-aged women with recurrent major depression, and found that left ventral ACC volume was reduced in both groups compared to age matched controls. Importantly, the difference between depressed and control groups was comparable between the early onset (19% reduction) and recurrent (20% reduction) groups. Findings such as this suggest that volumetric reduction is not secondary to the illness process. Intriguingly, one study found that while subjects with psychotic depression had the smallest ventral ACC compared with schizophrenics and controls, they were also the only group to show increases in grey matter density in the region after a follow up 2-8 years later (Coryell et al., 2005). However, interpretability of these findings was limited by small sample size and methodological differences in the follow-up protocol for each group.
More recently, some findings have surfaced indicating that illness course is related to ACC volume. Yücel and colleagues (2008) found that volumetric reduction in the left posterior ventral ACC was specific to depressed patients taking medication, and could not be explained by other clinical or demographic variables, raising the possibility that medication exposure affects ventral ACC volume, in addition to the demonstrated effects on ventral ACC functioning (e.g., Drevets et al., 2002a).

Frodl and colleagues (2008a) measured volumes of ventral, rostral and dorsal ACC in 78 people hospitalised for depression, and did not find volumetric differences with controls. However, smaller total left ACC volume was associated with greater illness severity as reflected in a larger number of previous admissions. Likewise, Yücel and colleagues (2008) found that ventral ACC reductions were present only in depressed individuals with a history of three or more episodes, and that volume did not differentiate between those with and without a family history. It has been suggested that, as discussed with the hippocampus, stress-induced morphological changes might account for volumetric reduction in the ACC. The ACC contains high concentrations of glucocorticoid receptors and may exert inhibitory control over the HPA axis (Ahima & Harlan, 1990; Akana, Chu, Soriano & Dallman, 2001; Dioro, Viau & Meaney, 1993). Furthermore, animal research has demonstrated that glucocorticoid concentrations can precipitate medial prefrontal cortex structural alterations (Radley et al., 2006; Cerqueira et al., 2005a; 2005b). Finally, in a meta-analysis of grey matter alterations in MDD, Bora, Harrison, Davey, Yücel and Pantelis (2012) found that reductions in the ventral ACC were limited to patients not being treated with antidepressants, suggesting that the pharmacotherapy may have exerted a protective or recuperative effect against pathophysiological processes associated with depression.

3.3.7.2 Dorsal anterior cingulate cortex

Given the centrality of cognitive symptoms, including impairment of executive function in depressive disorders (Douglas & Porter, 2009; McClintock, Husain, Greer & Cullum, 2010), it is reasonable to focus on the dorsal ACC as a structure potentially relevant to depression.

Resting state activity reduction has been observed in the dorsal ACC in depressed individuals (Haldane & Frangou, 2006; Drevets, 2000). Furthermore, decreased activation of the dorsal ACC has been associated with depressed mood in the context of tryptophan depletion, compared with controls during cognitive tasks (Smith, Morris, Friston, Cowen & Dolan, 1999). From findings such as these, a picture begins to emerge; heightened activity of the ventral, “affective” regions of the ACC and reduced activity of the dorsal, “cognitive” regions indicates some regulatory dysfunction (although the exact nature of the reciprocal suppression between ventral and dorsal
ACC is as yet unknown), and could be expected to give rise to increased negative affective experience and impairments in performance on cognitively demanding tasks, both core symptoms of depression.

Structural research specifically investigating dorsal ACC volumes in depression is relatively scarce. As noted earlier, Frodl and colleagues (2008a) did not find dorsal volumetric differences between people hospitalised for depression and controls. Chen and colleagues (2007) however found that in a longitudinal study of fluoxetine treatment for depression, symptom severity at baseline was negatively correlated with dorsal anterior cingulate volume, with some extension into the rostral ACC. These authors speculated that the affective-attentional functions thought to be localised in the dorsal ACC may exert a protective influence and therefore those with reduced dorsal grey matter may be more predisposed to depressive symptoms. Caetano and colleagues (2006b) used anatomical landmarks which effectively measured the rostral and dorsal ACC together, and found bilaterally reduced volumes in unipolar depressed patients compared with controls.

There is little research on volumetric alterations in the dorsal ACC and risk for depression. However if viewed through the lens of maturational disparity models, the dorsal ACC’s putative role in regulatory and executive functions, and its particular specialisation in the modulation of behaviour in conditions of affective and social significance make it likely to be salient for emotional regulation and risk for depression at the beginning of adolescence.

3.3.7.3 Rostral anterior cingulate cortex

Compared to the focus on ventral ACC and depression, research has only recently begun to focus on the rostral ACC. In many older studies, rostral ACC is included with ventral ACC as the affective subdivision of the ACC. As noted above, using a combined measure of rostral and dorsal ACC volume, Caetano and colleagues (2006b) found bilaterally reduced volumes in unipolar depressed patients compared with controls. In a sample of healthy children aged 7-17 years, a combined rostral/ventral left ACC volumetric measure was found to correlate negatively with sub-clinical depressive symptoms in the boys only, particularly those with a family history of depression (Boes, McCormick, Coryell & Nopoulos, 2008). Treadway, Grant, Ding, Hollon, Gore and Shelton (2009) found grey matter reduction localised in the right rostral ACC in a sample of 19 depressed adults. Mak and colleagues (2009) found that depressed patients showed reduced grey matter concentration and volume in the right rostral ACC, and that grey matter volume and concentration were positively correlated with success in down-regulating negative emotion. In a meta-analysis of voxel-based morphometry studies of brain structure and
depression, Bora and colleagues (2012a) found that the most robust volumetric effect noted was a reduction in the rostral ACC, which was more pronounced in those with longer illness durations.

There are some interesting, if somewhat contradictory, findings from functional neuroimaging studies that implicate the rostral ACC in depression. In terms of resting activity, both increased and decreased activity has been found to correspond with depressive symptoms (increased activity: Kennedy et al., 2001; Videbech et al., 2002; decreased activity: Ito et al., 1996; Mayberg, Lewis, Regenold & Wagner Jr, 1994). Decreased resting rostral ACC activity has also been found to predict a poor response to treatment for depression (Mayberg et al., 1997; Mülert et al., 2007; Pizzagalli et al., 2001) and hyperactivity of the rostral ACC has been shown to predict better response to antidepressant treatment in acute depression (Pizzagalli, 2011). Anhedonia has been linked to the strength of response in the rostral ACC to pleasant stimuli, in both depressed and healthy individuals. Keevall, Andrew, Williams, Brammer and Phillips (2005) found a positive correlation between anhedonia and blood-oxygen-level-dependent (BOLD) response to personally relevant pleasant stimuli in depressed participants. Harvey, Pruessner, Czechowska and Lepage (2007) reported the same pattern of findings in non-clinical participants. These findings are interesting given that increased activity in the rostral ACC is also associated with subjective ratings of pleasure in response to stimuli presented in a variety of modalities (Rolls, Grabenhorst & Parris, 2008; Rolls, Kringelbach & de Araujo, 2003; Grabenhorst, Rolls & Bilderbeck, 2008).

Wacker, Dillon and Pizzagalli (2009) also found an association between anhedonia in a non-clinical sample and resting EEG delta activity in the rostral ACC, such that low resting activation was associated with anhedonia. This makes intuitive sense in suggesting that anhedonia is linked with a tonic hypoactivation in the brain area linked with the subjective experience of pleasure.

The rostral ACC is also part of the “default network” – a network of brain regions that are thought to be active during times of task-independent speculation or introspection. The default network has been suggested to be involved with the anticipation and mental simulation of future events, including the anticipation of rewards (Buckner, Andrews-Hanna & Schacter, 2008). Wacker and colleagues (2009) speculated that the reduced rostral ACC resting activation they found in anhedonic individuals may indicate a reduced role of the rostral ACC in anticipating rewards during activity of the default network, and may correspond with the decreased sensitivity to and expectation of future rewards associated with anhedonia and depression.
While structural investigation into the rostral ACC and depression is at an early stage, the preliminary findings discussed above point to the rostral ACC as a potential site for volumetric reductions in depression. This, when considered in light of the region's putative role in reward processing (e.g., Risinger et al., 2005), social and affiliative processes (e.g., Somerville et al., 2006), and approach motivation (e.g., Rauch et al., 1999; Redouté et al., 2000; Canli et al., 2004; Youn et al., 2002), prioritises the rostral ACC as a site for further research into the aetiological processes of depression.

3.3.8 Summary and predictions

3.3.8.1 Ventral anterior cingulate cortex
Meta-analysis of ventral ACC volumes found that bilateral volumetric reductions were associated with adult depression, and that family history of depression particularly predicted left ventral ACC volumetric reduction (Hajek et al., 2008). It is unclear however whether volumetric reductions predate the development of depression, and whether there are relationships between illness course and volumetric alterations. For example, research has noted a lack of association between illness course and severity in some instances (e.g., Botteron et al., 2002; Drevets et al., 1997; Hajek et al., 2008). However other studies have reported associations between illness severity and volume (Frodl et al., 2008a), medication use and volume, and number of episodes and volume (Yücel et al., 2008). Given these contrasting findings, it was not possible to hypothesise whether structural alterations to the ventral ACC would be evident prior to depression onset in this sample.

3.3.8.2 Dorsal anterior cingulate cortex
Preliminary findings indicate that reduced dorsal ACC volume and activation is associated with depression (Chen et al., 2007; Caetano et al., 2006a). It was therefore tentatively hypothesised that smaller dorsal ACC would predict the onset of depression in this sample.

3.3.8.3 Rostral anterior cingulate cortex
Given the preliminary structural evidence pointing to reduced rostral ACC volume in depression (Caetano et al., 2006a; Boes et al., 2008; Treadway et al., 2009), it was hypothesised that reduced rostral ACC volume would predict the onset of depression in the current study.

3.4 Orbitofrontal cortex
The orbitofrontal cortex is a structurally and functionally heterogeneous area, comprised of the inferior-most aspect of the prefrontal cortex. Some accounts of orbitofrontal cortex function
and anatomy in depression include the ventral anterior cingulate cortex, however this region was dealt with separately in the previous section.

The orbitofrontal cortex receives taste (Rolls, 1990) and olfactory inputs (Morecraft, Geula & Mesulam, 1992; Rolls & Baylis, 1994) as well as inputs from visual association areas (Petrides & Pandya, 1988; Morecraft et al., 1992; Barbas, 1995). The amygdala and mediodorsal thalamus also project to the orbitofrontal cortex (Krettek & Price, 1977; Ray & Price, 1993). Projections from the orbitofrontal cortex reach structures including the inferior temporal and entorhinal cortices, anterior cingulate, hypothalamus, ventral tegmental area and caudate nucleus (Nauta, 1964; Kemp & Powell, 1970; Insausti, Amaral & Cowan, 1987).

3.4.1 Social processing
The orbitofrontal cortex is proposed to subserve recognition of emotional expression, and may be involved in forming associations between faces and appropriate emotional responses to individuals, and to types of facial expression (Rolls, 1996). Consistent with the orbitofrontal cortex’s proposed role in social behaviour, impairment in facial and vocal emotional expression recognition, and socially inappropriate and disinhibited behaviour has been observed in patients with ventral frontal lobe damage (Hornak, Rolls & Wade, 1996). These impairments do not necessarily reflect a broader impairment in face and voice recognition, or to rational judgment and awareness of social norms – they are specific to emotional aspects of these stimuli.

3.4.2 Reward processing
The somatosensory input received by the orbitofrontal cortex includes representation of primary reinforcers such as pleasant touch, tastes and odours (Francis et al., 1999; Rolls & Treves, 1998). Consistent with the combination of input from both somatosensory and emotional processing areas, the orbitofrontal cortex is thought to be involved in stimulus-reinforcer association learning, and rapid reversal of learning in non-reward conditions. In service of the latter, certain specialised orbitofrontal cortical neurons respond to situations in which reward is expected and not received (Thorpe, Rolls & Maddison, 1983). Accordingly, individuals with ventral frontal damage often perform poorly on tasks which require ongoing recalibration of risk and reward, in particular losing the ability to detect changed punishment schedules and disregarding increased risk contingencies or negative outcomes (e.g., Bechara, A. R. Damasio, H. Damasio & Anderson, 1994; Bechara et al., 1996). These impairments do not necessarily reflect a wider impairment of association-learning; rather, they uniquely affect learning which requires balancing of risk and reward.
The orbitofrontal cortex influences behaviour by signalling the likely value or behavioural relevance of available choices of action, and appears to particularly guide decision-making in circumstances where available information is incomplete or the situation is unpredictable. Certain neurons in the orbitofrontal cortex are active after behavioural response to stimuli, indicating that the region may also be involved in monitoring the consequences of behaviour (Thorpe et al., 1983).

3.4.3 Laterality
There is a large body of neuroimaging and psychophysiology research that has suggested that preferential processing of pleasant stimuli occurs in left prefrontal areas, and aversive stimuli in right prefrontal areas (reviewed by Davidson and Irwin, 1999).

Lateralisation of emotional processing in the orbitofrontal cortex has been further investigated through the framework of behavioural inhibition/activation systems, and regulatory focus theory. The behavioural inhibition system (BIS) and behavioural activation system (BAS) characterize aversive and appetitive motivation respectively, and their affective correlates (Depue & Collins, 1999). An association between BAS sensitivity and greater relative left frontal cortical activation has been demonstrated, as well as some indication of a relationship between BIS sensitivity and greater relative right frontal cortical activation (e.g., Coan & Allen, 2003; Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997).

Whilst related to the BIS/BAS system, regulatory focus is conceptualised as incorporating higher-order, abstract cognitive aspects of motivation. Regulatory focus theory identifies two types of goals; promotion goals, which aim for achievement or attainment of positive outcomes, and prevention goals which aim for the prevention of negative events and outcomes (Higgins, Shah & Friedman, 1997). Amodio, Shah, Sigelman, Brazy and Harmon-Jones (2004) found that chronic promotion focus corresponded to increased left frontal EEG activity, while chronic prevention focus was associated with increased right frontal activity.

3.4.4 Medial/ lateral parcellation
Several lines of investigation have indicated that different regions of the orbitofrontal cortex may be functionally specialised. The clearest functional division appears to be between the medial and lateral portions of the orbitofrontal cortex. Differences in cytoarchitecture and patterns of connectivity have been observed between medial and lateral orbitofrontal cortical regions (Elliott, Dolan & Frith, 2000). Specific and discrete learning impairments have been demonstrated in animal research for lesions to the medial and lateral orbitofrontal cortex,
implicating the medial section in associating stimuli with rewards, and the lateral section in reversal learning (Iversen & Mishkin, 1970).

Elliott and colleagues (2000) present the results of a series of activation studies which suggest that the medial orbitofrontal cortex is particularly involved in learning and updating associations between stimuli and rewarded responses, while the lateral orbitofrontal cortex was associated with inhibition of responses, particularly responses which were previously rewarded. In matching-to-sample tasks for example, the medial orbitofrontal cortex was activated in trials where the participant selected an image that matched a previously viewed stimulus, whereas the lateral orbitofrontal cortex was activated when participants were asked to select the stimulus which did not match the one previously viewed (Elliott & Dolan, 1999). The medial activation was interpreted in part as reflecting the intrinsically rewarding nature of familiarity (Zajonc, 1980) while the lateral activation was interpreted as reflecting the necessity to inhibit a rewarded response (i.e., the urge to select the familiar stimulus).

The lateral orbitofrontal cortex has also been shown to be activated in a behavioural task that required response to facial expressions – activation was specifically heightened for angry faces, which may be taken as a cue that the individual’s behaviour is not acceptable and needs to be modified (Blair, Morris, Frith, Perret & Dolan, 1999).

3.4.5 The orbitofrontal cortex and depression

A central clinical feature of depression is reduced hedonic and motivational responsiveness to events previously associated with pleasure or reward (Depue & Iacono, 1989). In light of the putative function of the orbitofrontal cortex in registering risk and reward and driving approach and withdrawal behaviour accordingly, it follows that the functioning of the orbitofrontal cortex may be altered in depression.

Functional imaging has revealed increases in resting cerebral blood flow and metabolism in the lateral orbitofrontal cortex in unmedicated, early onset depressed patients (reviewed in Drevets, Gadde and Krishnan, 2004). However, contradictory findings have hindered interpretation of this observation; for example, within depressed groups, lateral activation has been found to inversely correlate with depressive severity (Drevets, Spitznagle & Raichle, 1995). Extending the research of neural correlates of regulatory focus described above, Eddington, Dolcos, McLean, Krishnan, Cabeza and Strauman (2009) used fMRI to examine whether cortical activation in response to personalised prevention and promotion goal stimuli differed in depressed versus healthy adults. Controls exhibited significantly greater left orbitofrontal activation than depressed
patients when presented with stimuli representing their promotion goals, while the depressed group showed greater right orbitofrontal activation than controls in response to prevention goal stimuli. Moreover, the magnitude of the right orbitofrontal activation cued by prevention goal stimuli was positively correlated to depression severity. This provides compelling evidence of a neural basis for dysfunction of motivational drives in depression, in particular an over-activation of punishment-monitoring and inhibitory control, thought to be represented in the right orbitofrontal cortex.

Orbitofrontal activity has also been interpreted in the context of affect regulation as exerting an inhibitory influence on the amygdala in the voluntary suppression of sadness. A structural finding in support of this was reported by Mak and colleagues (2009) who observed that depressed patients had lower grey matter concentration in the right orbitofrontal cortex, and that grey matter concentration in the right lateral orbitofrontal cortex was positively related to participants’ ability to down-regulate negative emotions.

The most consistent finding in volumetric studies of the orbitofrontal cortex in depression is for reduced grey matter thickness in several areas. In a post-mortem study, Rajkowska, Miguel-Hidalgo, Wei, Dilley, Pittman, Meltzer and colleagues (1999) found that cortical thickness was reduced by 12% in the anterior orbitofrontal cortices of depressed individuals, compared with healthy controls, and was accompanied by reductions in neural size and density. Multiple imaging studies of orbitofrontal volume in adult and geriatric populations with major depression have also found bilateral reductions in grey matter volume (Lacerda et al., 2004; Bremner et al., 2002; Lai, Payne, Byrum, Steffens & Krishnan, 2000). A meta-analysis of volumetric abnormalities in major depression found that the orbitofrontal cortex was reduced bilaterally in MDD (Bora et al., 2012b).

The mechanisms behind orbitofrontal cortex volume reductions in depression are not well understood; it has been suggested that reductions may occur due to damage associated with excitotoxicity and inflammatory cytokines, or may represent compensatory processes linked to functional alterations in associated regions (Bora et al., 2012b). Reduced neuron size and neuronal and glial density have been observed in depressed individuals, however whether these differences represent neuronal atrophy or neurodevelopmental abnormalities is not known (Drevets, 2007). As with the hippocampus, glucocorticoid toxicity as a consequence of repeated depressive episodes has been suggested. This theory is supported by Bora and colleagues’ (2012b) meta-analysis which found that the orbitofrontal volumetric reductions noted in MDD were more pronounced in later life depression, and in those not treated with antidepressants –
perhaps indicating a neuroprotective effect of antidepressants related to BDNF similar to that observed in the hippocampus. This was also supported by Frodl and colleagues’ (2008c) prospective longitudinal finding – they measured grey matter density in adult inpatients with major depression, and re-scanned the same patients three years later. A bilateral reduction in medial orbitofrontal grey matter density over the three years was observed in depressed subjects as compared to controls. Research on orbitofrontal cortex volume in younger depressed populations, and prospective longitudinal research is required to clarify the nature of orbitofrontal abnormalities in depression.

Few studies reported to date have investigated orbitofrontal cortex volume in paediatric depression. Chen and colleagues (2008) compared data from healthy controls with 27 medication naïve children (mean age 14.4 years) suffering from major depressive disorder. They found no significant differences in total orbitofrontal volume or in grey matter volume between the two groups. They did note that right lateral orbitofrontal cortex total and grey matter volume was higher in the depressed group, however the finding was no longer significant after Bonferroni correction. A magnetic resonance spectroscopy study of 13-17 year olds with major depression found increased choline levels in the orbitofrontal cortex. While consensus has not yet been reached on the relationship between choline levels and affective states, this replicated similar findings in adults and indicates abnormal functioning of the orbitofrontal cortex in depressed adolescents (Steingard et al., 2000). There are also reports of altered orbitofrontal volume in adolescent bipolar and borderline personality disorder patients. First presentation borderline personality disorder patients, aged between 15 and 19 years, demonstrated reduced left orbitofrontal cortex grey matter compared to controls (Chanen et al., 2008). In a sample of bipolar patients aged between 10 and 21 years, females demonstrated larger left lateral orbitofrontal cortex regions, and larger right lateral orbitofrontal cortex regions at a trend level, whereas males demonstrated smaller right medial and lateral volumes compared with controls (Najt et al., 2007). Finally, a study of orbitofrontal morphology in drug naïve young adults (mean age 24.52 years) with a first episode of schizophrenia reported larger left lateral orbitofrontal volumes, and the severity of negative symptoms was positively correlated with left lateral volume (Lacerda, Hardan, Yorbik, Vemulapalli, Prasad & Keshavan, 2007). Studies such as these demonstrate that orbitofrontal cortex abnormalities (including both smaller and larger grey matter volumes) may play a role in the early stages of several psychiatric disorders, and may form a risk factor for psychopathology.
3.4.6 Summary and predictions

Bilateral reductions in orbitofrontal grey matter volume have repeatedly been observed in adults with depression (Rajkowska et al., 1999; Lacerda et al., 2004; Bremner et al., 2002; Lai et al., 2000). However, whether these volumetric reductions in adulthood predate depression onset, or are outcomes of disease processes is unknown. While there are indications of abnormal orbitofrontal cortex functioning in adolescent depression (e.g., Steingard et al., 2000) volumetric alterations in this population have not reliably been reported (e.g., Chen et al., 2008). Based on the preliminary evidence of orbitofrontal cortex volume abnormalities in the early stages of several other types of paediatric mental illness (e.g., Najt et al., 2007; Lacerda et al., 2007; Chanen et al., 2008), it was hypothesised that some alteration of orbitofrontal cortex volume would predict depressive symptom change in the current sample. However, there was insufficient evidence to form directional hypotheses regarding orbitofrontal cortex volume in the prediction of depressive illness.

3.5 Corpus callosum

The corpus callosum is the largest white matter tract in the brain and enables transfer and integration of information between the two cerebral hemispheres. The fibres of the corpus callosum topographically map corresponding cortical areas; small diameter fibres comprise the genu and splenium which connect prefrontal and temporo-parietal areas, while larger diameter fibres comprise the body and isthmus which connect somato-sensory, visual and auditory areas (Aboitiz, Scheibel, Fisher & Zaidel, 1992; De Lacoste, Kirkpatrick & Ross, 1985). Alterations in white matter have been found through the use of diffusion tensor imaging in individuals with depressive disorders; regions found to be affected include the superior longitudinal fasciculus (Murphy & Frodl, 2011), prefrontal regions (Bae, MacFall, Krishnan, Payne, Steffens & Taylor, 2006; Li et al., 2007; Murphy et al., 2007; Nobuhara et al., 2006; Shimony et al., 2009), the cingulate cortex (Murphy et al., 2007; Cullen et al., 2010; Taylor et al., 2011), and parahippocampal gyrus (Yang, Huang, Hong & Yu, 2007; Murphy et al., 2007). These alterations in white matter suggest the corpus callosum as a potential site of alteration in adolescent depression. White matter was not the core focus of this thesis, however the corpus callosum is a white matter structure that can be effectively measured using the imaging methodology employed for this thesis and therefore was included in an exploratory fashion.

Studies of corpus callosum volume in psychiatric disorders are relatively scarce, however research exists which links alterations in areas of the corpus callosum with schizophrenia.
(Arnone, McIntosh, Tan & Ebmeier, 2008), bipolar disorder (Brambilla et al., 2001), attention deficit disorder (Giedd et al., 1994), and major depression (Wu et al., 1993; Lacerda et al., 2002).

3.5.1 The corpus callosum and depression

Given findings discussed throughout this chapter that cortical and limbic functions and volumes are altered in depression, it is feasible that connectivity of these areas may also be altered, which may be reflected in corpus callosum volume. Further, altered cerebral lateralization has been noted in both paediatric and adult depression (e.g., Killgore, Gruber & Yurgelun-Todd, 2007; Bauer & Hesselbrock, 2002; Knott, Mahoney, Kennedy & Evans, 2001). This may also implicate the corpus callosum, as the structure most responsible for interhemispheric information transfer.

In volumetric studies of the corpus callosum, measures are usually taken from a midsagittal cross-section. Therefore in the following review, area refers to cross-sectional area, length refers to an anterior to posterior measure of the cross-section, and width refers to the inferior to superior measurement.

In an early report, Husain and colleagues (1991) found no association between depression diagnosis in adults and corpus callosum volume. Subsequently however, Wu and colleagues (1993) measured regional areas and length of the corpus callosum in 20 adults with unipolar depression. They found that the corpus callosum was larger in cross-sectional area for depressed participants in the anterior and posterior quadrants. They also noted that corpus callosum midlength was greater for depressed females than control females. Parashos, Tupler, Blitchington and Krishnan (1998) however noted no differences in corpus callosum total area of 72 adults with major depression. Brambilla and colleagues (2004) measured T1 signal intensity in depressed, bipolar, and control groups of adults, and noted decreased signal intensity in the bipolar group only (for discussion of T1 MRI scanning, see Chapter 6). This was interpreted as reflecting decreased myelination of corpus callosum fibres in bipolar disorder.

Walterfang and colleagues (2009c) measured midsagittal corpus callosum width, area, curvature and length in currently depressed, remitted, and control groups of adults. They found no significant differences on measures of total cross-sectional area or curvature. There was a trend for longer corpora callosa in the control group as compared with the depressed and remitted groups. Currently depressed patients also showed expansions in the width of the corpus callosum in regions of the posterior body and isthmus – these expansions were exaggerated in the depressed patients with comorbid anxiety. Conversely, Sun, Maller, Daskalakis, Furtado and Fitzgerald (2009) noted a decrease in the isthmus of adults with treatment resistant depression.
The isthmus and posterior body are largely composed of fibres connecting the primary motor and sensory areas of the hemispheres (Hofer & Frahm, 2006; Chao, Cho, Yeh, Chou, Chen & Lin, 2009), however these areas also contain fibres connecting the cingulate gyrus, insula, posterior parietal and superior temporal cortices (Pandya & Seltzer, 1986).

Lacerda and colleagues (2005) measured the length and regional areas of the corpus callosum in 22 adults with major depression. They found no differences in any measure between the depressed group and controls, or between euthymic and acutely depressed adults. However, those depressed participants with a family history of MDD had larger genu, anterior, and middle splenium than participants with non-familial depression, and larger middle genu areas compared with controls. None of these differences were significant once Bonferroni correction was applied. Amongst the depressed group, length of illness was correlated with corpus callosum midlength and posterior splenium area, and age of onset was inversely correlated with midlength, total area and splenium area.

There are some indications that structural integrity of the corpus callosum may be related to risk for depression in healthy individuals. Using diffusion tensor imaging, Frodl, Carballedo, Fagan, Lisiecka, Ferguson and Meaney (2012) found that compared with controls, unaffected healthy relatives of patients with major depressive disorder showed greater fractional anisotropy (a measure of microstructural integrity) in the in the posterior body and splenium of the corpus callosum, as well as several other white matter tracts.

Few studies have investigated corpus callosum morphology and depression in younger samples. In a study measuring corpus callosum area in young adults with dysthymic and depressive personality disorder, Lyoo and colleagues (2002) found that the depressed group exhibited smaller genu than controls, which was interpreted as reflecting frontal structural and functional abnormalities and abnormal lateralisation patterns observed in depression.

Particularly pertinent to the current research is Huang, Fan, Williamson and Rao’s (2011) finding that adolescents at risk for major depressive disorder displayed lower fractional isotropy in several areas including the splenium of the corpus callosum. Frodl and colleagues (2012) suggested that the reduced structural integrity in white matter areas for adolescents at risk for major depression found by Huang and colleagues may be a marker of vulnerability to disease, whereas the increased fractional anisotropy in adults at risk for, but unaffected by, depression found by Frodl and colleagues may be a marker of resilience.
In a matched sample of 16 adolescents with MDD, the depressed group displayed smaller total callosal area, which was largely accounted for by reduction in the genu and was interpreted as possibly reflecting a failure in myelination (MacMaster, Carrey & Langevin, 2012). Alternatively, it was suggested that lower numbers or excessive pruning of fibres crossing the genu accounted for the reduced area. The authors also noted the close association between the genu of the corpus callosum and prefrontal/medial prefrontal areas previously found to be associated with functions affected in depression, such as working memory and emotional processing.

In review, both expansions (Walterfang et al., 2009c; Wu et al., 1993; MacMaster et al., 2012) and reductions (Lyoo et al., 2002; Sun et al., 2009) in regions of the corpus callosum have been observed in association with depressive illness. There are also preliminary indications that other measures of callosal morphology such as length (Wu et al., 1993; Lacerda et al., 2005; Walterfang et al., 2009c) and alterations in microstructural integrity (Huang et al., 2011; Frodl et al., 2012) are associated with depression. Finally there are some indications that familial risk for depression may also be reflected in corpus callosum structure (Huang et al., 2011; Frodl et al., 2012). Abnormalities in size and structural integrity of callosal subregions have so far been interpreted with great caution. Some have suggested that increases in callosal area indicated a larger number of fibres, resulting in a better capacity for callosal transfer and consequently less lateralization of function (Witelson, 1983). On the other hand, Wu and colleagues (1993) speculated that greater numbers of callosal fibres may reflect less efficient processing of information, supported by their finding of reduced metabolism in larger corpora callosa, as well as diminished cortical metabolism asymmetry.

It is also possible that gender differences in the lateralisation of function play into a relationship between corpus callosum size and depression. The corpus callosum is the exception to the rule of greater male white matter growth in adolescence and there are some findings (although heavily debated) that in females the corpus callosum is larger in relation to overall brain size than in males (De Lacoste-Utamsing & Holloway, 1982; De Lacoste-Utamsing et al., 1986; Allen, Richey & Chai, 1991; Yoshi et al., 1986). Females have also been found to have less lateralised function in a range of domains (McGlone, 1980; Hagmann et al., 2006); it is possible that in combination with a greater reliance on bilateral information processing, an abnormally functioning corpus callosum may contribute to a specific risk pathway for females.

3.5.2 Summary and predictions

Both expansions (Walterfang et al., 2009c; Wu et al., 1993; MacMaster et al., 2012) and reductions (Lyoo et al., 2002; Sun et al., 2009) in regions of the corpus callosum have been
observed in association with depressive illness. There are also preliminary indications that other measures of callosal morphology such as length are associated with depression (Wu et al., 1993; Lacerda et al., 2005; Walterfang et al., 2009c). It is unknown whether white matter changes associated with depression precede the clinical manifestation of illness. Given the mixture of findings reported above, and the indicators that familial predisposition to depression may be reflected in corpus callosum structure, it is important to learn whether corpus callosum alterations are observable prior to disease onset. Given that volumetric research into the corpus callosum in depression is limited, it was not possible to form a hypothesis for the current research. Callosal measures of midsagittal area and length were entered into the analysis in an exploratory manner.

3.6 Restatement of hypotheses

3.6.1 Hippocampus

If, in the present study, hippocampal volume prior to depression onset is observed to predict emergence of depressive symptoms, this will lend compelling support to the theory that hippocampal volume is a risk factor for depressive illness. If however hippocampal volume is not related to depression onset, this will suggest that reduced hippocampal volume associated with depression is largely epiphenomenal, potentially as a result of cortisol related neurotoxicity.

3.6.2 Amygdala

It was predicted that there would not be a relationship between amygdala size in early adolescence and depressive symptomatology in mid-adolescence.

3.6.3 Anterior cingulate cortex

3.6.3.1 Ventral anterior cingulate cortex

Given the history of contrasting findings, it was not possible to hypothesise whether structural alterations to the ventral ACC would be evident prior to depression onset in this sample.

3.6.3.2 Dorsal anterior cingulate cortex

Preliminary findings indicate that reduced dorsal ACC volume and activation is associated with depression (Chen et al., 2007; Caetano et al., 2006a). It was therefore hypothesised that smaller dorsal ACC would also be observed to predict the onset of depression in this sample.
3.6.3.3 Rostral anterior cingulate cortex
Given the preliminary structural evidence pointing to reduced rostral ACC volume in depression (Caetano et al., 2006a; Boes et al., 2008; Treadway et al., 2009), it was hypothesised that reduced rostral ACC volume would predict the onset of depression in the current study.

3.6.4 Orbitofrontal cortex
Based on the preliminary evidence of orbitofrontal cortex volume abnormalities in the early stages of several other types of paediatric mental illness (e.g., Najt et al., 2007; Lacerda et al., 2007; Chanen et al., 2008), it was hypothesised that some alteration of orbitofrontal cortex volume would predict depressive symptom change in the current sample. However, there was insufficient evidence to form directional hypotheses regarding orbitofrontal cortex volume in the prediction of depressive illness.

3.6.5 Corpus callosum
Given that volumetric research into the corpus callosum in depression is limited, it was not possible to form a hypothesis for the current research. Callosal measures of midsagittal area and length were entered into the analysis in an exploratory manner.

3.7 Conclusion
This concludes the discussion of brain structure and depression. In the following chapters, the focus will turn first to the relationship between childhood adverse familial experiences and depression, and then to relationships between abuse and neglect and brain development.
Chapter 4: Childhood maltreatment and depression

Maltreatment of children is a significant and universal public health and social-welfare issue in Australia and internationally. It has been unambiguously associated with a range of suboptimal outcomes in terms of injury-related mortality and morbidity, compromised physical and mental health, and poorer socio-economic outcomes (Gilbert, Widom, Browne, Fergusson, Webb & Janson, 2009). Maltreatment is a leading preventable cause of major mental illness, and maltreatment-related early adversity confers a high degree of risk for depression, up to decades later in life (Chapman, Whitfield, Felitti, Dube, Edwards & Anda, 2004; Edwards, Holden, Anda & Felitti, 2003). This chapter discusses definitions of types of childhood maltreatment and their prevalence in Australia, explores factors that confer vulnerability for childhood maltreatment, and details some of the associated outcomes for affected individuals, with a focus on the relationship between childhood adversity and the development of depression in adolescence and adulthood.

Strong evidence exists describing the negative effects of childhood maltreatment on health and wellbeing for children, and for adults with histories of maltreatment. However less research has focussed specifically on relationships between childhood maltreatment and adolescent wellbeing (Hussey, Chang & Kotch, 2006). Given that adolescence is a time of both risk for the consolidation of maladaptive behaviours and patterns of emotional response into lifelong habits, and a time of opportunity for establishing more beneficial behaviours (Dahl, 2004), understanding the effects of childhood maltreatment on adolescents is an important step towards tailoring health and wellbeing services to their needs.

Whilst child maltreatment can be inflicted in a range of contexts by a variety of perpetrators, 80% of maltreatment is perpetrated by parents or parental guardians (with the exception of sexual abuse, which is not considered in this thesis; Gilbert et al., 2009). The current research focuses on child maltreatment in the family environment, and so in the literature reviewed below as well as the study described, maltreatment is taken to occur in the family environment unless otherwise defined.

4.1 Types and prevalence of childhood maltreatment

Childhood maltreatment is commonly defined as one or more of the following: emotional or physical abuse, neglect, and sexual abuse.
Physical abuse refers to deliberate, physically aggressive behaviour towards a child. According to studies of Australian community samples, prevalence rates of childhood physical abuse stand somewhere between 5% and 10% (Price-Robertson, Bromfield & Vassallo, 2010). The Australian Bureau of Statistics Personal Safety Survey \( (n = 16,500; \text{ABS, 2005b}) \) for example reported rates of deliberate physical injury by parents to be 9.4% and 10% in males and females respectively, while one study found a prevalence rate of 18% for any physical violence by parents towards children, as retrospectively reported by a sample of over 6,000 women (Mouzos & Makkai, 2004).

Physical neglect refers to failure to provide for a child’s basic physical needs, such as adequate and nutritious food, shelter, and medical attention. Prevalence rates for physical neglect in Australia have been estimated at between 1.6% (Rosenman & Rodgers, 2004) and 12.2% (Straus & Savage, 2005), with the latter figure coming from the study with the strongest methodology, but a small sample size.

According to the Australian Institute of Health and Welfare (AIHW; 2011), neglect was the primary issue in 28.7% of substantiated reports to child protective services in Australia in 2009-2010 (see Figure 5) highlighting it as a crucial concern in child welfare. While neglect is most often described in terms of physical needs, it is also possible to define emotional neglect, in caregivers’ withholding of affection and attention and failure to provide an emotionally nurturing and supportive environment (Tanaka, Wekerle, Schmuck, Paglia-Boak, MAP Research Team, 2011). As with emotional abuse (discussed below), emotional neglect is an emerging focus of study and prevalence rates are not yet available.
Emotional abuse is somewhat more difficult to define than physical abuse. The Australian Institute of Family Studies (AIFS) characterises emotional abuse as comprising inappropriate verbal or symbolic acts and lists examples such as rejecting, isolating, terrorising, corrupting, denigrating and belittling (Holzer & Bromfield, 2010). Emotional abuse was the cause behind the majority (37%) of substantiated child protection notifications in Australia in 2009-2010 and prevalence estimates range from 6% (Rosenman & Rodgers, 2004) to 17% (Price-Robertson, Smart & Bromfield, 2010).

Sexual abuse is the most thoroughly researched form of childhood abuse, and refers to sexual activity between an adult and a child below the age of consent, or non-consensual sexual activity between minors. Sexual activity includes physical acts, as well as exposing children to sexual stimuli such as pornography. Prevalence of sexual abuse varies widely, depending on definitions – for example, when broad definitions including experiences such as exhibitionism are used, estimates for women exceed 40% (e.g., Watson & Halford, 2010; Mazza, Dennerstein, Garamszegi & Dudley, 2001). Even when definitions are limited to penetrative sexual abuse,
prevalence estimates are high, ranging between 4-8% for males and 7-12% for females (Mamun, Lawlor, O’Callaghan, Bor, Williams & Najman, 2007; Najman, Dunne, Purdie, Boyle & Coxeter, 2005; Dunne, Purdie, Cook, Boyle & Najman, 2003; Mazza et al., 2001; Price-Robertson et al., 2010). However, due to methodological features of this research described in Chapters 6 and 7, sexual abuse was not included in the current study.

4.2 Predictors of childhood maltreatment

Child maltreatment is a universal problem occurring internationally, within different cultural, economic, familial and religious groups (Krug, Dahlberg, Mercy, Zwi & Lozano, 2002). However, there are individual, familial and contextual factors that confer greater risk for maltreatment onto certain children, some of which are discussed below.

4.2.1 Gender

The clearest finding in relation to gender and prevalence of maltreatment is that girls are at significantly greater risk for sexual abuse than boys (Gilbert et al., 2009). According to substantiated child protection notifications in Australia in 2009-10 (Australian Institute of Health and Welfare, 2011), up to three times as many girls as boys were exposed to sexual abuse, a finding which concords with international patterns. Gender as a risk factor for other forms of childhood maltreatment is less well-understood. There is some evidence that boys are more at risk for physical maltreatment (as was the pattern in Australian child protection substantiations in 2009-10) and that girls are more at risk for emotional maltreatment, however such findings are inconsistent. For example, in a US community sample of 5,673 people, Arnow, Blasey, Hunkeler, Lee and Hayward (2011) examined physical and emotional abuse and neglect, and found gender differences only for prevalence of emotional and sexual abuse, both of which were more common in females. In a meta-analysis of 155 studies, examining 39 risk factors for childhood neglect and abuse, gender was not a significant risk factor for either type of maltreatment (Stith, 2009). To explore this further, gender was included in all analyses of childhood maltreatment in the current study.

4.2.2 Age

According to child welfare reporting statistics, children aged less than 1 year tend to be at the highest risk for child abuse, followed by those aged 1-4 years, with risk decreasing as age increases. This pattern is reflected in child protection substantiations in Australia, with teenagers older than 15 years the least likely to be the subject of a substantiated report. However there is some contradiction between protective services reporting, and research on child maltreatment
which does not show such a strong relationship between child age and risk for abuse – for example in Stith’s (2009) meta-analysis, age was not a risk factor for neglect or abuse. The exception to this is sexual abuse, the risk of which rises as children grow older (Putnam, 2003). The current research involved an early adolescent sample within a narrow age range, however age was also included in analyses as a covariate.

4.2.3 Disability

There is strong evidence of an association between childhood maltreatment and child disability (Stalker & McArthur, 2012). For example, in a US study examining school, protective and welfare services records for over 50,000 children in the education system, Sullivan and Knutson (2000) found over three times the prevalence of recorded child abuse in children with a recorded disability, compared to those without a disability. Children with disabilities have also been found to experience more severe forms of maltreatment than those without (e.g., Kvam, 2004; Akbas, Turia, Karabekiroglu, Pazvantoglu, Kekskin & Boke, 2009).

However conclusions about the relationship between childhood disability and maltreatment are complicated by a number of methodological concerns. For example, most research on the topic does not allow for clarification of the direction of causality – in other words, whether the disability is a risk factor for, an outcome of, the maltreatment. Given that much of the maltreatment reported in large-scale studies on this topic was perpetrated on children with learning, concentration and communication difficulties, it is possible that experiences of maltreatment contributed to the aetiology of these disorders (Stalker & McArthur, 2012). There are also concerns that childhood maltreatment is under-reported in children with disabilities as compared to those without (Kvam, 2000; Cooke & Standen, 2002; Hershkowitz, Lamb & Horowitz, 2007).

4.2.4 Familial and neighbourhood socioeconomic disadvantage

The association between poverty and child maltreatment has been discussed in research and social policy documents from a range of high-income countries (e.g., Gillham, Tanner, Cheyne, Freeman, Rooney & Lambie, 1998; Jones & McCurdy, 1992; Frederick & Goddard, 2007; Sidebotham, Heron & Golding, 2002; Taylor, Spencer & Baldwin, 2000; Tuck, 2000). Although childhood maltreatment occurs in families of all socio-economic strata, children from low SES backgrounds are at greater risk, particularly for neglect and physical abuse (relationships between sexual or emotional abuse and poverty are less well established; Cawson, Wattam, Brooker & Kelly, 2000). For example, the British NSPCC found that young adults who reported having
experienced serious abuse or neglect were doubly likely to also report financial difficulties in their childhood (Radford et al., 2011).

The nature of the link between poverty and child maltreatment is difficult to characterise, as there are multidimensional relationships between a range of social and health problems (e.g., social exclusion, unemployment, mental illness and substance misuse), child maltreatment, and poverty (Hecht & Hansen, 2001). In a meta-analysis of 46 studies, Grant, Compas, Stuhlmacher, Thurm, McMahon and Halpert (2003) found that the relationship between poverty and psychopathology in children was mediated by negative parental behaviours. This accords with findings such as those of Peterson, Ewigman and Vandiver (1994), who found that parents from low-income families demonstrated more authoritarian parenting styles, and utilised physical punishment more often that other parents. The most widely cited causal explanation for this is that the stress associated with low socio-economic status impairs caregivers’ capacity to respond effectively to the demands of parenting (Whipple & Webster-Stratton, 1991; Hooper, Gorin, Cabral & Dyson, 2007; Hecht & Hansen, 2001). A proxy measure of SES – parental education level – was included as a covariate in all analyses for this study and is discussed in more detail in Chapter 6.

At the macro-cultural level, the broader environment in which a child lives has been shown to influence their development, as predicted by ecological and transactional models of child development (Bronfenbrenner, 1979; Cicchetti & Lynch, 1993). In a systemic review of multilevel studies, Sellstrom and Bremberg (2006) found that a number of aspects of neighbourhood context were related to child health and wellbeing above and beyond the individual aspects of the families living in these contexts. Coulton, Corbin and Su (1999) found that growing up in a poorer neighbourhood was associated with increased risk for maltreatment, even after controlling for individual socio-economic factors. Neighbourhood disadvantage was also found to weaken the influence of protective factors against maltreatment. Jaffee, Caspi, Moffitt, Polo-Tomas and Taylor (2007) found several individual strengths which distinguished children who were physically maltreated but who functioned well despite this. However, these resilience factors only influenced functioning under conditions of low, not high, family and neighbourhood stress.

4.2.5 Parental substance use and mental illness

In a prospective longitudinal study of parental characteristics using US population data, Chaffin, Kelleher and Hollenberg (1996) found that substance abuse disorders tripled the risk for child maltreatment, after other factors were controlled for. They also found that, after controlling for
other factors, parental depression was uniquely associated with physical abuse. Given the high prevalence of both substance use and depression in the population, these findings are cause for concern. In a study of court records pertaining to child maltreatment, Taylor and colleagues (1991) found that 84% of the parents involved had received a Diagnostic and Statistical Manual of Mental Disorders (DSM) III diagnosis with about a quarter of parents diagnosed with substance use disorders and affective disorders respectively. Of course, not all parents with mental health difficulties maltreat their children – many other factors such as insight into the mental illness, insight into children’s needs, cognitive abilities, realistic expectations of children’s behaviour, and social support contribute to the appropriateness of parenting behaviours (Mullick, Miller & Jacobsen, 2001; Hecht & Hansen, 2001; Gilbert et al., 2009).

Milner’s social information processing model posits that parents’ pre-existing cognitive schemas affect their perception and evaluation of child-related information, and their resulting parenting behaviours. For example, a parent may tend to make negative attributions for ambiguous or even positive child behaviours and respond with hostility. This is not limited to parents with mental health difficulties, but given the link between negatively biased schemas and psychopathology which underlies cognitive behavioural formulations of mental illness, this is likely to be especially pertinent to these parents’ negative behaviours towards their children. Attributions about children’s behaviour have also been linked to the level of information parents have about age-appropriate behaviours, with less knowledge about this being associated with worse maltreatment (Milner & Chilamkurti, 1991).

4.2.6 Family structure

Certain elements of family structure have been shown to contribute to risk for child maltreatment; most notably single parenthood and the presence of non-biological family members (e.g., step parents; Van IJzendoorn, Euser, Prinzie, Juffer & Bakermans-Kranenburg, 2009; Berger, 2004). The consideration of family structure and child maltreatment again raises the multidimensional nature of risk for child maltreatment; single parent homes are more likely to be experiencing economic hardship (Gelles, 1989), single parents often have less time and resources to protect their children from maltreatment by others, and often lack the social support thought to be a protective factor against child maltreatment (Wolfe & St Pierre, 1989; Berger, 2004; Hecht & Hansen, 2001).

Having discussed some of the risk factors for childhood maltreatment, the next section provides an overview of the adverse outcomes associated with these childhood experiences, beginning with socio-economic and health outcomes, and then focusing on mental health and depression.
4.3 Adverse sequelae of childhood maltreatment

4.3.1 Socio-economic and health outcomes

Multiple suboptimal outcomes have been observed for children who are maltreated. Deficits in educational achievement which extend into adolescence have been found for children with histories of maltreatment, who are more likely to struggle with school performance and attendance (Leiter, 1997), require special education services (Jonson-Reid, Drake, Kim, Porterfield & Han, 2004), and leave school before completion (Widom, 2000; Perez & Widom, 1994). As discussed above, it is difficult to disentangle the mechanisms for these relationships from one another – while in many studies, the relationship between maltreatment and poor educational outcomes has been found to persist after controlling for other variables such as SES, these factors clearly interact with each other (e.g., Boden, Horwood & Fergusson, 2007). Adverse educational outcomes for maltreated children also appear to extend into economic disadvantage as adults. Currie and Widom (2010) found that adults with histories of childhood maltreatment had poorer outcomes in terms of employment, earnings, and assets compared to matched controls, and that this effect was larger for women than for men.

Childhood maltreatment has been linked with a range of poor health outcomes in adolescence and adulthood. Several prospective longitudinal studies have found links between childhood adversity and obesity in adolescence (Johnson, Cohen, Kasen & Brook, 2002) young adulthood (Lissau & Sorensen, 1994) and adulthood (Thomas, Hyponnen & Power, 2008) that persisted after controlling for other factors. Relationships between childhood maltreatment and health difficulties in adulthood such as heart disease, lung disease, liver disease, cancer and chronic pain have also been reported (Felitti et al., 1998; Draper et al., 2008; Linton, 2002; Raphael, 2005; Brown, Berenson & Cohen, 2005). Risky sexual behaviour has also been strongly associated with childhood maltreatment – while this is most commonly researched in relation to sexual abuse (e.g., St Amand, Bard & Silovsky, 2008), risky sexual behaviour and associated adverse outcomes such as illegal prostitution, teenage pregnancy and sexually transmitted disease infection have been related to various forms of non-sexual child maltreatment, particularly for women (Merrick, Litrownik, Everson & Cox, 2008; Wilson & Widom, 2008; Arriola, Louden, Doldren & Fortenberry, 2005; Brown, Cohen, Chen, Smailes & Johnson, 2004). Both men and women with histories of maltreatment are also at increased risk for antisocial behaviour, including perpetrating crime and violence as young people and adults (Widom, 1989; Gilbert et al., 2009; Stouthamer-Loeber, Loeber, Homish & Wei, 2001; Egeland, Yates, Appleyard & van Dulmen,
2002; Hubbard & Pratt, 2002). This effect has been noted strongly for physical forms of abuse, but also for verbal abuse (Teicher, Samson, Polcari & McGreenery, 2006).

4.3.2 Psychopathology

In an aggregation of data from WHO World Mental Health Surveys from 21 countries (n = 51,945), Kessler and colleagues (2010) estimated that the eradication of childhood adversity would lead to a 32.3% reduction in mood, anxiety, behaviour and substance use disorders in adolescents. That study measured a range of adversity types, and found that after factor analysis two types of adversity emerged – those related to maladaptive family functioning, and other adversities. They noted that the childhood adversities clustered under maladaptive family functioning consistently predicted first onset of mental and behavioural disorders better than the other childhood adversities, reaffirming the particular salience of familial childhood adversity in the epidemiology of psychopathology.

Behavioural and emotional problems appear to be related to timing of maltreatment in a fairly predictable manner – while childhood behavioural problems are closely associated with early maltreatment, behavioural and emotional problems in adolescence can be related either to adolescent maltreatment or to cumulative effects of maltreatment across childhood (Thornberry, Ireland & Smith, 2001; Appleyard, Egeland, van Dulman & Sroufe, 2005; Gilbert et al., 2009).

Post-traumatic stress disorder (PTSD) is an obvious potential outcome for maltreated children, being by definition linked to a frightening event. The relationships between physical and sexual abuse and PTSD are well established for both adolescents and adults with histories of sexual and physical abuse, as well as neglect (Banyard, Williams & Seigel, 2001; Brewin, Andrews & Valentine, 2000). These relationships can be long-lasting, reaching well into adulthood (Widom, 1999).

Another strong body of evidence indicates that childhood maltreatment is associated with suicidality in adolescents and young adults. Physical and sexual abuse in particular have been associated with greatly elevated risk for suicide attempt, independent of other contextual and individual variables (Widom, 1998; Gilbert et al., 2009). A New Zealand study found that histories of severe sexual or physical abuse increased the likelihood of a suicide attempt up to ten times in adolescents and young adults (Fergusson, Boden & Horwood, 2008). Again, the cumulative nature of risk stemming from childhood maltreatment has been demonstrated by findings that accumulated experiences such as repeated abuse or long term neglect form
particularly potent risk factors for later suicidality (Afifi, Enns, Cox, Asmundson, Stein & Sareen, 2008; McHolm, MacMillan & Jamieson, 2003).

Although well acknowledged, the relationship between childhood maltreatment and drug and alcohol abuse is not entirely straightforward. While there does certainly appear to be a relationship between childhood maltreatment and alcohol problems in adolescence and adulthood, this appears to be specific to women (Widom, Ireland & Glynn, 1995; Simpson & Miller, 2002; Widom, White, Czaja & Marmorstein, 2007). Drug use in adulthood has been associated with childhood maltreatment in some studies (e.g., Widom, Marmostein & White, 2006) but not others (Widom, Weiler & Cottler, 1999). These contradictory findings may relate to the many methodological issues implicated in studying adult outcomes of childhood experiences.

4.3.3 Childhood maltreatment and depression

Up to one third of maltreated children experience case-level major depression in adolescence or young adulthood (Fergusson et al., 2008; Widom, Dumont & Czaja, 2007) and relationships have been found between all forms of maltreatment mentioned and depression (Gilbert et al., 2009). Within samples of maltreated children, exacerbating factors for the likelihood of adolescent depression appear to be female gender, childhood externalising behaviour, perceived lack of social support, and severity of maltreatment (Brensilver, Negriff, Mennen & Trickett, 2011; Seeds, Harkness & Quilty, 2010).

Many intersecting mechanisms for the association between childhood maltreatment and depression have been proposed. The following discussion will focus on interpersonal and cognitive aspects – neurobiological processes linking maltreatment and depression are explored in Chapter 5.

Given the fundamentally interpersonal nature of familial child maltreatment, it follows that disruptions to attachment are likely to be early and powerful consequences. There is a large body of evidence supporting the relationship between maltreatment and insecure attachment in children (Cicchetti, Rogosch & Toth, 2006; van Ijzendoorn, Schuengel & Bakermans-Kranenburg, 1999; Cicchetti & Barnett, 1991). Disrupted attachments are thought to foster negative internal models of the self and relationships, and there is strong evidence for the relationship between insecure attachment and adverse outcomes in childhood, adolescence and adulthood (e.g., van Ijzendoorn et al., 1999; Kim, Cicchetti, Rogosch & Manly, 2009, Bureau, Easterbrooks & Lyons-Ruth, 2009). The development of negatively biased representations of the
self and the world is also described in schema theory. Schemas are defined as complex and fundamental cognitive structures that are developed in childhood and which guide the way an individual attends to, perceives and interprets their environment (Beck, 1987). Early interpersonal experiences characterized by hostility, negativity and/or neglect are thought to give rise to negatively biased schemas about the self and the self in relation to others, which contribute to a depressogenic interpretation of events (Kovacs & Beck, 1978). An example of a cognitive bias which can be interpreted as corresponding to a negative schema was demonstrated by Pollack, Klorman, Thatcher and Cicchetti (2001) who found that maltreated children preferentially attended to displays of negative emotion compared to positive emotion. It has also been found in a young adult sample that cognitive styles mediated the relationship between emotional abuse and depression (Gibb et al., 2001).

Kayser, Scher, Mastnak and Resick (2005) studied depression and cognitions of women with histories of childhood maltreatment who had recently been exposed to a traumatic event (rape or physical assault). Their rationale was that the recent trauma would reactivate relevant depressive schemas developed over the period of childhood maltreatment. They found that, for childhood sexual abuse, the relationship between the childhood maltreatment and adult depressive symptoms was fully mediated by maladaptive cognitions about self and others. They also found that cognitions about others mediated the relationship between childhood physical abuse and adult depressive symptoms. The subjective experience of shame has also been found to be both an outcome of childhood maltreatment and a predictor of depression in adolescents and adults (Stuewig & McCloskey, 2005; Andrews, 1995).

Negative experiences of interpersonal relationships for maltreated children are often echoed in their own disrupted social development. Children with histories of maltreatment tend to display poorer social development, for example behaving more aggressively, showing poorer understanding of internal states and emotions, and delayed social awareness in relation to peers (Kolko, 1992; Cicchetti & Beeghly, 1987; Hecht & Hansen, 2001). The difficulties relating to others that these disruptions to social development produce serve to reinforce negative beliefs about competence and self-worth that are core features of depressive thinking (Beck, 1987).

It has also been suggested that the negative effects on interpersonal cognitions and experiences creates a greater vulnerability to depression for females with maltreatment histories. Women are thought to attribute more responsibility to themselves for the quality of interpersonal relationships (Nolen-Hoeksema & Jackson, 2001). In the context of maltreatment, this may correspond to a greater propensity for self-blame and internal attributions for abuse (Cutler &
Nolen-Hoeksema, 1991), which in turn are related to the development of depression in childhood and adolescence (Feiring, Taska & Chen, 2002). However, as discussed earlier, findings are not consistent with regard to gender-specific risk for depression in response to childhood maltreatment.

4.3.3.1 Stress-sensitization

As discussed in Chapter 2, depressive episodes are often preceded by negative life events (Kendler, Thornton & Gardner, 2000). The stress-sensitization hypothesis posits that exposure to negative life events increases an individual’s sensitivity to subsequent negative events (also known as a kindling effect; Post, 1992). This hypothesis accords with two major epidemiological patterns in depression; the first being that while initial episodes of affective disorder are likely to be precipitated by major negative life events, recurrence of the disorder is prompted by events of less and less objective severity, and the second being that the risk for depression in adulthood is heightened by experiences of childhood adversity. Research has explored the convergence of these patterns in demonstrating that for individuals with a history of childhood adversity, the severity of life events precipitating adolescent and adult onset affective disorder is less than for those without a history of childhood adversity. For example, in a population-based psychiatric epidemiological study (n = 34,653), McLaughlin, Conron, Koenen and Gilman (2009) found that major stressors were associated with a 27.3% increase in the risk of depression among individuals with three or more instances of childhood adversity, compared with a 14.8% increased risk among individuals without a history of childhood adversity. They noted that the stress-sensitizing effects of childhood adversity were demonstrable at a lower threshold of recent stress in men than in women. The study also found that individuals exposed to greater levels of childhood adversity appraised life events as more stressful than did those without histories of childhood adversity.

The findings of this study indicate that life stressors may be subjectively experienced as more stressful, and may be more potent precipitants of depression for individuals already sensitized to such stress through a history of childhood adversity. Other research has also indicated that the nature of stressors required to prompt a depressive response may differ based on history of childhood adversity. In a study particularly targeting depression in adolescents with and without histories of childhood adversity, Harkness, Bruce and Lumley (2006) found that both first onset and recurrent depression was associated with a history of childhood maltreatment. They also found that those reporting childhood maltreatment had a lower level of stressful life events prior to first depressive episode onset. An elevated level of chronic difficulties in the lives of those
with histories of maltreatment was observed, but this did not account entirely for differences in the rates of depression between the groups. In the maltreated group, many adolescents with a first episode of depression reported no precipitant life events. It is possible that the sensitizing effects of childhood maltreatment are so potent as to render ordinary life events stressful enough to precipitate depression. Alternatively, depression experienced by these individuals may be more independent of stressful life events (see Monroe and Harkness, 2005) or may be better measured under a transactional definition of life stressors, which replaces objective measures of the severity of life events with the definition of a stressful event as one which is appraised by that individual as exceeding their specific coping resources (Lazarus & Folkman, 1984, p.19).

4.4 Conclusion and hypotheses
This chapter has defined and characterised the prevalence of different types of childhood maltreatment in Australia and internationally, as well as factors which render children and families more vulnerable to childhood maltreatment. The intersection of individual risk factors with familial, socio-economic and macro-contextual influences was emphasised as well as the cumulative nature of risk both for childhood maltreatment and for the subsequent adverse outcomes discussed. An examination of the literature on the relationship between childhood adversity and the development of depression in adolescence and adulthood indicated that childhood maltreatment of each type defined above (physical and emotional neglect and abuse) both individually and additively form risk factors for adolescent depression. Many of the theories discussed above emphasised the interpersonal sequelae of childhood maltreatment. Disrupted attachment and the development of negative schemas about the self and others learned from maltreatment experiences are thought to be reactivated and strengthened by negative interpersonal experiences. Further, the experience of childhood maltreatment is associated with poor social development, placing maltreated children at a disadvantage in interacting with peers, and therefore more vulnerable to experiencing interpersonal failures. In combination with the high salience of peer interactions in adolescence, and the evidence reviewed in Chapter 2 that interpersonal failures become potent precipitants of depression in adolescence, maltreatment in childhood confers particular risk for adolescent onset depression. The evidence for relationships between maltreatment and depression is already strong, and so demonstrating this relationship was not a core focus of the current research; rather, it was an assumption upon which the rest of the research was designed. Therefore it was hypothesised that in the current study, each type of maltreatment measured would be associated with a higher prevalence of both case level depression and sub-syndromal depressive symptomatology in an adolescent sample.
Chapter 5: The neurobiology of childhood maltreatment

The links between childhood maltreatment and psychopathology, including adolescent onset depression, were examined in the previous chapter. As highlighted there, multiple types of suboptimal outcomes are associated with adverse childhood experiences. This precludes a straightforward account of the neurodevelopmental processes potentially impinged upon by childhood maltreatment. Furthermore, maltreatment does not constitute an easily integrated qualitative construct. The current research attempts to distinguish between neurodevelopmental sequelae of two types of childhood maltreatment: neglect and abuse. However, their chronicity and frequent co-occurrence complicate this distinction, and in the research reviewed below they are frequently used interchangeably (DeBellis, 2001).

The majority of imaging studies describing structural or functional alterations associated with childhood maltreatment have used samples of individuals experiencing psychiatric illness such as PTSD or affective disorders. These studies have not been able to conclude whether structural alterations following childhood maltreatment only occur in those individuals who later develop psychopathology, or whether these changes occur before the onset of any psychopathology. This thesis investigates whether structural changes are associated with childhood maltreatment in a healthy sample of young adolescents, allowing the separation of early experiential effects from later psychopathological processes. Mediation by brain volumes of the relationship between childhood maltreatment and adolescent depression was also tested for. This allows for structural alterations observed prior to depression onset to be investigated as possible neurobiological vulnerabilities conferred by childhood maltreatment.

Research in this field has generally viewed the effects of childhood maltreatment on developing neurobiological systems as being mediated through repeated and/or extreme inductions of stress responses and the subsequent effects on associated neural systems. This approach is appealing in unifying a diverse range of experiences with a common type of response; as DeBellis (2001, p. 540) states, “although there are an infinite number of stressors that can cause a subjective sense of overwhelming stress and distress in a child, there are finite ways that the brain and the body...can respond to those stressors”. This approach is reflected in the predominance of research linking childhood maltreatment to PTSD symptoms and their underlying neurobiological correlates. Indeed PTSD symptomatology is frequently used to preselect samples.
for these studies, while the number of studies explicitly linking childhood maltreatment, neurobiological development, and depression, is still relatively small. The use of PTSD as an outcome of interest is nevertheless relevant to the aims of the current research due to the mental health focus, and the comorbidity of PTSD and depression, as well as the well-established links between childhood PTSD and subsequent depression in adolescence and adulthood (Breslau, Davis, Peterson & Schultz, 2000). However it is worth noting that while PTSD is often observed in children with histories of maltreatment, it is not inevitable and cannot be regarded as a proxy for all outcomes related to childhood maltreatment. There are likely to be pervasive psychological and behavioural sequelae to chronic abuse and neglect that are not captured by the more discrete set of symptoms which comprise PTSD (Glaser, 2000).

Although it may be assumed that common elements of stress response will be activated for many adverse experiences, a particular type of experience is targeted in the current research. Unlike some other adverse and traumatic experiences, childhood familial neglect and abuse share an interpersonal core in the disruption and complication of childhood relationships and attachments. In this there is also an illustration of the utility of previous PTSD outcome studies, given that traumas with strong interpersonal implications (for example interpersonal violence and sexual assault) are more likely to result in PTSD than those without strong interpersonal elements (Breslau, Chilcoat, Kessler & Glenn, 1999; Kessler, Sonnega, Bromet, Hughes & Nelson, 1995). There is also reason to believe that early adverse experiences related to familial context have particular salience for brain development. Animal research has shown a relationship between early familial/parental care and brain development; for example, brief maternal separation in rats has been shown to alter the functioning of the HPA axis and glucocorticoid receptor gene expression in the hippocampus and frontal cortex (Francis & Meaney, 1999; Meaney et al., 1996) while naturally occurring differences in rat maternal behaviour are reflected in catecholamine regulation and fear behaviour in pups (Caldji, Tannenbaum, Sharma, Francis, Plotsky & Meaney, 1998).

Stress response systems are considered in more detail later in this chapter. However, prior to focusing in detail on the specific neurobiological systems impacted by childhood maltreatment, and the structural impacts of these experiences, consideration is given to some of the challenges and unanswered questions presented by a relatively recent aspect of enquiry into child maltreatment – the study of neurobiological sequelae of childhood neglect.
5.1 Studying the psychobiology of childhood neglect

Psychobiological enquiry into the consequences of childhood neglect is still a nascent research area and is hampered by multiple confounds, more so perhaps than the study of other childhood adverse experiences. It is inherently more difficult to measure the absence of something than its presence, and neglect refers not only to the absence of measureable commodities such as food and clothes, but less tangible though equally important influences on children, such as parental attention and warmth (Glaser & Prior, 1997).

Neglect may be accompanied by poverty or parental incapacity, and neurodevelopmental sequelae of childhood neglect need to be considered as potentially stemming from any of multiple types of sub-optimal childhood environments. Relationships between neglect and adverse outcomes may be mediated by lack of access to educational and other environmentally enriching experiences that may accompany poverty or parents’ lack of ability to place their children in enriching environments outside the home (Boyce, Frank, Jensen, Kessler, Nelson & Steinberg, 1998). Neglect may also be accompanied by physical influences such as poor nutrition, illness, and exposure to drugs and alcohol in utero. These influences are likely to exert effects on the developing brain, but are different in nature from the effects that can be attributed to the social and relational environments in which children learn to respond and regulate their responses.

Further, neglect is likely to be accompanied by other childhood adverse experiences such as parental substance abuse and domestic violence (Chaffin et al., 1996). Separating the effects of neglect and abuse would require the creation of an unnaturally specific sample; those children neglected by caregivers, who have not experienced other forms of childhood maltreatment. It is worth noting that these problems also apply to the study of abuse, in that many children experience abuse against a backdrop of neglect. Finally, common to both the study of neglect and abuse, is the possibility that genetic characteristics rendering parents more likely to engage in child maltreatment behaviours may also be carried by children, differentiating them from other children based on pre-existing characteristics, not necessarily shaped by the experiences of neglect or abuse themselves.

An interesting differentiator between neglect and abuse may be in the pervasiveness of these experiences in a child’s life. The nature of abuse is such that a child may experience abuse at the hands of one adult, while simultaneously being well cared for by other adults. Children with histories of maltreatment show greater resilience when there is at least one adult caregiver with whom they have a supportive relationship (Masten & Coatsworth, 1998; Werner & Smith, 1992).
Childhood neglect must be more pervasive in order to be detected by standard measures. If, for example, one parent neglects a child but the other does not, the net result may be an average score on a standard measure. Therefore, in neglected children’s homes, there may be a more unmitigated negative or emotionally impoverished atmosphere, compared to abused children’s homes, which may contain a more bipolar spectrum of emotional experiences.

Given how recent interest in neurodevelopmental impacts of childhood neglect is, animal models are still the most populated area from which hypotheses can be drawn. One of the most frequently used paradigms in animal studies of developmental stress is maternal separation. Given the disruption to normal attachment and social stimulation this entails, maternal separation paradigms may provide a starting point and be regarded as very loosely analogous to disruption of early nurturing relationships between a child and caregivers.

It is important to note the differences in the character of experience associated with childhood neglect versus abuse, and the current research hopes to further disentangle these. However, it is also possible to view childhood neglect as essentially a stress-provoking experience. This would suggest that the effects of neglect (and other forms of childhood maltreatment) on neurodevelopment are mediated through the experience of fear, stress, and anxiety, and the associated alterations in the development of biological stress-response systems. These stress response systems are outlined below.

5.2 Stress-response systems

It is necessary to briefly outline the major neurobiological stress response systems, as traumatic stress may have negative effects on the development of these systems’ component parts and their overall functioning (DeBellis & Putnam, 1994).

5.2.1 The catecholamine/sympathetic nervous system

The sympathetic nervous system (SNS) regulates the release of catecholamines in response to perceived threat. Catecholamines such as epinephrine, norepinephrine and dopamine contribute to physical preparation for threat response (i.e., flight, fight, or freeze). The locus coeruleus is responsible for the release of norepinephrine, which in turn stimulates release of epinephrine and cortisol from the adrenal gland. The locus coeruleus also communicates with the HPA axis, which works to regulate the stress response (Watts-English, Fortson, Gibler, Hooper & DeBellis, 2006).
Stress is associated with activation of the locus coeruleus, which is the major catecholamine (specifically norepinephrine) containing nucleus in the brain, and the sympathetic nervous system leading to the fight or flight suite of physiological responses. These responses include increase in catecholamine turnover in the brain, the SNS and adrenal medulla leading to increases in heart rate, blood pressure, metabolic rate, alertness, and circulating catecholamines (Charmandari, Tsigos & Chrousos, 2005). In adults with PTSD, maladaptive alterations have been observed in the catecholamine system and HPA axis. For example, increased sensitivity of the catecholamine system in experimentally induced stressful situations has been observed, as well as elevated 24-hour urinary catecholamine secretions in some studies (Southwick, Yehuda & Wang, 1998). Analogous results have been found in children; Queiroz and colleagues (1991) found that boys with clinical depression and a history of parental neglect showed evidence of increased 24-hour noradrenergic function. DeBellis and colleagues (1999a) found that prepubertal maltreated children with PTSD had higher 24-hour urinary excretions of norepinephrine and dopamine than both over-anxious non-maltreated children and controls, and higher levels of urinary epinephrine than over-anxious children. Similarly, there have been findings of elevated catecholamine activity in sexually abused girls (DeBellis, Lefter, Trickett & Putnam, 1994). Children hospitalised for psychiatric illness, with a history of early life neglect (with or without abuse) have demonstrated altered levels of dopamine beta hydroxylase, an enzyme involved in the conversion of dopamine to noradrenaline (Rogeness & McClure, 1996; Galvin et al., 1991). Perry’s (e.g., 1994) work with clonidine administration (which dampens catecholamine transmission) has also supported the theory that children with histories of adverse experiences demonstrate enhanced SNS tone and increased baseline functioning of the catecholamine system.

5.2.2 The hypothalamic-pituitary-adrenal axis

The HPA axis (comprised of the hypothalamus, and the pituitary and adrenal glands) was discussed in Chapter 3. Activity of the HPA axis is triggered by stress, and stimulates the secretion of glucocorticoids (mainly cortisol in humans) from the adrenal cortices. This results in stimulation of the SNS and centrally causes behavioural activation and arousal (DeBellis et al., 1999a). Whereas the catecholamine system takes effect within seconds of the stressor occurring, the effects of the HPA axis have a longer timeframe. Glucocorticoids are secreted in the minutes following a stressor, and take several hours to exert their effects (Howe, 1998).

There is evidence to suggest that altered HPA axis functioning is associated with chronic or extreme stress, as measured in adult PTSD sufferers. Alterations have been noted in central CRF
levels (Bremner et al., 1997) glucocorticoid receptors and 24-hour urinary free cortisol levels (Mason, Giller, Kosten, Ostroff & Podd, 1986; Yehuda, Southwick, Giller, Ma & Mason, 1991; Yehuda, Southwick, Giller, Ma & Mason, 1992; Yehuda, Kahana, Binder-Brynes, Southwick, Mason & Giller, 1995; Pittman & Orr, 1990; Lemieux & Coe, 1995).

Findings regarding cortisol levels in maltreated children have been mixed. Elevated basal cortisol levels have been reported in some studies (Carrion, Weems, Ray, Glaser, Hessl & Reiss, 2002; Cicchetti & Rogosch, 2001; DeBellis et al., 1999a) but not others (Kaufman et al., 1997b; Hart et al., 1995). A diurnal variation in cortisol levels is considered normal, with higher levels found in the morning, declining in the afternoon (Rose, Kreuz, Holaday, Sulak & Johnson, 1972). Trickett, Noll, Susman, Shenk and Putnam (2010) found evidence for elevated levels of morning cortisol in sexually abused girls measured within 6 months of disclosure. There are some indications that altered cortisol levels are only observable in maltreated children who also experience a concurrent affective disorder (Tarullo & Gunnar, 2006). Maltreated children have failed to show the expected diurnal decrease in cortisol secretion from morning to afternoon, however this effect was only observed in those who also had depression (Kaufman, 1991; Hart, Gunnar & Cicchetti, 1996).

DeBellis and colleagues (1999a) found that prepubertal maltreated children with PTSD demonstrated higher 24-hour levels of urinary free cortisol than controls, but not than over-anxious children. Levels of norepinephrine, dopamine, and urinary free cortisol also correlated positively with PTSD symptomatology. Dopamine and urinary free cortisol were also positively correlated with the Child Behavior Checklist Anxious/Depressed score, and dopamine, urinary free cortisol and epinephrine were positively correlated with the Internalizing score.

Corticotropin-releasing factor (CRF) hypersecretion in response to early adverse experiences has been demonstrated in both animals and humans (Heim et al., 2000; Coplan et al., 1996; Heim, Newport, Bonsall, Miller & Nemeroff, 2001). As the prime regulator of the endocrine stress response, CRF abnormalities constitute further evidence for HPA axis alterations that may mediate the relationship between early life adversity and increased vulnerability to stress-related psychiatric disorders (Heim & Nemeroff, 1999).

Childhood maltreatment has also been found to be associated with HPA axis functioning in adulthood. For example, elevated ACTH responsiveness to stressful situations has been found in both depressed and healthy women with histories of childhood maltreatment (Heim, Newport, Wagner, Wilcox, Miller & Nemeroff, 2002) and increased cortisol response to pharmacological
challenge has been reported in men with histories of maltreatment (Heim, Mletztko, Purselle, Musselman & Nemeroff, 2008).

In support of the conceptualisation of neglect and deprivation as stress-provoking experiences, Carlson and Earls (1997) found that at age 2, children reared in conditions of extreme deprivation (Romanian orphanages) did not show the usual diurnal variation of cortisol levels, compared with Romanian children raised at home. Likewise, Bruce, Fisher, Pears and Levine (2009) found that maltreated children entering foster placements showed blunted morning elevation in cortisol, and that this was particularly strong for those children with histories of physical neglect as compared with other forms of maltreatment. Finally, primates reared in conditions in which mothers are forced to spend large amounts of time foraging for food (thereby limiting the amount of care provided to the infant) have shown elevated cerebrospinal fluid levels of CRF (Coplan et al., 1996; Coplan et al., 2001; Smith, Batuman, Trost, Coplan & Rosenblum, 2002).

Despite a large number of findings such as those described above which suggest abnormal HPA axis functioning in response to stress, the directions of these findings have at times appeared contradictory and a coherent overall picture of HPA response to chronic and/or extreme stress is yet to resolve. Part of the confusion may be attributed to a process of compensatory adaptation of the HPA axis over time. It has been suggested that there is an initial elevation of central CRH and an associated hypersecretion of cortisol after stressful experiences. This is followed by a more long term (possibly post-pubertal) enhanced negative feedback inhibition of the pituitary for cortisol, resulting from a down-regulation of CRH receptors in the anterior pituitary as a result of CRH hypersecretion (DeBellis et al., 1994b; Bremner et al., 1997a; DeBellis et al., 1999a). In support of this, in a longitudinal study following 82 sexually abused girls from childhood/adolescence into young adulthood, a developmental transition was observed in non-stress morning cortisol (measured initially as serum and later as salivary cortisol) as compared with non-abused controls. The participants with histories of sexual abuse exhibited higher levels of morning cortisol in childhood, which transitioned to lower levels by early adulthood (Trickett et al., 2010). One consequence of a down-regulation of the HPA axis, thought to be a long-term consequence of chronic stress (Yehuda, Giller, Southwick, Lowy & Mason, 1991) may be hampered functioning of the amygdala, resulting in suboptimal responses to threat (McEwen & Gianaros, 2010).

The progression of alterations in stress-response may be linked to developmental processes. Responsivity to stress alters within individuals across the lifespan. For example, newborns
demonstrate increased cortisol levels in response to distressing stimuli, however this response decreases during the first year of life (known in animal research as a stress hyporesponsive period; Gunnar, Brodersen, Krueger & Rigatuso, 1996; Larson, White, Cochran, Donzella & Gunnar, 1998; Lewis & Ramsay, 1995). This hyporesponsivity appears to persist through childhood and diminish in adolescence (Gunnar & Cheatham, 2003; de Haan, Gunnar, Tout, Hart & Stansbury, 1998; Gunnar, Tout, de Haan, Pierce & Stansbury, 1997; Nachmias, Gunnar, Mangelsdorf, Parritz & Buss, 1996; Spangler & Schieche, 1998). It has been suggested that this occurs in order to protect the developing brain from the neurotoxic properties of stress hormones (Tarullo & Gunnar, 2006). Of particular relevance to the present research is the theory that HPA axis activity in early life is socially regulated, and that security of attachment and sensitivity of parenting act as a buffer for HPA axis responsivity during this time. For example, Nachmias and colleagues (1996) found that 18 month old children with insecure attachments to caregivers (who were present) showed elevations in salivary cortisol concurrent with fearful responses to a novel stimulus. In contrast, children with secure attachments showed no elevation of salivary cortisol, even while responding fearfully. Maltreated toddlers are more likely to be insecurely attached (Main & Solomon, 1990) and studies have noted elevated cortisol levels in maltreated toddlers during separation from caregivers (Hertsgaard, Gunnar, Erickson & Nachmias, 1995; Spangler & Grossman, 1993). Other evidence for the effects of maternal care on stress response systems comes from research showing that parental care in rodents has been found to influence HPA function through epigenetic programming of glucocorticoid receptor expression (Liu et al., 1997; Weaver et al., 2004). In an extension of preclinical research to a human sample, McGowan and colleagues (2009) found that hippocampal NR3C1 gene expression was decreased in suicide victims with a history of childhood abuse compared with controls, suggesting that childhood parental care affected the epigenetic regulation of hippocampal glucocorticoid receptor expression.

There is also evidence to suggest that stress responsiveness alters again during adolescence. Rodent studies have shown that, after a stress hyporesponsive period, HPA responsivity climbs during adolescence, with greater responses to stress in females than males emerging in late adolescence (reviewed in Spear, 2000).

### 5.3 Stress and reward systems

Early adverse experiences are understood to have the capacity to prompt significant and lasting changes in the development and functioning of neurostructural and neurochemical brain systems. While the effects of early stress are most frequently linked with lasting changes in stress
response, including perception and response to threat (in particular in the context of PTSD), there is also emerging evidence that childhood maltreatment has neurodevelopmental sequelae affecting substrates of reward perception and motivation, which are implicated in symptoms of depression such as anhedonia and amotivation (Guyer et al., 2006; Dillon, Holmes, Birk, Brooks, Lyons-Ruth & Pizzagalli, 2009).

For example, the centrality of dopamine in the brain’s reward system has long been established; it is thought that dopamine plays a particular role in attaching attributions of salience and motivational value to potentially rewarding stimuli (Berridge & Robinson, 1998). D1 receptors on projections from the prefrontal cortex to the nucleus accumbens are particularly important in salience attribution and have been found to undergo a transient elevation of expression in adolescent rats (Brenhouse, Sonntag & Andersen, 2008). This may be interpreted as contributing to the high sensitivity to certain reward cues characteristic of adolescence (e.g., Ernst et al., 2006) and in Brenhouse and colleagues’ study, was associated with enhanced preference for contexts paired with cocaine administration for adolescent rats. Disruption to the development of this circuitry by extreme stress associated with adolescent maltreatment may therefore have implications for the core depressive symptoms of anhedonia and amotivation, characterised behaviourally by underpursuit of rewarding stimuli, and reduced experience of pleasure in previously rewarding activities.

5.4 Maltreatment and the developing brain

Black and Greenough (1998) introduced the terms ‘experience-expectancy’ and ‘experience-dependency’ to describe qualitatively different mechanisms by which endogenous factors may impact neurodevelopment. Experience-expectant development involves a sensitive period during which certain environmental stimuli are necessary for normal neuronal development. Experience-dependent development refers to conditions in which environmental stimuli impinge upon the development of neuronal patterns, and may also involve sensitive periods whereby the developmental timing of significant events may render their influence on certain structures more far-reaching (Andersen, 2003). The discussion of the effects of childhood abuse on development is generally predicated on experience-dependent development of relevant structures and networks. Through this framework, abuse is conceptualised as a set of endogenous stimuli that may impact on the (presumably) otherwise normal development of a structure. Neglect, on the other hand, may be more pertinent to experience-expectant forms of neuronal development – in other words, neglect may lead to the absence of experiences and stimuli considered necessary for
optimal neurodevelopment. However, it is also possible to view childhood neglect as essentially a traumatic, stress-provoking experience.

Overall, the effects of childhood stress on the brain are understood to be qualitatively and quantitatively different from stressors on the adult brain. While the mature brain is thought to attempt to compensate for stressful experiences, the immature brain incorporates the effects of such experience into its structure and function (Andersen, 2003). Some of the individual structures implicated in the neurodevelopmental models of affect and depression reviewed in Chapter 2 are also thought to be particularly developmentally vulnerable to the effects of childhood maltreatment; the research on links between each structure and childhood experience are discussed in the next section.

5.5 Structural neuroanatomical correlates of childhood maltreatment

Having discussed the effects of early life stress and maltreatment on neurobiological stress systems, the discussion now turns to the structural neuroanatomical evidence for altered trajectories of brain development as a response to childhood maltreatment. Based on their examination of preclinical studies, Teicher, Andersen, Polcari, Anderson, Navalta and Kim, (2003, p. 34) suggested three features of brain regions particularly vulnerable to early stress:

- Protracted postnatal development
- High density of glucocorticoid receptors
- Some degree of postnatal neurogenesis

Each of the structures selected for the current research evidences some of these features, as discussed below.

5.5.1 Hippocampus

The hippocampus is thought to be one of the brain structures most vulnerable to extreme or prolonged stress, in part due to the high density of glucocorticoid receptors it contains (Patel, Lopez, Lyons, Burke, Wallace & Schatzberg, 2000). Long-term, progressive adverse effects on cell survival and dendritic branching have been demonstrated in the developing hippocampus after early-life exposure to corticotropin-releasing hormone (Brunson, Eghbal-Ahmadi, Bender, Chen & Baram, 2001). This structure is also marked by protracted postnatal development and neurogenesis (Gould & Tanapat, 1999). The postnatal development of the hippocampus is characterised by dense arborisation and receptor overproduction extending into late childhood, and a postpubertal period of pruning and elimination (Purves & Lichtman, 1980; Teicher et al.,
2003). A heightened sensitivity of the hippocampus to stress during early childhood has also been suggested based on the presence of a special population of cells in the immature hippocampus, but not in the adult hippocampus, which can release CRH in response to stress (Chen et al., 2004b).

There is evidence that, in adults, reduced hippocampal volumes are associated with a history of childhood maltreatment. Hippocampal degeneration has been observed in non-human primates exposed to prolonged social stress (Uno, Tarara, Else, Suleman & Sapolsky, 1989). Smaller hippocampi have also been observed in adults with PTSD (Bremner et al., 1995; Gurvits et al., 1996). Volumetric studies of the hippocampus and early life adversity have tended to find that adults with adverse childhood experiences and subsequent psychiatric illness often demonstrate reduced hippocampal volume. For example, Driessen and colleagues (2000) found bilateral hippocampal volume reductions in adult women with histories of childhood abuse and current diagnoses of borderline personality disorder. Bremner and colleagues (1997b) found that adults with histories of childhood maltreatment and current PTSD had reduced left hemispheric hippocampal volumes, while Stein, Koverola, Hanna, Torchia and McClarty (1997) noted a similar finding in women with histories of childhood sexual abuse and current diagnoses of dissociative identity disorder.

However, studies of children with histories of maltreatment, with and without psychiatric comorbidity tend not to demonstrate hippocampal volume alterations. For example, two studies investigating hippocampal volume in children with and without histories of maltreatment and with or without PTSD failed to observe any differences in hippocampal volume between groups (DeBellis et al., 1999b; Carrion et al., 2001). The observation of hippocampal volume reduction in adults with histories of maltreatment and comorbid psychiatric disorder, but not in children with similar histories, has several possible interpretations. It has been suggested that psychiatric disorders such as PTSD may effect ongoing, cumulative damage to the hippocampus, possibly related to stress-toxicity processes, which require time to become visible and therefore would not be observed in young subjects (Teicher et al., 2003). Conversely, there is evidence that reduced hippocampal volumes in themselves form a risk factor for depression.
It is possible that the smaller hippocampal volumes observed in people with both histories of childhood adversity and later mental illness are not caused by the early trauma, but were a risk factor for pathologic responses to traumatic experience. This was the case in pairs of monozygotic twins discordant for trauma exposure, where both the exposed and unexposed twins showed smaller hippocampi in cases where the exposed twin developed PTSD. This implicated smaller hippocampi as a heritable risk factor for pathological response to trauma (Gilbertson et al., 2002). Rao and colleagues’ (2010) longitudinal findings particularly supported this theory. They found relationships between early life adversity and smaller hippocampi, and smaller hippocampi predicted subsequent depression onset. However, the probability of a major depressive episode in the follow-up period was only elevated for those with both high adversity and the smaller hippocampus, indicating that the smaller hippocampus increased the likelihood of a depression in combination with childhood adversity.

However Dannlowski and colleagues (2012) noted reduced right hippocampal volumes in a large sample of adults with histories of childhood maltreatment and no current or past psychiatric disorder. Teicher, Anderson and Polcari (2012) recently found that childhood maltreatment-related volume reductions in the left hippocampus of young adults were not mediated by lifetime MDD or PTSD diagnosis. Their method also allowed for a high degree of anatomical specificity from which they were able to glean that the hippocampal subfields most strongly affected by early life adversity were also those identified through animal research as being especially glucocorticoid-sensitive.

Another explanation is that alcohol and substance abuse, which are particularly prevalent in those with traumatic life histories and related psychiatric diagnoses (Ellason, Ross, Sainton & Mayran, 1996), may contribute to the loss of hippocampal volume in adulthood (DeBellis et al., 2000b).

The question remains, why are hippocampal reductions that are associated with childhood maltreatment observable in adulthood, but not childhood? Given the increase in hippocampal volume observed during adolescence (Giedd et al., 2006) it is possible that processes related to early life stress may stunt this normative growth, resulting in reductions only observable after puberty (as discussed in DeBellis, Hall, Boring, Frustaci & Moritz, 2001). So far, evidence for this line of reasoning is promising but inconclusive. Edmiston and colleagues (2011) studied a group of adolescents who had experienced childhood maltreatment but had no psychiatric diagnoses, and found bilateral hippocampal grey matter reduction in adolescents exposed to emotional neglect. Given that the sample had no mental health diagnoses and was largely in the
mid-adolescent age range, this lends support to the theory of disrupted hippocampal development during adolescence, as opposed to hippocampal atrophy as a result of mental illness processes.

Several other studies also support the proposition that reduction in hippocampal volume is related to adolescent maturation. Rao and colleagues (2010) found that childhood adversity was associated with hippocampal reduction in adolescents, including after they controlled for chronic stress during adolescence. Anderson and Teicher (2004) examined the effects of early maternal deprivation on synaptic density in rats and found a reduction in density in the hippocampus, which only emerged well after the early life stress. Specifically, they found that the rats exposed to early life stress did not demonstrate the developmentally normal overproduction of synapses expected in the CA1 and CA3 regions of the hippocampus. However, DeBellis and colleagues (2001a) conducted a prospective longitudinal study with a small sample of prepubertal children with PTSD secondary to maltreatment. Children underwent repeat MRI scans 2-3 years later, while in the late stages of puberty and volumes were compared to a yoked control group. No significant differences in hippocampal volume were observed between groups at either time point – the findings did not support the theory of neurodevelopmental hippocampal stunting during puberty. The authors suggested that, if stress-induced hippocampal damage drives adult hippocampal reductions, it may not be observable until postpubertal development.

5.5.1.1 Summary and predictions
The findings reviewed suggest that the hippocampal reductions observed in adults exposed to childhood maltreatment may either be due to disruptions to the adolescent development of the hippocampus, or to smaller hippocampi conferring higher risk for pathological responses to traumatic experience. The sample for this research underwent brain scans in early adolescence, before the putative disruption to adolescent hippocampal development would occur, and had no current or past depression. Therefore it was hypothesised that no reduction in hippocampal volume would be associated with childhood maltreatment.

5.5.2 Amygdala
With such a strong role in the processing of threat, the amygdala is another candidate for study in understanding the neurobiological consequences of severe or prolonged stress during development. Overactivity of the amygdala has been demonstrated as a result of trauma – for example, Dannlowski and colleagues (2012) found right sided amygdala hyper-responsiveness to negative stimuli in healthy adults with histories of childhood maltreatment. Such amygdala overactivity has been linked with the process of kindling – whereby repeated neuronal
stimulation results in increased excitability of those neurons and eventual overactivity including spontaneous discharges (Post, Rubinow & Ballenger, 1984) – and implicated in the symptomatology of PTSD (Villarreal & King, 2001). In the context of stressful experiences, kindling means that an individual’s threshold for stress reaction is reduced. Early stress has been found to be associated with a reduction of central benzodiazepine and GABA-A receptors in the rat amygdala (Caldji, Francis, Sharma, Plotisky & Meaney, 2000), which in turn is thought to contribute to such seizure-like activity in the amygdala and associated areas, known as “limbic irritability” (Teicher et al., 2003). In support of this, Teicher and colleagues have found that, on a scale designed to measure symptoms of limbic irritability, adults with histories of abuse and psychiatric diagnoses endorsed elevated symptoms (Teicher, Glod, Surrey & Swett Jr, 1993) and that children with histories of abuse and current psychiatric diagnoses showed EEG abnormalities in the fronto-temporal region which could be interpreted as stemming from limbic irritability (Ito, Teicher, Glod, Harper, Magnus & Gelbard, 1993). Such paroxysmal EEG disturbances have also been linked with suicidal ideation and behaviour in adult populations (Struve, 1983; Struve, Klein & Saraf, 1972).

Several studies examining amygdala volumes in adults with histories of childhood trauma and PTSD have observed no volumetric differences compared to controls (Bremner et al., 1997b; Stein, 1997; DeBellis et al., 1999b; Andersen, Tomada, Vincow, Valente, Polcari & Teicher, 2008). However, studies of childhood maltreatment and other mental illnesses in adulthood have found relationships with amygdala volume.

A recent study of 45 first episode psychosis patients exposed to childhood trauma (largely familial, such as loss of a parent or abuse) found that reduced bilateral amygdala volume was associated with childhood trauma in first episode psychosis patients, and that this relationship was particularly evident for those with more severe trauma histories (Aas et al., 2012). Childhood trauma was also associated with poorer performance on a range of cognitive domains (including working memory, language, executive function, attention and concentration). Most interestingly, the authors found that reduced left amygdala volume mediated the relationship between childhood trauma and poor cognitive performance in these patients. This finding is concordant with other research indicating that as well as emotional processing, the amygdala contributes to higher functions and suggests that these may be linked with vulnerability to psychopathology conferred by early childhood experiences. Related to this are findings that the volume of the amygdala was associated with worse performance on cognitive tasks in individuals with affective disorders (Killgore, Rosso, Gruber & Yurgelun-Todd, 2009; Li et al., 2010).
There is also some evidence that amygdala volumes are reduced in adults with borderline personality disorder who report a history of childhood maltreatment (Driessen et al., 2000; Schmahal, Vermetten, Elzinga & Bremner, 2003). Bilateral reduction in amygdala volume was reported in two studies of women with borderline personality disorder and early trauma histories (Driessen et al., 2000; Weniger, Lange, Sachsse & Irle, 2009). Likewise, there is evidence of reduced amygdala volume in adult PTSD sufferers with dissociative disorders (Vermetten, Schmahal, Lindner, Loewenstein & Bremner, 2006) although a later study found that while adult PTSD sufferers with histories of severe childhood abuse had smaller amygdalae than controls, those with dissociative identity disorder did not, suggesting that the PTSD diagnosis rather than dissociative disorder was related to reduction in amygdala size.

There have been some findings hinting at a structural relationship between the amygdala and trauma in children, although these findings have also been mixed. Carrion and colleagues (2001) found no relationship between amygdala volume and PTSD in children. DeBellis and colleagues’ (2001a) prospective longitudinal study found no significant differences in amygdala volume between children with PTSD secondary to maltreatment and sociodemographically matched controls. However a meta-analysis by Karl, Schaefer, Malta, Dörfel, Rohleder and Werner (2006) found that in both adults and children with PTSD from various types of trauma, smaller left amygdala volume was associated with PTSD. A later meta-analysis found no volumetric alterations in the amygdalae of child sufferers of maltreatment-related PTSD (Woon & Hedges, 2008). However, when the authors broadened their criteria for study inclusion in the analysis, a weak effect for reduced amygdala size was observed. In their study of healthy adolescents exposed to childhood maltreatment, Edmiston and colleagues (2011) found bilateral amygdala volume reduction was associated with childhood emotional neglect.

Conversely, animal studies have found that larger amygdala cell size was associated with the heightened amygdalar reactivity described (Vyas, Mitra, Shankaranarayana, Rao & Chattarji, 2002; Vyas, Pillai & Chattarji, 2004), and in two studies of children removed from institutional conditions of profound deprivation, amygdala volumes were found to be increased (Tottenham et al., 2009; Mehta et al., 2009). Hence although the amygdala has a well-established role in fear and threat perception and response, and demonstrates volume alterations related to some psychological conditions, findings have been mixed.

5.5.2.1 Summary and predictions
Based on the emerging body of work suggesting that volume alterations associated with childhood trauma (in the context of adult psychopathology in most studies) tend towards
reduction and particularly in the left amygdala (Aas et al., 2012; Karl et al., 2006; Edmiston et al., 2011), it was hypothesised that childhood neglect and/or trauma would be associated with reduced amygdala volumes in this sample.

5.5.3 Anterior cingulate cortex

While volumetric findings regarding the ACC and childhood maltreatment are sparse, there are other forms of evidence connecting the two. The ACC has been implicated in the inhibition of fear-related limbic activation, and the extinction of conditioned fear responses, and therefore has been an area of interest for researching neural correlates of PTSD symptoms (Hamner, Lorberbaum & George, 1999). Functional imaging has demonstrated reduced blood flow to regions of the ACC in women with PTSD and histories of sexual abuse (Shin et al., 1999; Bremner, Narayan, Staib, Southwick, McGlashan & Charney, 1999) and combat veterans with PTSD (Bremner, Staib, Kaloupek, Southwick, Soufer & Charney, 1999) in response to trauma-related stimuli. This hypoactivation is associated with greater activation of the amygdala, suggesting an impairment of medial prefrontal regulation of limbic activation (DeBellis, 2001).

There are also indications of cellular alterations in response to early life stress. Mathew and colleagues (2003) found that 10 years after rearing in conditions with limited access to maternal care, adult macaque monkeys showed significantly decreased ratios of N-acetylaspartate to creatine in the dorsal anterior cingulate. Additionally, choline-containing compounds to creatine ratios in both the medial temporal lobe and dorsal anterior cingulate were significantly elevated compared with control subjects. Both decreased N-acetylaspartate to creatine and increased choline to creatine ratios have been interpreted as indicators of glial-cell proliferation in the anterior cingulate, and mossy fibre sprouting in the hippocampus, although the precise significance of these markers is open to debate (Mathew et al., 2003; Brunson et al., 2001). Similarly, in children with maltreatment related PTSD, analysis of relative N-acetylaspartate and creatine concentrations has indicated neuronal loss and dysfunction in the anterior cingulate cortices (DeBellis, Keshavan, Spencer & Hall, 2000).

A small number of structural studies have found alterations of the ACC associated with childhood maltreatment. In a study in which rhesus monkeys were reared either by parents in social groups, or without parents but with same-aged peers, the peer-reared monkeys had larger dorsal ACCs than the maternally-reared monkeys, and also had larger medial prefrontal cortical areas, which incorporated the rostral ACC (Spinelli, Chefer, Suomi, Higley, Barr & Stein, 2009). Rao and colleagues (2010) found that parental nurturance at age four predicted smaller right
cingulate volumes in adolescents. In a study of human participants with histories of childhood emotional maltreatment, van Harmelen and colleagues (2010) found that emotional maltreatment was associated with reduction in left dorsal medial prefrontal cortical grey matter, extending into the dorsal anterior cingulate. This was found even when the sample was reduced to exclude those with concomitant histories of physical maltreatment. Similarly, Edmiston and colleagues (2011) found that childhood emotional neglect was associated with reduced dorsal anterior cingulate grey matter, as well as reduced ventral ACC volume.

Treadway and colleagues (2009) found that adults with histories of childhood maltreatment showed reduced volumes on the rostral ACC, and volumes were negatively correlated with cortisol levels. This suggests that the rostral ACC may be vulnerable to prolonged glucocorticoid exposure resulting from chronic stress, which in turn may decrease its ability to exert negative feedback control over HPA activity.

5.5.3.1 Summary and predictions

The research reviewed above implicates each of the three cingulate areas measured in this research as potential sites affected by childhood maltreatment. However, evidence regarding structural alterations to rostral and ventral ACC is insufficient to form hypotheses. There is a small number of studies indicating that a relationship may exist between childhood maltreatment and reduced dorsal ACC volume. Based on the findings of Harmelen and colleagues (2010) and Edmiston and colleagues (2011) in human samples, it was hypothesised that childhood maltreatment would be associated with reduced dorsal anterior cingulate volumes.

5.5.4 Orbitofrontal cortex

The prefrontal cortex has the most protracted development of all neocortical areas, with myelination of major projections continuing through adolescence and early adulthood (Fuster, 1980). The orbitofrontal cortex in particular has an inhibitory relationship with stress-response systems in the brain, and itself has a high concentration of glucocorticoid receptors (Sánchez et al., 2000).

In a study of white matter connectivity with a small sample of children exposed to early profound institutional deprivation, Eluvathingal and colleagues (2006) found reduced fractional anisotropy in the left uncinate fasciculus. The uncinate fasciculus connects with Brodmann’s area 11 – corresponding with the orbitofrontal cortex. In a previous positron emission tomography (PET) study they also noted hypometabolism in Brodmann’s area 11 bilaterally (H. T. Chugani, Behen, Muzik, Juhasz, Nagy & D. C. Chugani, 2001).
There is some evidence that childhood maltreatment is associated with reductions to orbitofrontal grey matter. Rao and colleagues (2010) found that parental nurturance at age eight predicted smaller orbitofrontal cortex volumes bilaterally in adolescents. Likewise Dannlowski and colleagues (2012) found bilateral grey matter reduction in the orbitofrontal cortex in a large sample of healthy adults with histories of childhood maltreatment. Edmiston and colleagues (2011) found reductions in right orbitofrontal cortex volume in healthy adolescents with histories of physical abuse and emotional neglect. Within the females, bilateral orbitofrontal cortex volume reductions were observed. In early adolescents, Hanson and colleagues (2010) found that physical abuse in childhood predicted smaller right orbitofrontal cortex volume, and smaller right orbitofrontal cortex volume predicted problems in children’s academic abilities and family relationships. However, contrary to the above findings, in their study on synaptic production in rats, Anderson and Teicher (2004) found that in contrast with both the hippocampus and the amygdala, there was no effect of early life maternal separation on synaptic density in the prefrontal cortex.

There is some evidence that the timing of maltreatment may determine whether the orbitofrontal cortex is affected. Andersen and colleagues (2008) found that while early childhood sexual abuse was associated with hippocampal alterations, experiences of sexual abuse in adolescence were associated with prefrontal cortex alterations including synaptic loss. Adolescent stress has also been shown to result in prefrontal synaptic loss in rats and was associated with concurrent onset of depressive behaviours (Leussis, Lawson, Stone & Andersen, 2008). Andersen and Teicher (2008) suggest that such stressful experience during adolescence may act directly on the prefrontal cortex, which is in a developmentally important period during adolescence, and may not demonstrate the incubation period associated with stress-related alterations to other structures. Rather, the altered development of the prefrontal cortex, already implicated in triadic models of affect dysregulation, may contribute to affective distress in and of itself and may further compound consequences of limbic and striatal alterations as a result of earlier stressful experiences.

5.5.4.1 Summary and predictions

An emerging body of evidence suggests that childhood maltreatment is associated with reductions in orbitofrontal cortex volumes in adolescence (Rao et al., 2010; Edmiston et al., 2011; Hanson et al., 2010; Andersen et al., 2008). Therefore it was hypothesised that childhood maltreatment would be associated with reduced orbitofrontal cortex volumes.

97
The hormonal sequelae of early life stress have been found to suppress glial cell division, which is critical for myelination (Lauder, 1983). As the densest white matter tract in the brain, the corpus callosum is naturally implicated in any disruption to myelination. A fairly consistent finding in animal research is that early life experience affects the morphology of the corpus callosum. For example, increased maternal attention (elicited by brief handling) corresponded with larger and more regularly shaped corpora callosa in male but not female rats (Berrebi, Fitch, Ralphe, Denenberg, Friedrich Jr & Denenberg, 1988) while monkeys raised in isolated environments had smaller corpora callosa than those raised in naturalistic environments (Sànchez, Hearn, Do, Rilling & Herndon, 1998). Interestingly, Juraska and Kopcik (1988) noted that while early rearing environment was reflected in corpus callosum structure in both male and female rats, in female rats the number of myelinated axons was increased with environmental quality, whereas in male rats the diameter of myelinated axons was increased.

Frodl and colleagues (2012) found greater fractional anisotropy values in the corpora callosa of unaffected healthy relatives of major depression patients. They also found that while there was no main effect of childhood stress on white matter structural integrity, there was an interaction between childhood stress and familial risk for depression. In several areas, including right frontal and orbitofrontal regions, and the splenium and body of the corpus callosum, childhood stress correlated positively with fractional anisotropy in the relatives of depressed patients, but correlated negatively with fractional anisotropy in the controls. They suggested that the increased fractional anisotropy in non-depressed but at-risk individuals may have reflected resilience factors.

White matter tract abnormalities have been observed in children raised in conditions of profound institutional deprivation (Eluvathingal et al., 2006). However, less extreme early childhood maltreatment may also be reflected in white matter development. Adults reporting a history of parental verbal abuse have shown microstructural alterations in the arcuate fasciculus in the left superior temporal gyrus, the cingulum bundle by the posterior tail of the left hippocampus, and the left body of the fornix (Choi, Jeong, Rohan, Polcari & Teicher, 2009).

Several studies have noted specific alterations in corpus callosum size and shape in children with histories of maltreatment. DeBellis and colleagues (1999b) found that reduction in the size of the corpus callosum, in particular the middle and posterior regions, was the most striking anatomical correlate of childhood abuse in children with PTSD, and noted that the midsagittal volume of the corpus callosum was negatively correlated with the duration of abuse. Teicher and colleagues
also found reductions in the midsection of the corpus callosum in child psychiatric inpatients with histories of abuse (Teicher, Ito, Glod, Andersen, Dumont & Ackerman, 1997). Both of these studies noted that the effects on corpus callosum size and shape were greater for boys. Similarly, DeBellis and colleagues (2002) found reduced corpus callosum area in children with maltreatment-related PTSD compared with sociodemographically matched controls.

One of the few extant studies specifically focusing on neglect and brain development found that boys’ corpora callosa were particularly affected by childhood experiences of neglect, while for girls, experiences of sexual abuse were more strongly reflected in corpus callosum morphology (Teicher, Dumont, Ito, Vaituzis, Giedd & Andersen, 2004). Specifically, several subregions of the corpus callosum (the rostral, anterior, and posterior midbody, and splenium, measured midsagittally) were smaller in a sample of maltreated boys with comorbid psychiatric diagnoses. Importantly, a control group of children with psychiatric diagnoses but no history of maltreatment was included, and it was demonstrated that callosal reductions could not be accounted for by psychiatric illness. For girls, an association of volume reduction with neglect was less marked and was limited to the most posterior aspects of the corpus callosum. However, sexual abuse was associated with reductions in the rostral, anterior, and posterior midbody and isthmus in girls, but only with a trend level reduction in the splenium for boys. The authors suggested that boys have an increased need for early stimulation in order to develop the corpus callosum compared to girls – given that neglect is likely to occur earlier than sexual abuse (US Department of Health and Human Services, 2010), an increased need for stimulation renders boys more vulnerable to its absence. Girls’ callosal development on the other hand is thought to extend further into childhood and is therefore more vulnerable to later experiences of abuse. Preclinical studies of environmental influences on the corpora callosa of adult rats have also provided evidence of differential responses to environmental influences in the male and female corpus callosum (Liu, Caldji, Sharma, Plotsky & Meaney, 2000; Juraska & Kopcik, 1988).

It has been suggested that alterations in corpus callosum morphology may bear relation to altered patterns of structural and functional laterality observed in maltreated children (e.g., Carrion et al., 2001; Ito, Teicher, Glod & Ackerman, 1998). There is a body of EEG research that focuses particularly on hemispheric lateralisation in people with histories of maltreatment; for example in recalling memories of adverse childhood experiences, those with histories of childhood trauma showed marked lateralisation of temporal function compared to a more even pattern of hemispheric activity for those without childhood trauma histories (Schiffer, Teicher & Papanicolaou, 1995). This finding may reflect poorer communication between hemispheres as a
result of attenuated corpus callosum development in maltreated children. This complements structural findings of greater volume and neuronal growth in the left than right hemisphere of non-abused participants, and an opposite pattern of asymmetry in adults with early trauma histories (Teicher et al., 2003).

5.5.5.1 Summary and predictions

In summary, there is a strong body of evidence that early life experience is reflected in corpus callosum morphology. Animal studies have observed smaller corpus callosum volumes in animals reared in less advantageous environmental conditions (Berrebi et al., 1988; Sánchez et al., 1998). Research with humans has also found reductions in the corpus callosum in maltreated children with PTSD (DeBellis et al., 1999b; DeBellis et al., 2002) and other psychiatric conditions (Teicher et al., 1997; Teicher et al., 2004). Finally, there are indications that alterations in white matter related to childhood maltreatment are not entirely accounted for by psychiatric illness (Teicher et al., 2004; Frodl et al., 2012).

Given this body of research, it was hypothesised that a reduction in midsagittal corpus callosum area would be associated with neglect and abuse in the current sample. A measure of callosal midlength was included in an exploratory fashion.

5.6 Restatement of hypotheses

This chapter has reviewed the extant research on the neurobiological effects of childhood maltreatment, with particular emphasis on the putative effects of maltreatment on stress response systems. The alteration of these stress-response systems is presumed to affect the development and functioning (and therefore structural features) of the brain regions discussed above. This thesis tested for relationships between childhood experiences of neglect and abuse and the volumes of these brain regions, with the following hypotheses:

5.6.1 Hippocampus

Research reviewed suggested that the hippocampal reductions observed in adults exposed to childhood maltreatment are due to disruptions to the adolescent development of the hippocampus. Therefore, in the sample for this research, who underwent brain scans in early adolescence and therefore before this putative disruption would occur, no reduction in hippocampal volume was expected in association with childhood maltreatment.
5.6.2 Amygdala
An emerging body of work suggests that volume alterations associated with childhood trauma (in the context of adult psychopathology in the research studies reviewed) tend towards reduction and particularly in the left amygdala. Therefore it was hypothesised that childhood neglect and/or trauma would be associated with reduced amygdala volumes in this sample.

5.6.3 Anterior cingulate cortex
Based on the findings of van Harmelen and colleagues (2010) and Edmiston and colleagues (2011) in human samples, it was hypothesised that childhood maltreatment would be associated with reduced dorsal anterior cingulate volumes.

5.6.4 Orbitofrontal cortex
Based on Edmiston and colleagues’ (2011) research, it was tentatively hypothesised that childhood maltreatment would be associated with reduced orbitofrontal cortex volumes.

5.6.5 Corpus callosum
It was hypothesised that a reduction in midsagittal corpus callosum area would be associated with neglect and abuse in the current sample. A measure of callosal midlength was included in an exploratory fashion.

5.7 Mediation analysis
The evidence reviewed in the above chapters has shown that exposure to early stressful events appears to prompt alterations in the HPA axis (Heim et al., 2000; Heim et al., 2001; Coplan et al., 1996), and also increases vulnerability for depression. Extensive evidence was also discussed in Chapter 3 linking the development of depression with morphology and function of brain structures involved in or affected by the HPA axis. It is therefore possible that the increased vulnerability to stress-related psychiatric disorders observed in people exposed to early life stresses may be mediated by alterations in brain structures involved in or affected by functioning of the HPA axis (Heim & Nemeroff, 1999). To test for such relationships, mediation analyses was included in the research design, placing brain volumes in early adolescence as potential mediators of the relationship between childhood maltreatment and adolescent onset depression. The structures to be included in the mediation analysis for Research Question 4 were contingent on the relationships observed under each of the other three preceding Research Questions. Based on the a priori hypotheses put forward for relationships between maltreatment, neuroanatomical variables, and depression, the sites of particular interest for mediation analyses
were likely to be in the prefrontal cortical regions: the anterior cingulate cortex and the orbitofrontal cortex.
Chapter 6: Method

The following chapter begins with an overview of the design and method of this study. Detail on each method and measure discussed is provided in subsequent sections.

6.1 Design

The current research was undertaken as part of the Adolescent Development Study (ADS), a ten-year longitudinal study conducted by the Orygen Research Centre (ORC) in Melbourne, Australia in collaboration with the Melbourne Neuropsychiatry Centre (MNC). The design was a multi-method (questionnaire, interview and neuroimaging), prospective longitudinal investigation of childhood neglect and abuse, structural neuroanatomy, and adolescent onset depressive symptomatology. The study was prospective in that a group of young adolescents without significant depressive symptomatology were selected as participants. They undertook MRI scans prior to the development of any depressive symptoms, and were reassessed for depression 2-3 years later with the aim of identifying predictive relationships between premorbid structural neuroanatomy and the onset of depression. Childhood maltreatment was measured retrospectively, and relationships between maltreatment and structural neuroanatomy were also investigated.

This research drew on three waves of data collection from the larger ADS project: an initial screening assessment for the recruitment of participants; a first wave of intensive data collection (Time 1), and a second wave of data collection (Time 2), which was conducted 2-3 years after Time 1.

During the screening wave, participants were chosen from a larger sample of Victorian Grade 6 primary school students on the basis of a measure of affective temperament (the Early Adolescent Temperament Questionnaire – Revised; EATQ-R). During this wave, participants were administered structured diagnostic interviews in order to screen out those with pre-existing depressive, psychotic or substance-use disorders. At Time 1, participants (mean age = 12 years 10 months) undertook multiple assessments including a semi-structured clinical interview (the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version; KSADS-PL), a questionnaire assessing depressive symptomatology (the Centre for Epidemiological Studies – Depression questionnaire; CES-D), cognitive testing (including subscales from the Wechsler Intelligence Scale for Children – Fourth edition; WISC-IV) and structural neuroimaging (MRI). At Time 2, participants (mean age = 15 years) were re-administered the clinical interview (KSADS-PL) and depressive symptoms
questionnaire (CES-D), as well as a questionnaire retrospectively assessing lifetime experiences of familial neglect and abuse (the Childhood Trauma Questionnaire; CTQ). The variables of primary interest were those concerning childhood experiences of abuse or neglect, structural neuroanatomy measures at Time 1, and depressive symptomatology and diagnosis at Time 2.

6.2 Measures

6.2.1 Early Adolescent Temperament Questionnaire – Revised Adolescent Report

The EATQ-R (Ellis & Rothbart, 2001) is a revision of the 1992 instrument developed by Capaldi and Rothbart (1992), and is designed to assess temperament and self-regulation in adolescents aged 9-16 years. The adolescent report form of the questionnaire consists of 65 statements that respondents rate on a scale of 1 (“Almost always untrue of you”) to 5 (“Almost always true of you”).

Dimensions of temperament are assessed using 10 subscales (Activation Control, Affiliation, Attention, Fear, Frustration, Surgency, Inhibitory Control, Shyness, Pleasure Sensitivity, and Perceptual Sensitivity), which have been found to display adequate internal consistency, dimensionality and discriminant validity (Ellis & Rothbart, 2001). The revised questionnaire also contains two behavioural scales, Depressive Mood and Aggression, to allow examination of relationships between temperament and social-emotional functioning.

The 10 subscales have been found to load onto four higher order factors: Surgency (comprising Surgency, low levels of Fear, and low levels of Shyness), Negative Affectivity (comprising Frustration), Effortful Control (comprising Attention, Activation Control, and Inhibitory Control) and Affiliation (comprising Affiliation, Pleasure Sensitivity, and Perceptual Sensitivity) (Ellis & Rothbart, 2001; Putnam, Ellis & Rothbart, 2001).

6.2.2 Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version

The KSADS-PL is a semi-structured interview which provides a case-level diagnosis of depressive illness (including major depressive disorder, major depressive disorder atypical and melancholic types, adjustment disorder with depressed mood, dysthymic disorder, and major depressive disorder not otherwise specified) as well as other DSM-IV affective and psychotic disorders. The KSADS-PL has been validated with children and adolescents, and demonstrated very good inter-rater reliability and test-retest reliability, and consistency with other child diagnostic interviews (Kaufman et al., 1997a).
6.2.3 Centre for Epidemiological Studies – Depression questionnaire

The CES-D self-report questionnaire is a well validated instrument which measures total depressive symptomatology and includes four subscales: Wellbeing, Depressed Affect, Somatic and Interpersonal symptoms (Radloff, 1977). This measure was chosen due to its validation with adolescent populations (Radloff, 1991); reliability coefficients for American Junior High and High School students were .85 and .86 respectively. The measure has demonstrated moderate test-retest reliability (between .4 and .7 depending on the length of time between administrations). The CES-D also provides information on depressive symptoms that may not reach case level – this was important given that the second time point in this research was chosen as a time of high risk for emergence of depressive illness. Subsyndromal depressive symptoms, aside from conferring significant illness burden in themselves, are also highly predictive of progression towards case level depression and therefore it was considered important to include subsyndromal depression in outcome measurement (Judd et al., 1998).

The inclusion of four subscales allowed for investigation of differences in aetiology between different symptom types. Despite the overall organisation into one nosological category, depression is not a strongly homogeneous clinical syndrome. As with most psychiatric disorders, depression is diagnosed by the co-occurrence of a subset of potential symptoms and the symptom profile can vary considerably from person to person, implicating a potentially large number of complex and interacting causal factors (Kendler, Eaves, Neale, Heath & Kessler, 1996). The standard method of diagnosis has often proven itself inadequate for accurate prediction of response to existing psychosocial and psychopharmacological treatments (National Institute of Mental Health, 2003).

There have been many investigations into neurobiological markers of psychiatric disorders, including depression, however this pursuit has been more successful in finding markers for individual symptoms rather than disorders characterized by complex patterns of symptoms (Hahn et al., 2011). It is unlikely that deficits in particular neurobiological processes will map precisely onto descriptive psychiatric diagnostic categories reliant upon clinical description and the naming of behavioural signs and symptoms. Therefore it is important to experiment with multiple measures and characterisations of depression in any research into the area.

Variability in clinical presentation, course and outcome of depressive illness poses a major challenge to researchers attempting to understand and treat the disorder, but also suggests an opportunity in characterising causal factors and effective treatments for individuals based on symptom profiles within the broader diagnosis.
6.2.4 Childhood Trauma Questionnaire

The sample for this research was not selected with risk for, or indications of, childhood maltreatment in mind. It was expected that relatively low levels of severe, documented maltreatment would be present in the sample (i.e., maltreatment warranting protective intervention), therefore a self-report, dimensional measure of childhood maltreatment was chosen in order to capture more subtle gradations of the childhood familial environment.

The CTQ retrospectively measures lifetime experiences of familial neglect and abuse (Bernstein, 1995) and has been validated for use with adolescents (Bernstein, Ahluvalia, Pogge & Handelsman, 1997), exhibiting high internal consistency, and strong convergent and discriminant validity when compared with clinician ratings based on interview. The CTQ asks respondents how true a range of statements is of their childhood familial environment. The instrument is divided into Physical Neglect (e.g., “I didn't have enough to eat”), Emotional Neglect (e.g., “People in my family felt close to each other”), Physical Abuse (e.g., “People in my family hit me so hard that it left me with bruises or marks”), Emotional Abuse (e.g., “I felt that someone in my family hated me”) as well as Sexual Abuse, and Minimization/Denial (neither of which were used in the current thesis).

6.2.5 Wechsler Intelligence Scale for Children – Fourth Edition

Intelligence was not intended to be a variable of central importance in the current research, but the estimate of full scale intelligence quotient (FSIQ) gained from these four subtests was included in preliminary analyses as a potential covariate.

There has been some evidence to suggest that lower childhood FSIQ is associated with greater risk for adult psychopathology (Batty, Mortensen & Osler, 2005; Koenen et al., 2009), and may be related to individuals’ abilities to cope adaptively with trauma (Koenen, Moffit, Poulton, Martin & Caspi, 2007; Saigh, Yasik, Oberfield, Halamandaris & Bremner, 2006). There is also evidence that FSIQ has relationships with grey matter volume in diffuse cortical areas (Karama et al., 2009; Haier, Jung, Yeo, Head & Alkire, 2005). For this reason, estimates of FSIQ were analysed to check for relationships with the measures of interest in the current study.

The WISC-IV is an extensively standardised and validated instrument for assessing cognitive ability of children between the ages of 6 years through to 16 years 11 months via individual administration (Wechsler, 2003).

The WISC-IV is composed of 10 core and 5 supplemental subtests, which contribute to indices of Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed, as
well as a measure of FSIQ. Four subtests, one from each index, were chosen to comprise a short form of the WISC-IV. The individual subtests (which were selected based on the aims of research not presented here) were Vocabulary, Matrix Reasoning, Letter-Number Sequencing and Symbol Search. These subtests represent a range of cognitive capacities and have obtained reliability coefficients ranging from .79 to .90 (Williams, Weiss & Rolfus, 2003).

6.2.6 Edinburgh Handedness Inventory

Handedness was measured in order to account for possible relationships between handedness and lateralised neuroanatomical features (e.g., Geschwind, Miller, DeCarli & Carmelli, 2002). The Edinburgh Handedness Inventory (EHI; Oldfield, 1971) is a self-report questionnaire which assesses direction and strength of hand laterality. Participants indicate their preferred hand, and the strength of the preference, for a series of ten physical tasks such as writing, throwing, or striking a match. No preference for a task is allocated 0 points, while 1 point is allocated for some preference and 2 points for a strong preference. The sum of scores for each hand is calculated and the left score is subtracted from the right, leaving a figure which by its position on one side of the median score indicates direction of hand laterality, and by its size indicates the strength of the hand preference.

6.2.7 Parent education

The relationships between SES and both childhood maltreatment and depression were reviewed in the introductory chapters. For example, Sentse, Veenstra, Lindenberg, Verhulst, and Ormel (2009) found that SES mediated the risk conferred by childhood temperament for adolescent internalising and externalising psychopathology. In the current research, parent education was used as a proxy variable for SES. SES is generally estimated based on one or a combination of occupational position, education, and income (Oakes & Rossi, 2003). The Report of the APA Taskforce on Socioeconomic Status stated that, “Education is perhaps the most fundamental aspect of SES” (American Psychological Association, 2007, p. 9). Higher levels of education are associated with better economic outcomes, greater social and psychological resources, and fewer health risk behaviours (Ross & Wu, 1995). Backlund, Sorlie and Johnson (1999) found that the positive effects of education did not increase in a linear relationship with the number of years of education. Rather, benefits were discontinuous, with increase in positive outcomes associated with gaining educational milestones usually involving the conferring of a qualification or degree. For these reasons, parent education was chosen as an indicator of SES, and was characterised categorically as attainment on a scale of qualifications or degrees.
6.3 Structural magnetic resonance imaging

Structural MRI provides static anatomical information about soft tissue in the body (as compared with functional MRI, which provides dynamic physiological information).

A magnetic resonance scanner uses a magnetic field to align the magnetization of hydrogen protons in the body with the direction of the field. Radio frequency fields are then introduced to produce varying electromagnetic fields, which flip the spin of the protons in the static magnetic field. The frequency required for this effect is known as the resonance frequency. Once the radio frequency field ceases, the magnetization of the protons relaxes back into alignment with the initial, static magnetic field. Systemically altering the alignment of magnetization in this way produces a radio frequency signal that is detected by receiver coils in the scanner and used to construct the image. The relaxation rates of protons in different tissues vary, allowing for the differentiation of different tissue types in structural MRI (Hendee & Morgan, 1984).

The location of protons in 3D space is detected by generating electric currents through gradient coils, causing the strength of the magnetic field to vary at different positions relative to the magnet. Thus the frequency of the radio signal released also varies depending on the location of its original. The inverse of the Fourier transform is then used to mathematically determine the location of the source of the signal.

In recent years, progress has been made allowing higher image quality in MRI. Image quality is largely determined by spatial resolution and signal to noise ratio. Spatial resolution depends on the number of pixels (image components) in the frequency and phase encoding directions within image slices, and by slice thickness. Pixel size and slice thickness also determine signal to noise ratio, along with the scan time (including number of phase encoding steps) and the sequence used. The ability to distinguish between different tissues is based on the use of different pulse sequences. The most frequently used sequences for research and clinical applications are T1 and T2 weighted scans (Edelman & Warach, 1993).

T1-weighted three dimensional high resolution structural MRI is the gold standard for in vivo research into the volume and morphometry of brain structures, and was used in this thesis. These scans use differences in the relaxation time of protons within different tissues, allowing, for example, the depiction of contrast between grey and white matter in the brain (Hendee & Morgan, 1984; Symms, Jager, Schmierer & Yousry, 2004). All magnetic resonance imaging scans were performed on the same General Electric 3 Tesla scanner, using a gradient echo volumetric acquisition sequence (repetition time = 36 milliseconds; echo time = 9 milliseconds; flip angle =
35°, field of view = 20 cm², pixel matrix = 410 x 410) to obtain 124 T1-weighted contiguous 2mm thick slices (voxel dimensions = 0.4883 x 0.4883 x 2mm). More detail on image acquisition and preprocessing is contained in Section 6.5.5.

6.3.1 Image analysis
T1-weighted images can be used to gather information about the size and shape of individual brain structures. The gold standard for measuring anatomical volume in predefined structures of interest is manual delineation of regions of interest. This involves tracing each structure by hand on contiguous 2D slices of the image, then summing the voxels (image elements) from all 2D slices to yield an estimate of total volume. An alternative method is voxel-based morphometry (VBM). This is an automated method that requires that each image is spatially normalised to a standardised brain template in order to remove gross differences in brain shape between individuals. VBM also requires that voxels are smoothed, meaning that each voxel represents the average partial volume of grey matter of itself and adjacent voxels. This has the effect of more normally distributing data and increasing the validity of subsequent parametric statistical tests. Images are then compared voxel-by-voxel to detect differences in tissue characteristics such as density and volume. Some advantages of VBM are that it is fast, does not require hypothesis-based selection of areas of interest, and can highlight very localised differences in tissue density (Ashburner & Friston, 2000). However, disadvantages of VBM include variability in measures introduced by differences in work-station type and operating system version (Gronenschild et al., 2012), possible confounds between registration and neuroanatomical variability in cortical thickness and structural volumes (Bookstein, 2001), and variability in subcortical measurements depending on software version (Dewey et al., 2010) and lack of sensitivity to group differences in subcortical measurements (Bergouignan et al., 2009).

Comparisons of VBM and manual delineation have found that while the two methods may complement one another, neither is an adequate replacement for the other (Giuliani, Calhoun, Pearlson, Francis & Buchanan, 2005; Wilke, de Haan, Juenger & Karnath, 2011). Each retains distinct characteristics that require a considered choice of the most appropriate methods given the requirements of the research in question.

Manual delineation of regions of interest was chosen as the most appropriate method of image analysis for this research¹. This was because there were a number of structures for which

¹ With the exception of the corpus callosum area and length
established manual delineation protocols existed, that were theorised *a priori* to be implicated in the development of adolescent depression. Although VBM allows for a more exploratory investigation into structural neuroanatomy, it requires normalization of images into standard stereotaxic space. Given the assumption driving this research, that early experiences may have observable effects on the structure of the maturing brain, and the inter-individual variability in timing and pattern of adolescent brain changes, the importance of maintaining the images in their native space was considered paramount. There may be some trade-off between reliability and validity in the choice between VBM and manual delineation – for the purposes of this research, the emphasis was on validity. The disadvantages of manual delineation are that it is time and labour-intensive, and that it allows for intra- and inter-rater differences in tracing, and may be less reproducible due to differences in the method of delineating structures. Subcortical structures tend to be difficult to delineate due to issues with image quality, including less clear differentiation between tissue types than in the cerebral cortex, and movement artefact caused by the large volume of blood flow through arteries crossing subcortical areas. Image quality tends to be better in neocortical regions, however differentiation between neocortical areas is less easily agreed upon due to the lack of clearly distinguishable structures, leading to inconsistencies between studies based on the use of functional imaging findings, sulcal and gyral landmarks, cytoarchitectonic features or semi-arbitrary geometric boundaries for various delineation protocols. These issues were dealt with the current research by rigorous training of raters, conducting inter- and intra-rater reliability analysis on tracings of each region of interest, using pre-defined, well validated manual delineation protocols where available, and documenting protocols in detail, for future replication. However, certain areas implicated in the literature (for example, the nucleus accumbens and dorsolateral prefrontal cortex) could not be delineated manually, and may be suitable for analysis using VBM in future research. The following sections describe the delineation protocols used for each region of interest in the current research.

**6.3.2 Whole brain volume**

It is well established that individual structure volumes vary in size as a function of total brain volume, which is itself influenced by body size, gender, and age (O'Brien et al., 2006). Therefore in order to meaningfully compare structure sizes across groups that vary in total brain volume (such as males and females), structure volumes need to be corrected for whole brain volume.

The most commonly used measures of head size are whole brain volume and intracranial volume, and for younger, non-pathological samples, either is considered valid (O'Brien et al., 2006). In the current research, the stripped and registered images were segmented into grey
matter, white matter and cerebrospinal fluid using FAST (FMRIB’s Automated Segmentation Tool; Zhang, Brady & Smith, 2001) and grey and white matter counts were summed to yield the whole brain volume, against which all region of interest measures were corrected.

6.3.3 Amygdala

The amygdala is composed of multiple nuclei and is collocated with the hippocampal formation in the dorsomedial portion of the temporal lobe (LeDoux, 2007). These structures tend to share similar signal intensities in T1-weighted MRI images, making it difficult to distinguish the boundaries between amygdalar and hippocampal structures.

Considerable variability in estimates of amygdala volume have been noted between various MRI studies, as well as between MRI estimates of volume and post-mortem studies, with the latter generally finding smaller volumes. Brierley, Shaw and David (2002) noted in their review of 39 studies using manual delineation of the amygdala on T1 weighted MRI images that estimates of amygdala volume ranged from 1050 to 3880mm$^3$. They concluded that the size of this range was only partially due to age, gender and individual differences, and was heavily influenced by differences in delineation protocols. The main differences were due to difficulties in the definition of the anterior emergence of the amygdala, and the ventral boundary between the amygdala and hippocampus posteriorly. After consideration of all documented delineation methods, Brierley and colleagues recommended a method based closely on Watson and colleagues’ (1992) protocol, which was used in a third of the studies reviewed.

The guidelines and boundaries used to trace the amygdala for this research were likewise based on those of Watson and colleagues (1992). The amygdala was traced on coronal slices, beginning at the posterior end. The posterior boundary consisted of the first appearance of the amygdala superior to the temporal horn. The superior lateral boundary was marked by the thin strip of white matter separating the amygdala from the claustrum and tail of the caudate, and the inferior lateral boundary by the temporal lobe white matter and extension of the temporal horn.

The superior medial border was defined by the semilunar gyrus, and the inferior medial border by the subamygdaloid white matter which separates the amygdala from the entorhinal cortex. The anterior boundary was defined by the most posterior of either the joining of the optic chiasm or the point where the lateral sulcus closes to form the entorhinal sulcus. At the posterior end of the amygdala, the boundary from the hippocampus was marked by the uncul recess of the temporal horn, or if this was not visible, the alveus and semilunar gyrus were used as markers.
Figure 6 shows examples of posterior and anterior amygdala boundaries, as well as delineation between the amygdala and hippocampus.

Figure 6. Representative tracings of the left (yellow) and right (blue) amygdala at the anterior (a) and posterior boundaries (c), as well as differentiation between amygdala and hippocampus (left: red, right: green).
6.3.4 Hippocampus

In a review of 423 records yielding 115 original protocols, Gueze, Vermetten and Bremner (2005) concluded that the largest contributor to differences in hippocampal volumetric measurements stemmed from inter-rater variability. They also noted the considerable variation between anatomical guidelines for delineation, particularly around the inclusion or exclusion of the alveus, subiculum, and uncal cleft.

The guidelines followed in the current research were adapted from Cook, Fish, Shorvon, Straughan and Stevens (1992), cited in the Gueze and colleagues review (2005) as one of the more commonly replicated protocols. The delineation used in this research includes the hippocampus proper, the dentate gyrus, the subiculum, and parts of the fimbria and alveus. The posterior boundary was defined as the section with the greatest length of continuous fornix. Laterally, the hippocampus was bounded by the temporal horn of the lateral ventricle. The posterior medial boundary was the open end of the hippocampal fissure, and the uncal fissure and medial aspect of the ambient gyrus bounded the anterior medial hippocampus. Anterior differentiation of the hippocampus followed the method described in the amygdala tracing protocol, and the inferior boundary was marked by white matter. The anterior boundary of the hippocampus was determined based on the movement of the temporal horn from the lateral position to a medial, inferior position. Representative tracings of the hippocampus at its anterior and posterior ends are seen in Figure 7.
6.3.5 Anterior cingulate cortex

The anterior cingulate is most simply described as comprising Brodmann Area (BA) 24, however cytoarchitectonic inhomogeneities within BA24 have lead some to specify anatomical subdivisions of area 24a, extending from the callosal sulcus to the surface of the cingulate gyrus, adjacent to 24b on the gyral crown, 24c, on the ventral bank of the cingulate sulcus, and 24’ as the area caudal to the genu and dorsal to the corpus callosum. Running parallel to areas 24 and
24’ on the rostral-caudal axis are areas 32 and 32’. Based on differential connectivity patterns (as observed in non-human primates), areas 24c and 32, as well as 24c’ and 32’, have been termed the paracingulate cortex (see Fornito, Whittle, Wood, Velakoulis, Pantelis and Yücel, 2006, for a review).

The ACC is often subdivided into dorsal (comprising BA24’ and 32’), rostral (BA24 and 32) and ventral (subgenual areas of BA24 and 32) subsections based on functional and cytoarchitectonic heterogeneities. The other major structural division that can be observed in the ACC is between the cingulate proper, lying directly adjacent to the corpus callosum, and the paracingulate region which lies parallel to the cingulate (Yücel et al., 2003). Considerable inter-individual variability in the sulcal and gyral anatomy of this region has further bearing on any attempts to delineate cingulate and paracingulate anatomical subsections – most prominently, the presence or absence of the paracingulate sulcus. This is a sulcus running dorsal and parallel to the cingulate sulcus, which is present in 30-60% of cases, and more frequently in the left hemisphere. When the paracingulate sulcus is present, this is associated with expansion of the paracingulate cortex that extends over the crown of the paracingulate gyrus, and an associated decrease in the size of the cingulate cortex. In the absence of the paracingulate sulcus, the paracingulate cortex is buried in the dorsal bank of the cingulate sulcus (B. A. Vogt et al., 1995; Yücel et al., 2001; Paus et al., 1996b). Relationships between patterns of cortical folding in the anterior cingulate have been found for psychopathologies such as schizophrenia (Rametti et al., 2010; Clark et al., 2010), and OCD (Shim et al., 2009).

Based on the above considerations, Fornito and colleagues (2006) designed a delineation protocol for the anterior cingulate cortex that provides dorsal, rostral and ventral divisions, each further subdivided into a cingulate and paracingulate section. This protocol was used in the current research, and representative tracings of each section, in cases with and without a prominent paracingulate sulcus, are shown in Figure 8.

The posterior border of the ACC was defined as the first coronal slice posterior to the anterior commissure. The boundary between the dorsal and rostral sections was defined by the first slice in which the corpus callosum was seen to connect the two hemispheres. This also provided the boundary between the rostral and ventral sections, inferior to the genu. The posterior boundary of the ventral section was determined by the appearance of the internal capsule separating the caudate nucleus from the putamen. After boundaries were defined using coronal slices, the tracing was performed on sagittal slices, beginning medially and moving laterally. Coronal views were then used to edit medial borders.
This tracing method is relatively intricate and is described in detail by Fornito and colleagues (2006). In brief, where applicable, the anterior cingulate was bounded by the callosal and cingulate sulci. In cases where the cingulate sulcus was not present in ventral ACC regions, only the grey matter on the outer bank of the callosal sulcus was included. If the paracingulate sulcus was found to be present (running parallel to the cingulate sulcus for ≥20mm or three contiguous sagittal slices) it formed the outer border of the paracingulate regions. In cases where the paracingulate sulcus was absent, only the grey matter from the outer bank of the cingulate sulcus was included in sections where the paracingulate sulcus was absent. If the paracingulate sulcus was absent but the cingulate sulcus had overlapping segments greater than 20mm, the section of overlap was traced as paracingulate, serving as the outer border of the region.

In the rostral and ventral portions of the ACC, there is some variability in the relationship between the cingulate sulcus and the superior rostral sulcus (Ono, Kubik & Abernathey, 1990). A minority of cases show continuity between the cingulate sulcus and the superior rostral sulcus. Where this was the case, the inferior paracingulate regions included only the grey matter on the outer bank of the cingulate sulcus. Where the cingulate and rostral sulci were separate, the ventral paracingulate region was classified as the area lying between the cingulate and superior rostral sulci.
Figure 8. Representative tracings of dorsal paracingulate (cyan), dorsal cingulated (blue), rostral paracingulate (green), rostral cingulate (red), ventral paracingulate (yellow) and ventral cingulated (pink) regions in cases with (a) and without (b) a paracingulate sulcus.
6.3.6 Orbitofrontal cortex

The orbitofrontal cortex is a structurally and functionally heterogeneous area, comprised of the inferior-most aspect of the prefrontal cortex. Ongür, Ferry and Price demonstrated the cytoarchitectonic diversity contained within the human orbitofrontal cortex in their 2003 post-mortem study. While there are some relatively consistent sulcal and gyral patterns observable across individuals, there is also considerable variability in even major sulcal and gyral landmarks (Ono et al., 1990). Tracing protocols whose boundaries are determined by sulcal and gyral patterns have been used (e.g., Crespo-Facorro et al., 1999), however the inhomogeneity of these landmarks is a potentially significant challenge to reliability. While the inferior and lateral boundaries of the orbitofrontal cortex are relatively easy to delineate, the superior and posterior boundaries are not easily defined by any aspect of orbitofrontal morphometry. For these reasons, and in the interest of preserving adequate reliability, many researchers have preferred geometric methods for delineating the more problematic boundaries of the orbitofrontal cortex (e.g., R. E. Gur et al., 2000; Riffkin et al., 2005). The protocol used in the current research uses a combination of sulcal and geometric boundaries, and is based on the protocol of Riffkin and colleagues, (2005), with the addition of a medial-lateral division. The superior boundary was marked as the horizontal plane aligned with the anterior and posterior commissures and the poster boundary by the coronal plane showing the most posterior aspect of the olfactory sulcus. Lateral and inferior boundaries were provided by the boundaries between cortex and non-brain tissue and the boundary between lateral and medial regions was determined by the olfactory sulcus (see Figure 9 and Figure 10).
Figure 9. Representative tracing of the left medial (cyan) and lateral (yellow) and right medial (pink) and lateral (blue) orbitofrontal cortices (reproduced from Cheetham, Allen, Whittle, Simmons, Yücel & Lubman, 2012).
Figure 10. Sagittal view of lateral orbitofrontal cortex tracing (reproduced from Cheetham et al., 2012).

6.3.7 Corpus callosum

Recent research by Walterfang and colleagues has examined volumetric and morphometric aspects of the corpus callosum in relation to bipolar disorder (Walterfang et al., 2009b), borderline personality disorder (Walterfang et al., 2010) and depression (Walterfang et al., 2009c). Walterfang and colleagues’ automated method of delineation and measurement of corpus callosum area and length was used in the current research and is detailed below.

6.3.7.1 Area

All measures were drawn from the midsagittal slice, which was identified as showing minimal white matter in the cortical mantle adjacent to the callosum, the interthalamic adhesion (or minimum medial thalamic tissue), and transparent septum pellucidum and patent cerebral aqueduct (Talairach & Tournoux, 1993). This slice was interpolated to a voxel dimension of 0.5mm x 0.5mm in the y and z planes. White matter voxels were identified using a histogram segmentation procedure (Otsu, 1979) and non-callosal voxels were manually removed. Based on the size of this midsagittal cross-section, a measure of callosal area in mm² was calculated. Note that unlike the other region of interest volumes in this research, this is a two-dimensional measure.
6.3.7.2 Length

Voxels composing the edges of the corpus callosum were identified and ventral and dorsal edges were defined in relation to rostral and caudal endpoints. The upper and lower edges were divided into 39 equidistant nodes, and a line segment was generated which connected rostral and caudal endpoints, following the midpoints between the corresponding nodes on the upper and lower edges. Rostral and caudal endpoints were calculated using an iterative search for endpoint locations that maximised the length of the line segment connecting them. Finally, a smooth curve connecting these endpoints was obtained with cubic spline interpolation, and the length of this curve formed the measure of callosal length. Representations of this method for determining callosal length and area are depicted in Figure 11.

Figure 11. a) Midslice corpus callosum image; b) Callosal area; c) Callosal midlength, measured via midspline connecting endpoints and traversing midpoints of dorsal-ventral line segments. Reproduced from Walterfang and colleagues (2009a).
Procedure

6.4 Recruitment
Recruitment was conducted in three stages; target population selection, screening for affective temperament, and recruitment for intensive assessment.

6.4.1 Target population selection
The target population consisted of final year Primary School students aged 10-12 years from generalist primary schools in metropolitan Melbourne, Australia, as defined by the Victorian Department of Education. The schools were stratified to reflect each sector’s contribution to total school enrolments:

- Government Schools 65%
- Catholic Schools 22.5%
- Independent Private Schools 12.5%

One hundred and seventy-five schools (4,587 students) were selected at random, with a probability proportional to the number of students enrolled in each school, via a one-stage cluster sampling procedure. Of the 175 schools approached, 97 (56%) chose to participate in the study. Grade 6 students from participating schools were provided with information on the study, and written consent was obtained from parents, as well as verbal consent from students.

6.4.2 Screening for affective temperament
As discussed in Chapter 1, certain dimensions of temperament are thought to predispose children to developing depression as adolescents or adults. In order select a sample of children within which enough would develop depression to enable analysis, temperament in late childhood was measured and children at extreme ends of the measured dimensions were oversampled in order to create a risk-enriched sample. A total of 2,453 students (53.5% of the total sampling population) participated in the temperament screening assessment. The mean age was 11 years 7 months (SD = 5 months) and 52% of screening participants were female. The proportion of students participating from Government (70%), Catholic (21%) and Independent Private Schools (9%) was comparable to enrolment in the target population ($\chi^2(2) = 0.81, \ p = .67$).

The screening sample participated in classroom administration of the EATQ-R. As discussed above, the EATQ-R is specifically designed to assess trait affective temperaments in early
adolescents. Confirmatory factor analysis was used to derive ten lower order factors, corresponding largely to the a priori scales specified by Ellis and Rothbart (2001), with the exclusion the behavioural scales, and five poorly performing items. Internal consistency figures are given for the ten derived subscales in Table 1a below. Consistent with previous research, four higher order factors of Surgency, Negative Affectivity, Effortful Control, and Affiliativeness were also derived, and details of their internal consistency and component subscales are provided in Table 1b below.

Table 1

Internal consistencies for lower (a) and higher order (b) EATQ-R factors derived from screening sample (n=2453)

a)

<table>
<thead>
<tr>
<th>EATQ-R Subscale</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation Control</td>
<td>.70</td>
</tr>
<tr>
<td>Affiliation</td>
<td>.66</td>
</tr>
<tr>
<td>Attention</td>
<td>.77</td>
</tr>
<tr>
<td>Fear</td>
<td>.80</td>
</tr>
<tr>
<td>Frustration</td>
<td>.82</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>.54</td>
</tr>
<tr>
<td>Pleasure Sensitivity</td>
<td>.75</td>
</tr>
<tr>
<td>Perceptual Sensitivity</td>
<td>.64</td>
</tr>
<tr>
<td>Shyness</td>
<td>.75</td>
</tr>
<tr>
<td>Surgency</td>
<td>.64</td>
</tr>
</tbody>
</table>

b)

<table>
<thead>
<tr>
<th>Higher Order Factor</th>
<th>EATQ-R Subscales</th>
<th>Cronbach’s alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgency</td>
<td>Fear</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>Shyness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgency</td>
<td></td>
</tr>
<tr>
<td>Negative Affectivity</td>
<td>Frustration</td>
<td>.82</td>
</tr>
<tr>
<td>Affiliativeness</td>
<td>Affiliation</td>
<td>.77</td>
</tr>
<tr>
<td></td>
<td>Pleasure sensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perceptual sensitivity</td>
<td></td>
</tr>
<tr>
<td>Effortful Control</td>
<td>Activation Control</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>Attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitory Control</td>
<td></td>
</tr>
</tbody>
</table>
6.4.3 Final sample selection

From the temperament screening sample, a subsample of 425 was constructed to over-represent adolescents at the extreme ends of temperament. Equal numbers of students were selected with scores falling 0-1, 1-2, 2-2.5 and greater than 2.5 standard deviations from the mean on the four higher order temperament factors, with particular emphasis on Negative Affectivity and Effortful Control, both of which have been found to be associated with depressed mood in adolescents (Ellis & Rothbart, 2001). Of the selected 425, 245 (50.60% female) agreed to participate in the Time 1 intensive assessment phase. Of the 245 adolescents who participated in the Time 1 Home Assessment, 153 (82 male) completed the MRI scan. The scans from two further participants were unusable due to artefact caused by orthodontic braces. There were no differences in gender or EATQ-R scores between those participants who did and did not participate in MRI scanning. However, an independent samples t test revealed that those who agreed to undertake MRI scans had higher mean CES-D Depressed Affect scores than those who did not (see Table 2). As the sample was constructed to include more individuals at risk of developing depression in the future, and as none of the individuals included in the sample were diagnosed with case-level depression at Time 1, the heightened level of subsyndromal depressive symptomatology is not likely to adversely affect the design of the study and in fact may have enhanced the risk-enrichment of the sample.

Table 2

Independent samples t-test comparing CES-D scale scores between participants who did and did not opt in for MRI scanning

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>MRI M</th>
<th>SD</th>
<th>No MRI M</th>
<th>SD</th>
<th>Mean Diff.</th>
<th>SE</th>
<th>T</th>
<th>Df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wellbeing</td>
<td>7.0769</td>
<td>2.552</td>
<td>6.837</td>
<td>2.745</td>
<td>-.240</td>
<td>.361</td>
<td>-.664</td>
<td>225</td>
<td>.507</td>
</tr>
<tr>
<td>Somatic</td>
<td>11.964</td>
<td>3.724</td>
<td>11.605</td>
<td>3.590</td>
<td>-.359</td>
<td>.505</td>
<td>-.710</td>
<td>225</td>
<td>.478</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>3.110</td>
<td>1.623</td>
<td>2.800</td>
<td>1.395</td>
<td>-.314</td>
<td>.204</td>
<td>-1.541</td>
<td>195.308</td>
<td>.125</td>
</tr>
</tbody>
</table>
Of the 153 participants who completed MRI scanning, 137 also participated in the Time 2 home assessment. There were no differences in gender, CES-D or EATQ-R scores between those participants who did and did not participate in the Time 2 assessment.

All further data analysis refers to the final sample of 137 participants (74 male, mean age at scan of 12 years 10 months, $SD = 5$ months) who completed Time 1 Home Assessment, MRI scanning and Time 2 Home Assessment (mean age = 15 years, $SD = 6$ months). Figure 12 gives a summary of the sampling frame.

![Sampling frame for temperament screening, Time 1 and Time 2 assessments.](image)

**Figure 12.** Sampling frame for temperament screening, Time 1 and Time 2 assessments.

### 6.5 Procedure

#### 6.5.1 Temperament screening

Primary schools selected within the sampling frame were approached to participate by letter and telephone. Study information was provided by letter to parents of children enrolled in participating schools, explicit consent was sought from a parent or guardian, and assent was gained from each student. The EATQ-R was then administered onsite by ORC staff and
teachers in primary school class groups of approximately 18-25. Participants who were not able to complete the assessment in school were sent questionnaires by mail. In order to preserve confidentiality, each participant was assigned an identification number which was used thereafter to identify their questionnaire responses.

6.5.2 Time 1 home assessment
As described earlier, a subgroup of potential participants were selected for invitation to the intensive assessment phase based on their EATQ-R responses. The families of these individuals were contacted by phone and invited to participate in a meeting to learn more about the project. Meetings took place in the participants’ homes – for those that agreed to participate, the initial interview with the adolescent was conducted at the same time. After obtaining consent from a guardian and assent from the adolescent, the KSADS-PL was administered, as well as a repeat administration of the EATQ-R and a range of other measures not included within the current research.

6.5.3 Time 1 MRI and cognitive assessment
Those participants who met inclusion criteria after assessment with the KSADS-PL were invited to participate in a range of assessments, including the neuroimaging and cognitive testing assessment. Families who expressed interest in the neuroimaging assessment were sent a video or DVD that explained the basic concepts of MRI and depicted an adolescent preparing for and participating in a scan. Scanning was conducted at the Brain Research Institute (BRI), Austin Hospital, Heidelberg, Victoria, Australia. Upon arrival at BRI, participants were invited to explore a child-friendly ‘mock’ scanner. The mock scanner replicated many of the conditions of MRI scanning, including an accurate representation of the enclosed space, and the sounds made during scanning. Adolescents were asked to lie in the mock scanner for at least five minutes, after which they decided whether they wished to continue to the real scan.

Explanation of the MRI scanning procedure and any risks involved was then given to adolescents and their accompanying parent or guardian before consent and assent were attained. Participants completed a checklist to eliminate any medical issues that would exclude them from undertaking the MRI, and the radiographer on staff ensured all safety conditions were met before proceeding with the scan, which took approximately 20 minutes. Participants were provided with a panic button to hold in case they wished to end the scan early, and were able to watch and listen to a video during the scan. After completing the scan, participants were given a debriefing document and were able to ask questions about the study or procedure. After images were processed, sample images from their scan and a certificate of appreciation were sent to each
participant. On the same day at BRI, participants were administered a range of cognitive assessments, including selected subscales from the WISC-IV.

All scans were screened for clinical abnormalities by BRI staff. Twelve participants’ scans were reported to a neurologist at the Royal Children’s Hospital, Melbourne, for further review, and referrals were made as necessary. All of these participants’ data were included in analyses; the referrals were found to be minor individual variations in brain structure, which were not clinically significant.

6.5.4 Time 2 home assessment

Home assessments for Time 2 were undertaken approximately two years after the Time 1 Home Assessment. In the intervening years, participants were contacted intermittently with birthday cards, news and updates about the ADS project. Families were contacted by phone with invitations to participate in the second wave of home assessment. For those who consented, ORC staff attended their homes and administered the K-SADS-PL and CTQ to adolescents, as well as a range of other measures not relevant to the current project. Recordings of 25% of all K-SADS-PL interviews undertaken at Time 2 were rated by a second coder. The kappa coefficient for diagnosis-level agreement was 0.84, suggesting acceptably high inter-rater reliability. Information and materials provided to participants during the screening, home assessments and MRI assessment are attached as Appendix 1.

6.5.5 Magnetic resonance imaging: Acquisition, preprocessing and region of interest delineation

6.5.5.1 Image acquisition

All magnetic resonance imaging scans were performed at BRI on the same General Electric 3 Tesla scanner, using a gradient echo volumetric acquisition sequence (repetition time = 36 milliseconds; echo time = 9 milliseconds; flip angle = 35°, field of view = 20 cm², pixel matrix = 410 x 410) to obtain 124 T1-weighted contiguous 2mm thick slices (voxel dimensions = 0.4883 x 0.4883 x 2mm).

6.5.5.2 Image preprocessing

Images were transferred to an SGI/Linux workstation for morphometric analysis. Visual inspection for gross artifacts, inhomogeneity and movement related artifact confirmed that all images were of adequate quality for analysis. Image preprocessing was conducted using tools from the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (http://www.fmrib.ox.ac.uk/fsl). Each three-dimensional scan was stripped of all nonbrain tissue first using BET (Brain Extraction Tool; Smith, 2002), and then checked and if required,
adjusted manually. Images were then resampled to 1mm³, and registered to the Montreal Neurological Institute 152 average template (six-parameter rigid body transform with trilinear interpolation) using FLIRT (FMRIB's Image Registration Tool; Jenkinson & Smith, 2001). This served to align each image axially along the anterior commissure-posterior commissure plane and sagittally along the interhemispheric fissure without any deformation. Images were inspected for visual quality – while some Gibbs ringing or flow artefacts were observed, only in two cases were images unusable due to artefact (due to orthodontic braces).

6.5.5.3 Morphometric analysis
Regions of interest were traced using the software package ANALYZE (Mayo Clinic, Rochester, MN; http://www.mayo.edu/bir). Brain tissue was segmented into gray matter, white matter, and cerebrospinal fluid using an automated algorithm, as implemented in FAST. Whole brain volume was estimated by summing gray and white matter pixel counts. ACC and orbitofrontal cortex estimates were based on gray matter pixel counts contained within the defined regions of interest. Corpus callosum, amygdala and hippocampal estimates were based on total voxels within the defined regions of interest.

6.5.5.4 Region of interest tracing reliabilities
Inter- and intra-rater reliability coefficients were calculated and found to be acceptable for left and right tracings of all regions of interest, and are given in Table 3.

Table 3

| Intra- and inter-rater reliabilities for manual tracings of neuroanatomical regions of interest |
|-----------------------------------------------------|-----------------|-----------------|-----------------|
| Hippocampus                                         | .95             | .98             | .91             | .92             |
| Amygdala                                            | .97             | .93             | .88             | .85             |
| Orbitofrontal Cortex Total                          | .95             | .96             | .90             | .92             |
| Orbitofrontal Cortex Medial                         | .77             | .78             | .76             | .77             |
| Orbitofrontal Cortex Lateral                        | .95             | .95             | .98             | .98             |
| Rostral Anterior Cingulate                          | .99             | .99             | .97             | .99             |
| Rostral Anterior Paracingulate                      | .82             | .89             | .94             | .95             |
| Dorsal Anterior Cingulate                           | .98             | .91             | .95             | .83             |
| Dorsal Anterior Paracingulate                       | .97             | .95             | .94             | .91             |
| Ventral Anterior Cingulate                          | .97             | .94             | .96             | .98             |
| Ventral Anterior Paracingulate                      | .90             | .91             | .82             | .91             |

Values are intraclass correlation coefficients based on absolute agreement.
The corpus callosum was delineated with an automated method, therefore no reliabilities were calculated.
6.6 Summary of research structure and measures

Table 4 below provides a summary of the structure of the current research and methods and measures employed at each of the three data collection stages. Description of the four Research Questions linking the constructs measured, and methods of analysing the putative relationships between them is presented in Chapter 7.

Table 4

Summary of research methods and measures

<table>
<thead>
<tr>
<th>Time point</th>
<th>Construct</th>
<th>Method</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Affective temperament</td>
<td>Adolescent self-report questionnaire</td>
<td>EATQ-R</td>
</tr>
<tr>
<td></td>
<td>Pre-existing depression, psychosis, substance abuse</td>
<td>Adolescent diagnostic interview</td>
<td>KSADS-PL</td>
</tr>
<tr>
<td>Time 1</td>
<td>FSIQ</td>
<td>Adolescent cognitive assessment</td>
<td>WISC-IV subscales</td>
</tr>
<tr>
<td></td>
<td>Handedness</td>
<td>Adolescent self-report questionnaire</td>
<td>EHI</td>
</tr>
<tr>
<td></td>
<td>Parent education</td>
<td>Parent self-report</td>
<td>Demographic questionnaire</td>
</tr>
<tr>
<td></td>
<td>Structural neuroanatomy</td>
<td>Magnetic resonance imaging</td>
<td>Region of interest volumes*</td>
</tr>
<tr>
<td></td>
<td>Current depressive symptomatology</td>
<td>Adolescent self-report questionnaire</td>
<td>CES-D</td>
</tr>
<tr>
<td>Time 2</td>
<td>History of familial maltreatment</td>
<td>Adolescent self-report questionnaire</td>
<td>CTQ</td>
</tr>
<tr>
<td></td>
<td>Current depressive symptomatology</td>
<td>Adolescent self-report questionnaire</td>
<td>CES-D</td>
</tr>
<tr>
<td></td>
<td>Current or past case-level depression</td>
<td>Adolescent diagnostic interview</td>
<td>KSADS-PL</td>
</tr>
</tbody>
</table>

*Right and left amygdala, hippocampus, medial and lateral orbitofrontal cortex, dorsal, rostral, and ventral cingulate and paracingulate cortex, and corpus callosum area and length.
Chapter 7: Results

7.1 Data analysis introduction

Data analysis is presented in the following sections:

First, a description of data preparation for questionnaire, interview and neuroanatomical region of interest data is given. This incorporates missing data, examination of distribution characteristics, transformations and corrections.

Next, descriptive characteristics of Time 1 and Time 2 questionnaire data and Time 1 region of interest measures are given. Examination of gender differences and relationships with age, handedness, FSIQ, and parent education is undertaken for all measures.

The four Research Questions are then addressed sequentially through a series of hierarchical regression models, followed by examination of meditational models. Rationale and structure of regression and mediation analyses is discussed under the relevant Research Question headings. A summary of Research Questions and statistical analyses used is presented in Figure 13.

Figure 13. Summary of variables, Research Questions, and statistical techniques used in data analysis.
The neurobiological study of developmental traumatology and psychopathology is a relatively new field, and the research design mixed exploratory and confirmatory elements, as reflected in the hypotheses. Relationships between all variables of interest were explored, despite the presence of hypotheses for some and not others, and corrections for multiple comparisons were not applied. Correcting for multiple comparisons is a somewhat conservative approach, and can lead to loss of power and inflation of Type II error (Nakagawa, 2004). The research attempted to measure subtle neuroanatomical differences associated with reports of personal experience, using imaging which, while the state of the art, can only capture a crude estimate of the exquisitely complex structures targeted. In this context, and in an emerging field, conservative analysis was not considered appropriate, and the cost of Type II error was judged to be higher than that of Type I. However, findings should be interpreted with this in mind, and considered primarily as grounds for for future experimental and confirmatory work.

7.2 Missing data

The rate of missing data was generally low across measures. For those measures where data were missing, percentages are listed in Table 5 below. There was a somewhat elevated rate (8%) of missing data for Time 1 CES-D. An independent samples t-test indicated that there was no difference between those who did and did not complete the scale at Time 1 on any questionnaire measure, (CES-D Scales, KSADS-PL Depression diagnosis, and CTQ Neglect and Abuse scales) (see Appendix 2 for t-test results). Therefore, in order to maximise power, pairwise deletion was used for each analysis for Research Questions 1, 2 and 3, meaning that those with missing data on some measures were included in regressions not involving those measures. As handedness was considered peripheral to the main aims of the study, means substitution was used to enable the inclusion of the four cases for which handedness was missing.

For Research Question 4 (mediation analysis) it was necessary to create a subsample of cases for each model tested, in which each case had data for all three variables contained within the model.
Table 5

Missing data rates

<table>
<thead>
<tr>
<th>Missing</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh Handedness Inventory</td>
<td>2.90%</td>
</tr>
<tr>
<td>Left Ventral Cingulate ACC</td>
<td>1.50%</td>
</tr>
<tr>
<td>Left Ventral Paracingulate ACC</td>
<td>.70%</td>
</tr>
<tr>
<td>Right Ventral Paracingulate ACC</td>
<td>3.60%</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>1.50%</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>1.50%</td>
</tr>
<tr>
<td>Corpus Callosum Width</td>
<td>1.50%</td>
</tr>
<tr>
<td>T1 CES-D</td>
<td>8.00%</td>
</tr>
<tr>
<td>T2 CES-D</td>
<td>.70%</td>
</tr>
<tr>
<td>WISC-IV</td>
<td>2.90%</td>
</tr>
</tbody>
</table>

Any measure not listed had a missing data percentage of 0.

7.3 Data preparation

7.3.1 Questionnaires
The distribution of each questionnaire measure was examined for departures from normality, measured using the Shapiro-Wilk test. All questionnaire data were positively skewed, indicating that the majority of participants reported low levels of depressive symptoms, neglect and abuse. Natural log transformations improved the skewness of most subscales, however even after transformations, no scale was distributed normally (this was not unexpected given the non-clinical sample). Skewness and kurtosis measures, Shapiro-Wilk statistics, and transformations for the CES-D and CTQ scales are detailed in Appendices 3 and 4. Outliers were detected and removed at the multivariate level by visual examination of Cook’s distances for each analysis.

7.3.2 Region of interest measures
The distributions of neuroanatomical volumes were tested for normality using the Shapiro-Wilk test. Transformations were applied to non-normal distributions where transformation either led to a non-significant Shapiro-Wilk statistic, or clearly improved skewness. Skewness and kurtosis measures, Shapiro-Wilk statistics, and transformations are detailed in Appendix 5. Outliers were detected and removed at the multivariate level by visual examination of Cook’s distances for each analysis. The removal of outliers affected results in some cases, causing findings to cross into, or out of significance. In each instance where this occurred, the data for the participant concerned were inspected to ensure that a high score on one of the variables of interest (depressive symptomatology or history of maltreatment) was not driving the classification of that
case as an outlier. The use of a multivariate distance reduced this possibility, and a conservative approach to removal of outliers was adopted.

In order to meaningfully compare structure sizes across groups that vary in total brain volume (such as males and females), structure volumes need to be corrected for whole brain volume. This was done using a covariance approach, as described in Jack, Twomey, Zinsmeister, Sharborough, Petersen and Cascino, (1989). Each region of interest was entered as the dependent variable in a regression predicting regional volume from whole brain volume (grey and white matter). The unstandardised residuals were then used as the corrected regional volume measures. This meant that regional volume values could be negative, where the region of interest volume was smaller than predicted by the whole brain volume.

7.3.3 KSADS-PL depressive disorders
The KSADS-PL depressive disorders interview schedule enables diagnoses of major depressive disorder, dysthymia, adjustment disorder with depressed mood, schizoaffective disorder – depressed type, and depressive disorder not otherwise specified, as well as specification of atypical, melancholic, seasonal, and psychotic features.

Diagnoses were made for current episodes or any episode commencing after the Time 1 interview. Sixteen cases with probable, definite, or in remission diagnoses of a past or current depressive disorder were coded as a positive diagnosis in a dichotomous KSADS-PL depressive disorders variable. Frequencies of diagnostic subtypes are detailed in Table 6.

Table 6

<table>
<thead>
<tr>
<th>KSADS-PL depressive disorder diagnoses at Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Adjustment Disorder With Depressed Mood</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>Major Depressive Disorder Atypical Type</td>
</tr>
<tr>
<td>Major Depressive Disorder Melancholic Type</td>
</tr>
<tr>
<td>Depressive Disorder Not Otherwise Specified</td>
</tr>
</tbody>
</table>
7.4 Descriptive statistics

7.4.1 Handedness

The EHI was administered at the Time 1 MRI scan. Scores were strongly skewed towards right hand dominance, with a median score of 34 ($SD = 8.606$).

![Distribution of scores on the Edinburgh Handedness Inventory](Edinburgh_Handedness_Inventory.png)

*Higher scores indicate a stronger right hand preference*

*Figure 14. Distribution of scores on the Edinburgh Handedness Inventory.*

7.4.1.1 Handedness and age

A two-tailed bivariate correlation indicated that the children who were older at the time of scanning were also more strongly right-handed ($r(131) = .180, p = .038$). This is consistent with evidence that in the general population, mixed and left-handedness decrease as age increases (Coren, 1995). It is however unusual that this pattern reached significance in a relatively small sample, and within a narrow age range.
7.4.1.2 Handedness and gender
An independent samples t-test indicated no differences in handedness between males and females ($t(131) = .081, p = .935$).

7.4.2 Parent education
The modal level of parent education was a bachelor degree (see Figure 15) – this is likely to reflect a higher level of education in the parents of the current sample, as compared with the general population. For example, according to the ABS, in 2005 15% of Victorians aged between 25 and 69 had attained a bachelor degree, compared to 40% of the current sample, while 32% of 25-69 year olds had not completed high school, as compared to 16% in the current sample (ABS, 2005a).

![Figure 15. Highest level of education attained by either parent.](image)

7.4.2.1 Parent education and age
A one-way analysis of variance (ANOVA) indicated that participant age was not related to parental education level ($F(4,132) = 1.115, p = .352$).

7.4.2.2 Parent education and gender
A chi-square test indicated that gender and parent education were not related ($\chi^2(4, N = 137) = 3.718, p = .445$).
7.4.3 FSIQ

The WISC-IV full scale IQ (FSIQ) was normally distributed with a mean of 107.989 (SD = 16.593). It appears that this sample had a slightly higher mean FSIQ than the population average of 100 (SD = 15; Wechsler, 2003) although still within the normal range.

7.4.3.1 FSIQ and age

There was a significant negative correlation between age and FSIQ (r(131) = -.254, p = .003).

7.4.3.2 FSIQ and parent education

One-way ANOVA indicated that there was a relationship between parental education and participant FSIQ (F(4.128) = 6.388, p < .001). Significant Scheffe post-hoc contrasts are detailed in Table 7 below.

Table 7

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Mean Difference</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete High School - Bachelor Degree</td>
<td>-14.046</td>
<td>3.902</td>
<td>.014*</td>
</tr>
<tr>
<td>Complete High School - Bachelor Degree</td>
<td>-13.992</td>
<td>4.114</td>
<td>.025*</td>
</tr>
<tr>
<td>TAFE - Bachelor Degree</td>
<td>-12.213</td>
<td>3.841</td>
<td>.044*</td>
</tr>
</tbody>
</table>

*Significant at α=.05

Children of parents with less than a bachelor degree had lower mean FSI IQ, as compared with children of parents with bachelor degrees.

Figure 16. WISC-IV (short form) FSIQ by highest level of parent education
7.4.4 CES-D

7.4.4.1 Factor structure

Confirmatory factor analysis on the CES-D Time 2 data indicated that, with the exception of two items, the established four-factor structure fitted the data well (see Table 8).

Table 8

Four-factor structure of CES-D at Time 2

<table>
<thead>
<tr>
<th>Item</th>
<th>CES-D Subscale</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felt fearful</td>
<td>Depressed Affect</td>
<td>.644</td>
<td>.105</td>
<td>.178</td>
<td></td>
</tr>
<tr>
<td>Felt depressed</td>
<td>Depressed Affect</td>
<td>.638</td>
<td>.195</td>
<td>.365</td>
<td>.258</td>
</tr>
<tr>
<td>Felt sad</td>
<td>Depressed Affect</td>
<td>.626</td>
<td>.152</td>
<td>.334</td>
<td>.389</td>
</tr>
<tr>
<td>Crying spells</td>
<td>Depressed Affect</td>
<td>.600</td>
<td>.169</td>
<td>.104</td>
<td></td>
</tr>
<tr>
<td>Could not shake the blues</td>
<td>Depressed Affect</td>
<td>.578</td>
<td>.193</td>
<td>.287</td>
<td></td>
</tr>
<tr>
<td>Felt lonely</td>
<td>Depressed Affect</td>
<td>.574</td>
<td>.249</td>
<td>.106</td>
<td>.435</td>
</tr>
<tr>
<td>Bothered by things</td>
<td>Depressed Affect</td>
<td>.502</td>
<td>.273</td>
<td>.269</td>
<td></td>
</tr>
<tr>
<td>Enjoyed life</td>
<td>Wellbeing</td>
<td>.468</td>
<td>.677</td>
<td>.145</td>
<td>.217</td>
</tr>
<tr>
<td>Felt as good as other people</td>
<td>Wellbeing</td>
<td>.642</td>
<td>.137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felt hopeful</td>
<td>Wellbeing</td>
<td>.598</td>
<td>.164</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felt happy</td>
<td>Wellbeing</td>
<td>.399</td>
<td>.565</td>
<td>.124</td>
<td>.228</td>
</tr>
<tr>
<td>Thought life had been a failure</td>
<td>Depressed Affect</td>
<td>.416</td>
<td>.418</td>
<td>.123</td>
<td></td>
</tr>
<tr>
<td>Did not feel like eating</td>
<td>Somatic</td>
<td>.379</td>
<td>.176</td>
<td>.640</td>
<td></td>
</tr>
<tr>
<td>Could not get going</td>
<td>Somatic</td>
<td>.150</td>
<td>.109</td>
<td>.577</td>
<td>.203</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>Somatic</td>
<td>.118</td>
<td>.188</td>
<td>.513</td>
<td>.169</td>
</tr>
<tr>
<td>Talked less</td>
<td>Somatic</td>
<td>.212</td>
<td></td>
<td>.510</td>
<td></td>
</tr>
<tr>
<td>Sleep was restless</td>
<td>Somatic</td>
<td>.195</td>
<td>.367</td>
<td>.216</td>
<td></td>
</tr>
<tr>
<td>People were unfriendly</td>
<td>Interpersonal</td>
<td></td>
<td>.129</td>
<td>.850</td>
<td></td>
</tr>
<tr>
<td>People disliked me</td>
<td>Interpersonal</td>
<td>.353</td>
<td>.234</td>
<td>.673</td>
<td></td>
</tr>
<tr>
<td>Everything was an effort</td>
<td>Somatic</td>
<td></td>
<td></td>
<td></td>
<td>.294</td>
</tr>
</tbody>
</table>

Extraction Method: Principal Axis Factoring. Bartlett’s test of sphericity: $\chi^2(190) = 1168.795$, $p < .001$
Rotation Method: Varimax with Kaiser Normalization. KMO Measure of Sampling Adequacy = .845

One of the two discrepant items, (“I thought my life had been a failure”) loaded on the Wellbeing factor only very slightly better than on the Depressed Affect factor (its original subscale). Given the well-validated nature of the CES-D’s established factor structure, and the strong internal consistency demonstrated for established subscales in this sample (see Table 9 below), the original structure was retained in all analyses.
7.4.4.2 Internal consistency

Cronbach’s alpha for CES-D Total and subscales is given in Table 9.

Table 9

Internal consistency of Time 1 and 2 CES-D subscales

<table>
<thead>
<tr>
<th>Cronbach's Alpha</th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D Total</td>
<td>.896</td>
<td>.866</td>
</tr>
<tr>
<td>CES-D Depressed Affect</td>
<td>.881</td>
<td>.970</td>
</tr>
<tr>
<td>CES-D Wellbeing</td>
<td>.636</td>
<td>.768</td>
</tr>
<tr>
<td>CES-D Somatic</td>
<td>.731</td>
<td>.904</td>
</tr>
<tr>
<td>CES-D Interpersonal</td>
<td>.752</td>
<td>.928</td>
</tr>
</tbody>
</table>

7.4.4.3 CES-D symptom change

Repeated measures \( t\)-tests were conducted comparing Time 1 and Time 2 CES-D Total and subscales. Depressive symptom severity appeared to reduce from Time 1 to Time 2 on the Depressed Affect and Wellbeing subscales. Descriptive statistics and \( t\)-test results are detailed in Table 10 below.

Table 10

Descriptive statistics and repeated measures \( t\)-test results for Time 1 and Time 2 CES-D scales

<table>
<thead>
<tr>
<th></th>
<th>Time 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>Mean Diff.</td>
<td>SD</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>31.891</td>
<td>10.367</td>
<td>136</td>
<td>30.033</td>
<td>8.229</td>
<td>1.505</td>
<td>10.498</td>
</tr>
<tr>
<td>Depressed Affect</td>
<td>126</td>
<td>10.059</td>
<td>4.248</td>
<td>136</td>
<td>9.044</td>
<td>3.103</td>
<td>.836</td>
<td>4.177</td>
</tr>
<tr>
<td>Wellbeing</td>
<td>126</td>
<td>7.143</td>
<td>2.498</td>
<td>136</td>
<td>6.444</td>
<td>2.472</td>
<td>.608</td>
<td>2.658</td>
</tr>
<tr>
<td>Somatic</td>
<td>126</td>
<td>12.028</td>
<td>3.841</td>
<td>136</td>
<td>11.648</td>
<td>3.311</td>
<td>.275</td>
<td>4.237</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>126</td>
<td>3.103</td>
<td>1.594</td>
<td>136</td>
<td>2.897</td>
<td>1.278</td>
<td>.200</td>
<td>1.796</td>
</tr>
</tbody>
</table>

*Significant at \( \alpha=.05 \)

Symptom change was also measured using unstandardised residuals from the regression of Time 2 CES-D scale scores onto Time 1 scores (descriptive statistics are provided as Table 11).
Table 11

Unstandardised residuals from regression of Time 2 onto Time 1 CES-D scale scores

<table>
<thead>
<tr>
<th>CES-D Scale Residual</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Residual</td>
<td>126</td>
<td>.000</td>
<td>7.851</td>
</tr>
<tr>
<td>Depressed Affect Residual</td>
<td>125</td>
<td>.000</td>
<td>3.001</td>
</tr>
<tr>
<td>Wellbeing Residual</td>
<td>125</td>
<td>.000</td>
<td>2.278</td>
</tr>
<tr>
<td>Somatic Residual</td>
<td>125</td>
<td>.000</td>
<td>3.205</td>
</tr>
<tr>
<td>Interpersonal Residual</td>
<td>125</td>
<td>.000</td>
<td>1.253</td>
</tr>
</tbody>
</table>

7.4.4.4 CES-D and gender

Gender differences were evident in two instances in the Time 1 and Time 2 CES-D data. At Time 1, males endorsed more Somatic symptoms than females, and at Time 2, females endorsed more Depressed Affect symptoms than males. All means comparisons are detailed in Table 12.

Table 12

Descriptive statistics and independent samples t-test results comparing CES-d scale scores between males and females

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>T1 Total</td>
<td>69</td>
<td>33.066</td>
<td>10.442</td>
</tr>
<tr>
<td>T1 Depressed Affect</td>
<td>69</td>
<td>10.314</td>
<td>4.481</td>
</tr>
<tr>
<td>T1 Wellbeing</td>
<td>69</td>
<td>7.029</td>
<td>2.280</td>
</tr>
<tr>
<td>T1 Somatic</td>
<td>69</td>
<td>12.669</td>
<td>3.910</td>
</tr>
<tr>
<td>T1 Interpersonal</td>
<td>69</td>
<td>3.319</td>
<td>1.770</td>
</tr>
<tr>
<td>T2 Total</td>
<td>73</td>
<td>28.783</td>
<td>6.877</td>
</tr>
<tr>
<td>T2 Depressed Affect</td>
<td>73</td>
<td>8.397</td>
<td>2.332</td>
</tr>
<tr>
<td>T2 Wellbeing</td>
<td>73</td>
<td>6.329</td>
<td>2.224</td>
</tr>
<tr>
<td>T2 Somatic</td>
<td>73</td>
<td>11.164</td>
<td>3.028</td>
</tr>
<tr>
<td>T2 Interpersonal</td>
<td>73</td>
<td>2.890</td>
<td>1.318</td>
</tr>
</tbody>
</table>

*Significant at α=.05

7.4.4.4.1 CES-D symptom change and gender

Different patterns of symptom change were observed for males and females. With the exception of Interpersonal symptoms, males demonstrated significant symptom reduction across time points (see Table 13), whereas females demonstrated no significant change (see Table 14).
Table 13

Descriptive statistics and repeated measures t-test results comparing Time 1 and Time 2 CES-D scale scores:

Males

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Time 1</th>
<th></th>
<th></th>
<th>Time 2</th>
<th></th>
<th></th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M (SD)</td>
<td></td>
<td>N</td>
<td>M (SD)</td>
<td>Mean</td>
<td>Diff.</td>
<td>SD</td>
<td>t</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>33.066 (10.442)</td>
<td></td>
<td>73</td>
<td>28.783 (6.877)</td>
<td>3.697 (2.952)</td>
<td>67</td>
<td>.004*</td>
<td></td>
</tr>
<tr>
<td>Depressed Affect</td>
<td>69</td>
<td>10.314 (4.481)</td>
<td></td>
<td>73</td>
<td>8.397 (2.332)</td>
<td>1.657 (3.247)</td>
<td>67</td>
<td>.002*</td>
<td></td>
</tr>
<tr>
<td>Wellbeing</td>
<td>69</td>
<td>7.029 (2.280)</td>
<td></td>
<td>73</td>
<td>6.329 (2.224)</td>
<td>.632 (2.174)</td>
<td>67</td>
<td>.033*</td>
<td></td>
</tr>
<tr>
<td>Somatic</td>
<td>69</td>
<td>12.669 (3.910)</td>
<td></td>
<td>73</td>
<td>11.164 (3.028)</td>
<td>1.297 (2.616)</td>
<td>67</td>
<td>.011*</td>
<td></td>
</tr>
<tr>
<td>Interpersonal</td>
<td>69</td>
<td>3.319 (1.770)</td>
<td></td>
<td>73</td>
<td>2.890 (1.318)</td>
<td>.382 (1.537)</td>
<td>67</td>
<td>.129</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at α=.05

Table 14

Descriptive statistics and repeated measures t-test results comparing Time 1 and Time 2 CES-D scale scores:

Females

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Time 1</th>
<th></th>
<th></th>
<th>Time 2</th>
<th></th>
<th></th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M (SD)</td>
<td></td>
<td>N</td>
<td>M (SD)</td>
<td>Mean</td>
<td>Diff.</td>
<td>SD</td>
<td>t</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>30.492 (10.189)</td>
<td></td>
<td>63</td>
<td>31.482 (9.411)</td>
<td>-1.066 (10.191)</td>
<td>-7.97</td>
<td>57</td>
<td>.429</td>
</tr>
<tr>
<td>Depressed Affect</td>
<td>57</td>
<td>9.751 (3.966)</td>
<td></td>
<td>63</td>
<td>9.794 (3.686)</td>
<td>-1.144 (3.955)</td>
<td>-2.275</td>
<td>56</td>
<td>.785</td>
</tr>
<tr>
<td>Wellbeing</td>
<td>57</td>
<td>7.281 (2.753)</td>
<td></td>
<td>63</td>
<td>6.577 (2.743)</td>
<td>.579 (2.960)</td>
<td>1.476</td>
<td>56</td>
<td>.145</td>
</tr>
<tr>
<td>Somatic</td>
<td>57</td>
<td>11.251 (3.640)</td>
<td></td>
<td>63</td>
<td>12.209 (3.554)</td>
<td>-0.945 (4.120)</td>
<td>-.731</td>
<td>56</td>
<td>.089</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>57</td>
<td>2.842 (1.320)</td>
<td></td>
<td>63</td>
<td>2.905 (1.241)</td>
<td>.018 (1.420)</td>
<td>-.093</td>
<td>56</td>
<td>.926</td>
</tr>
</tbody>
</table>

In the residual variables, a pattern of negative residuals for males (interpreted as symptom improvement from Time 1 to Time 2) and positive residuals for females (interpreted as symptom exacerbation from Time 1 to Time 2) was observed (see Figure 17). This may explain the lack of symptom change in the overall sample for CES-D Total. Gender differences proved significant for CES-D Total, Depressed Affect, and Somatic residual variables; all gender comparisons are detailed in Table 15.
Table 15

Descriptive statistics and independent samples t-test results comparing male and female CES-D scale residual scores

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Males</th>
<th>Females</th>
<th>Mean Diff.</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>-1.532</td>
<td>6.849</td>
<td>58</td>
<td>1.797</td>
<td>8.6</td>
<td>-3.329</td>
</tr>
<tr>
<td>Depressed Affect</td>
<td>68</td>
<td>-0.719</td>
<td>2.374</td>
<td>57</td>
<td>.858</td>
<td>3.437</td>
<td>-1.578</td>
</tr>
<tr>
<td>Wellbeing</td>
<td>68</td>
<td>-0.115</td>
<td>2.054</td>
<td>57</td>
<td>.138</td>
<td>2.532</td>
<td>-0.253</td>
</tr>
<tr>
<td>Somatic</td>
<td>68</td>
<td>-0.593</td>
<td>2.91</td>
<td>57</td>
<td>.707</td>
<td>3.416</td>
<td>-1.300</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>68</td>
<td>-0.020</td>
<td>1.352</td>
<td>57</td>
<td>.024</td>
<td>1.135</td>
<td>-0.043</td>
</tr>
</tbody>
</table>

*Significant at α=.05

While the repeated measures t-tests indicate that the change in severity of symptoms was not significant for females, the analysis of residuals suggest that males and females were following significantly different trajectories in the experience of several aspects of depressive symptomatology.

Figure 17. CES-D scale residual means for males and females.
7.4.4.5 CES-D and parent education

Univariate ANOVAs indicated that Depressed Affect was related to parent education at Time 1 ($F(4,121)=2.542, p=.043$) and Time 2 ($F(4,131)=2.638, p=.037$)(for all CES-D by Parent Education analyses, see Appendix 6). Games-Howell post-hoc tests were used, as Levene’s test indicated that heterogeneity of variance was present for these three subscales. With the exception of one comparison, the significant post-hoc contrasts indicated that children of parents with higher educational qualifications endorsed fewer depressive symptoms (see Table 16).

Table 16

Games-Howell post-hoc comparisons indicating relationships between parent education and child CES-D Scale scores

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Comparison</th>
<th>Mean Difference</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1 Depressed Affect</td>
<td>3.914</td>
<td>1.132</td>
<td>.014*</td>
</tr>
<tr>
<td></td>
<td>T1 Interpersonal</td>
<td>1.216</td>
<td>.422</td>
<td>.055</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.017</td>
<td>.296</td>
<td>.009*</td>
</tr>
<tr>
<td></td>
<td>T2 Depressed Affect</td>
<td>2.992</td>
<td>1.037</td>
<td>.059</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1.582</td>
<td>.445</td>
<td>.006*</td>
</tr>
</tbody>
</table>

*Significant at $\alpha=.05$

7.4.4.6 CES-D and age

There were no correlations between age and CES-D scores at Time 1 or Time 2, and no correlations between the amount of time between interviews and the CES-D residual scores for each participant (see Table 17 and Table 18).
Table 17

Pearson correlations between age at MRI and time between interviews and Time 1 and 2 CES-D scale scores

<table>
<thead>
<tr>
<th></th>
<th>Age at T1 MRI</th>
<th>Time between interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>T1 CES-D</td>
<td>-.111</td>
<td>.218</td>
</tr>
<tr>
<td>T2 CES-D</td>
<td>-.008</td>
<td>.931</td>
</tr>
<tr>
<td>T1 CES-D Depressed Affect</td>
<td>-.144</td>
<td>.107</td>
</tr>
<tr>
<td>T2 CES-D Depressed Affect</td>
<td>.009</td>
<td>.919</td>
</tr>
<tr>
<td>T1 CES-D Somatic</td>
<td>-.130</td>
<td>.146</td>
</tr>
<tr>
<td>T2 CES-D Somatic</td>
<td>.013</td>
<td>.883</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>.017</td>
<td>.850</td>
</tr>
<tr>
<td>T2 CES-D Wellbeing</td>
<td>.012</td>
<td>.892</td>
</tr>
<tr>
<td>T1 CES-D Interpersonal</td>
<td>-.068</td>
<td>.447</td>
</tr>
<tr>
<td>T2 CES-D Interpersonal</td>
<td>-.112</td>
<td>.195</td>
</tr>
</tbody>
</table>

Table 18

Pearson correlations between time between interviews and CES-D scale residual scores

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Time Between Interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Total Residual</td>
<td>.004</td>
</tr>
<tr>
<td>Depressed Affect Residual</td>
<td>.045</td>
</tr>
<tr>
<td>Wellbeing Residual</td>
<td>.014</td>
</tr>
<tr>
<td>Somatic Residual</td>
<td>-.019</td>
</tr>
<tr>
<td>Interpersonal Residual</td>
<td>-.041</td>
</tr>
</tbody>
</table>

7.4.4.7 CES-D and FSIQ

There were no relationships between FSIQ and Time 1, Time 2, or residual CES-D scores (see Table 19).
Table 19

*Pearson correlations between CES-D scale scores and residuals and WISC-IV (Short Form) Full Scale IQ*

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>FSIQ</th>
<th>r</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Total</td>
<td>FSIQ</td>
<td>-.078</td>
<td>.390</td>
<td>124</td>
</tr>
<tr>
<td>T1 Depressed Affect</td>
<td></td>
<td>-.019</td>
<td>.833</td>
<td>123</td>
</tr>
<tr>
<td>T1 Wellbeing</td>
<td></td>
<td>-.127</td>
<td>.162</td>
<td>123</td>
</tr>
<tr>
<td>T1 Somatic</td>
<td></td>
<td>-.124</td>
<td>.173</td>
<td>123</td>
</tr>
<tr>
<td>T1 Interpersonal</td>
<td></td>
<td>.000</td>
<td>.995</td>
<td>123</td>
</tr>
<tr>
<td>T2 Total</td>
<td>FSIQ</td>
<td>-.055</td>
<td>.535</td>
<td>132</td>
</tr>
<tr>
<td>T2 Depressed Affect</td>
<td></td>
<td>-.015</td>
<td>.866</td>
<td>132</td>
</tr>
<tr>
<td>T2 Wellbeing</td>
<td></td>
<td>-.084</td>
<td>.340</td>
<td>132</td>
</tr>
<tr>
<td>T2 Somatic</td>
<td></td>
<td>-.058</td>
<td>.507</td>
<td>132</td>
</tr>
<tr>
<td>T2 Interpersonal</td>
<td></td>
<td>-.003</td>
<td>.974</td>
<td>132</td>
</tr>
<tr>
<td>Total Residual</td>
<td>FSIQ</td>
<td>-.035</td>
<td>.697</td>
<td>123</td>
</tr>
<tr>
<td>Depressed Affect Residual</td>
<td></td>
<td>-.010</td>
<td>.917</td>
<td>122</td>
</tr>
<tr>
<td>Wellbeing Residual</td>
<td></td>
<td>-.033</td>
<td>.714</td>
<td>122</td>
</tr>
<tr>
<td>Somatic Residual</td>
<td></td>
<td>-.036</td>
<td>.697</td>
<td>122</td>
</tr>
<tr>
<td>Interpersonal Residual</td>
<td></td>
<td>-.002</td>
<td>.981</td>
<td>122</td>
</tr>
</tbody>
</table>

7.4.5 KSADS-PL depressive disorders

The sample was constructed such that no participant exhibited case-level depression as measured using the KSADS-PL at Time 1. At Time 2, 16 (11 female) participants had met case-level for depression either currently or since Time 1 assessment.

7.4.5.1 KSADS-PL depressive disorders and CES-D scales

Independent samples *t*-tests revealed no relationships between KSADS-PL depression diagnosis at Time 2 and CES-D scores at Time 1, strengthening the assumption that case-level depression observed at Time 2 had its onset after Time 1. Case-level depressive disorder as diagnosed using the KSADS-PL was reflected in higher Time 2 CES-D scores and residuals for all subscales except Interpersonal. CES-D scores for those with and without a KSADS-PL depressive disorder are described in Table 20. Table 21 gives the independent sample *t*-test results comparing Time 2 CES-D scale and residual scores for those with and without depression diagnoses.
Table 20

*Time 1 and Time 2 CES-D scale scores for those with and without a KSADS-PL depressive disorder diagnosis at Time 2*

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>KSADS-PL Depression</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>T1 Total</td>
<td>31.441</td>
<td>.913</td>
<td>34.707</td>
</tr>
<tr>
<td>T1 Depressed Affect</td>
<td>9.680</td>
<td>.366</td>
<td>11.645</td>
</tr>
<tr>
<td>T1 Wellbeing</td>
<td>6.940</td>
<td>.230</td>
<td>8.177</td>
</tr>
<tr>
<td>T1 Somatic</td>
<td>11.926</td>
<td>.364</td>
<td>12.045</td>
</tr>
<tr>
<td>T1 Interpersonal</td>
<td>3.064</td>
<td>.147</td>
<td>3.200</td>
</tr>
<tr>
<td>T2 Total</td>
<td>28.511</td>
<td>.618</td>
<td>41.800</td>
</tr>
<tr>
<td>T2 Depressed</td>
<td>8.400</td>
<td>.210</td>
<td>14.067</td>
</tr>
<tr>
<td>T2 Wellbeing</td>
<td>6.136</td>
<td>.208</td>
<td>9.000</td>
</tr>
<tr>
<td>T2 Somatic</td>
<td>11.174</td>
<td>.275</td>
<td>15.267</td>
</tr>
<tr>
<td>T2 Interpersonal</td>
<td>2.800</td>
<td>.120</td>
<td>3.467</td>
</tr>
</tbody>
</table>

Table 21

*Results of independent samples t-tests comparing Time 2 CES-D Scale and residual scores for those with and without KSADS-PL depressive disorders diagnosis at Time 2*

<table>
<thead>
<tr>
<th>Mean</th>
<th>Diff.</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 CES-D Total</td>
<td>-12.500</td>
<td>2.888</td>
<td>-4.33</td>
<td>134</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>T2 Depressed Affect</td>
<td>-5.404</td>
<td>1.158</td>
<td>-4.67</td>
<td>134</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>T2 Wellbeing</td>
<td>-2.543</td>
<td>.882</td>
<td>-2.88</td>
<td>134</td>
<td>.011*</td>
</tr>
<tr>
<td>T2 Somatic</td>
<td>-3.869</td>
<td>1.087</td>
<td>-3.56</td>
<td>134</td>
<td>.002*</td>
</tr>
<tr>
<td>T2 Interpersonal</td>
<td>-.683</td>
<td>.336</td>
<td>-2.03</td>
<td>134</td>
<td>.044*</td>
</tr>
</tbody>
</table>

Total Residual     | -12.284| 3.065  | -4.01 | 124 | .001* |

Depressed Affect Residual | -5.148 | 1.192  | -4.32 | 123 | .001* |
Wellbeing Residual    | -2.323 | .912   | -2.55 | 123 | .022* |
Somatic Residual      | -4.062 | 1.158  | -3.51 | 123 | .003* |
Interpersonal Residual| -.641  | .341   | -1.88 | 123 | .063  |

*Significant at α=.05

7.4.5.2 KSADS-PL depressive disorders and age

There was no difference in age at Time 2 interview between those with and without case-level depression ($t(135) = .643, p = .522$).
7.4.5.3 KSADS-PL depressive disorders and gender
Chi-square analysis showed that there was significantly more case-level depression diagnosed in females than males in this sample ($\chi^2(1, N = 137) = 3.780, p = .047$).

7.4.5.4 KSADS-PL depressive disorders and IQ
There was no difference in FSIQ (measured at Time 1) between participants with and without case-level depression at Time 2 ($t(131) = -0.035, p = .972$)

7.4.5.5 KSADS-PL depressive disorders and parental education
Chi-square analysis showed a significant relationship between parent education and case-level depression ($\chi^2 (4, N = 137) = 10.828, p = .029$) such that children of parents with incomplete secondary school education were over-represented in the depressed subgroup.

7.4.6 Childhood Trauma Questionnaire

7.4.6.1 Factor structure
CTQ was collected at Time 2 only. CTQ subscales of interest were Emotional Neglect, Physical Neglect, Emotional Abuse, and Physical Abuse. Internal consistency measures indicated that the Physical Neglect Subscale was performing poorly (see Table 22).

Table 22

<table>
<thead>
<tr>
<th>CTQ Subscale</th>
<th>Cronbach's Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Neglect</td>
<td>.465</td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>.883</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>.629</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>.857</td>
</tr>
</tbody>
</table>

Confirmatory factor analysis yielded a four-factor structure markedly different to established subscales (see Appendix 7), which was not easily interpretable. When constrained to two factors however, a clear division between neglect and abuse items emerged. Therefore two variables were created, labelled Neglect and Abuse, which each contained the relevant physical and emotional subscales (see Table 23). There was one item originally from the Physical Neglect subscale, which in the two-factor analysis loaded more strongly on the Abuse factor. However, as the difference in loading on the Abuse and Neglect factors was .003, the item was analysed as part of the Neglect factor.
### Table 23

**Two-factor structure for the Childhood Trauma Questionnaire**

<table>
<thead>
<tr>
<th>CTQ Item</th>
<th>CTQ Subscale</th>
<th>Factor Neglect</th>
<th>Factor Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. People in my family looked out for each other.</td>
<td>Emotional Neglect</td>
<td>.792</td>
<td>.298</td>
</tr>
<tr>
<td>19. People in my family felt close to each other.</td>
<td>Emotional Neglect</td>
<td>.784</td>
<td>.179</td>
</tr>
<tr>
<td>28. My family was a source of strength and support.</td>
<td>Emotional Neglect</td>
<td>.760</td>
<td>.320</td>
</tr>
<tr>
<td>5. There was someone in my family who helped me feel that I was</td>
<td>Emotional Neglect</td>
<td>.632</td>
<td>.223</td>
</tr>
<tr>
<td>important or special.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I knew that there was someone to take care of me and protect me.</td>
<td>Physical Neglect</td>
<td>.585</td>
<td></td>
</tr>
<tr>
<td>26. There was someone to take me to the doctor if I needed it.</td>
<td>Physical Neglect</td>
<td>.350</td>
<td></td>
</tr>
<tr>
<td>1. I didn't have enough to eat.</td>
<td>Physical Neglect</td>
<td>.309</td>
<td></td>
</tr>
<tr>
<td>6. I had to wear dirty clothes.</td>
<td>Physical Neglect</td>
<td>.194</td>
<td></td>
</tr>
<tr>
<td>18. I felt that someone in my family hated me.</td>
<td>Emotional Abuse</td>
<td>.278</td>
<td>.716</td>
</tr>
<tr>
<td>15. I believe that I was physically abused.</td>
<td>Physical Abuse</td>
<td>.706</td>
<td></td>
</tr>
<tr>
<td>11. People in my family hit me so hard that it left me with bruses or</td>
<td>Physical Abuse</td>
<td>.134</td>
<td>.657</td>
</tr>
<tr>
<td>marks.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. People in my family said hurtful or insulting things to me.</td>
<td>Emotional Abuse</td>
<td>.258</td>
<td>.635</td>
</tr>
<tr>
<td>3. People in my family called me things like &quot;stupid&quot;, &quot;lazy&quot; or &quot;ugly&quot;.</td>
<td>Emotional Abuse</td>
<td>.291</td>
<td>.578</td>
</tr>
<tr>
<td>8. I thought that my parents wished I hadn't been born.</td>
<td>Emotional Abuse</td>
<td>.385</td>
<td>.575</td>
</tr>
<tr>
<td>25. I believe that I was emotionally abused.</td>
<td>Emotional Abuse</td>
<td>.219</td>
<td>.570</td>
</tr>
<tr>
<td>17. I got hit or beaten so badly that it was noticed by someone like a</td>
<td>Physical Abuse</td>
<td>.443</td>
<td></td>
</tr>
<tr>
<td>teacher, neighbour, or doctor.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I was punished with a belt, a board, a cord, or some other hard</td>
<td>Physical Abuse</td>
<td>.177</td>
<td>.368</td>
</tr>
<tr>
<td>object.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I got hit so hard by someone in my family that I had to see a doctor</td>
<td>Physical Abuse</td>
<td>.209</td>
<td>.362</td>
</tr>
<tr>
<td>or go to the hospital.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. My parents were too drunk or high to take care of the family.</td>
<td>Physical Neglect</td>
<td>.126</td>
<td>.129</td>
</tr>
</tbody>
</table>

**Extraction Method:** Principal Axis Factoring.  
**Bartlett’s test of sphericity:** $\chi^2(190) = 1144.363, p < .001$  
**Rotation Method:** Varimax with Kaiser Normalization.  
**KMO Measure of Sampling Adequacy** = .826

#### 7.4.6.2 Internal consistency

Cronbach’s alpha was .845 for the Neglect variable, and .824 for the Abuse variable. Neglect and Abuse were strongly correlated ($r(137) = .577, p < .001$).

#### 7.4.6.3 CTQ and gender

Means and results of independent samples t-tests for gender differences in CTQ Neglect and Abuse are presented in Table 24 below. There was no difference in the amount of neglect
reported by males and females, however females reported experiencing significantly more abuse than males.

Table 24

Descriptive statistics and results of independent samples t-tests comparing CTQ Neglect and Abuse scores for males and females

<table>
<thead>
<tr>
<th>CTQ Scale</th>
<th>Male N</th>
<th>M</th>
<th>SD</th>
<th>Female N</th>
<th>M</th>
<th>SD</th>
<th>Mean Diff.</th>
<th>SD</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td>74</td>
<td>12.541</td>
<td>3.172</td>
<td>63</td>
<td>14.460</td>
<td>5.509</td>
<td>-1.920</td>
<td>.786</td>
<td>-2.443</td>
<td>95.473</td>
<td>.016*</td>
</tr>
<tr>
<td>Neglect</td>
<td>74</td>
<td>14.797</td>
<td>5.187</td>
<td>63</td>
<td>14.857</td>
<td>5.983</td>
<td>-0.060</td>
<td>.954</td>
<td>-0.063</td>
<td>135</td>
<td>.950</td>
</tr>
</tbody>
</table>

*Significant at α=.05

7.4.6.4 CTQ and FSIQ

There was no correlation between FSIQ (measured at Time 1) and CTQ Neglect ($r(133) = -.040$, $p = .645$) or Abuse ($r(133) = -.022$, $p = .802$) (reported at Time 2).

7.4.6.5 CTQ and parent education

One way analysis of variance revealed no relationship between parent education and levels of Abuse ($F(4,132) = .575$, $p = .681$) or Neglect ($F(4,132) = .219$, $p = .927$) reported by participants.

7.4.6.6 CTQ and age

There was no correlation between age (at Time 2, when the CTQ was administered) and CTQ Neglect ($r(137) = .070$, $p = .415$) or Abuse ($r(137) = .035$, $p = .684$).

7.4.7 Neuroanatomical regions of interest

For total, male and female means and standard deviations for all regions of interest see Appendix 8. For correlations between structures, see Appendix 9.

7.4.7.1 Regions of interest and gender

Whole brain volume (grey and white matter) was 7.6% larger for males ($M = 1349544.16$, $SD = 11165.27$) than females ($M = 1247498.93$, $SD = 11861.54$). This is consistent with frequent reports of male total brain size ~8-10% larger than female total brain size (Goldstein, Seidman, Horton, Makris, Kennedy & Caviness Jr, 2001). A series of independent samples t-tests conducted on region of interest data after whole brain volume correction revealed no gender differences (see Appendix 10).
7.4.7.2 Regions of interest and age

For all region of interest analyses, age was measured in days on the occasion of the child’s MRI scan. Mean age was 4616 days (12yrs 7mths, \( SD = 157 \) days); there was no difference in the mean age between males and females. To measure whether individual structure sizes were positively correlated with age at scanning, a series of one-tailed bivariate correlations were conducted on the region of interest data (after transformation and correction for whole brain volume). The volumes of several structures were positively associated with age, as listed in Table 25 below.

Table 25

*Significant Pearson correlations between neuroanatomical regions of interest and age*

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>( p^a )</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Hippocampus</td>
<td>.244</td>
<td>.002</td>
<td>137</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>.239</td>
<td>.002</td>
<td>137</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>.204</td>
<td>.008</td>
<td>137</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>.213</td>
<td>.006</td>
<td>137</td>
</tr>
<tr>
<td>Left Ventral Paracingulate ACC</td>
<td>.152</td>
<td>.039</td>
<td>136</td>
</tr>
<tr>
<td>Right Dorsal Cingulate ACC</td>
<td>.181</td>
<td>.017</td>
<td>137</td>
</tr>
<tr>
<td>Right Ventral Paracingulate ACC</td>
<td>.154</td>
<td>.039</td>
<td>132</td>
</tr>
</tbody>
</table>

\( ^a \) One-tailed

\( ^* \) Significant at \( \alpha = .05 \)

For all correlations between regions of interest and age, see Appendix 11.

7.4.7.3 Regions of interest and handedness

A series of two-tailed bivariate correlations indicated that there were no significant relationships between whole brain or individual structure volume and handedness, however there were trends for negative relationships between EHI score and left orbitofrontal cortex volume (\( r(133) = -.163, p = .061 \)) and left lateral orbitofrontal cortex volume (\( r(133) = -.154, p = .076 \)).

For all correlations between regions of interest and handedness, see Appendix 12.

7.4.7.4 Regions of interest and FSIQ

There were no relationships between any region of interest volume and FSIQ (see Appendix 13).


7.4.7.5 Regions of interest and parent education

A series of univariate ANOVAs were conducted to measure whether corrected region of interest volume was related to parent education. Analysis revealed a significant relationship between left rostral paracingulate ACC volume and parent education ($F(4,132) = 3.986, p = .018$). Scheffe post hoc comparisons indicated that left rostral paracingulate ACC was larger in children with Secondary School educated parents compared to those with Bachelor Degree educated parents (Mean difference = 1149.5508, $SE = 341.333, p = .010$).

7.5 Regression models

A series of hierarchical regressions were conducted to investigate each Research Question. Where the dependent variables were questionnaire measures or regions of interest, linear regression was used, and binary logistic regression was used where KSADS-PL depressive disorder diagnosis was the outcome variable. For each regression, age, gender, parent education, and handedness were entered in Step 1 as covariates. Parent education was coded as a series of forward difference dummy variables, such that each category was compared with the subsequent category. As there were no relationships between FSIQ and any of the main variables of interest, this variable was not included in any further analyses. The independent variable was entered in Step 2 in each model, and in Step 3 an interaction term between the independent variable and gender was entered. Where a significant interaction was discovered, gender was removed from Step 1, and separate regression analyses were run for males and females. Gender interactions are illustrated throughout with graphs generated using O’Connor’s (1998) SPSS Macros for simple slopes analysis, and indicate predicted values on $y$ given $x$ values $+/-2SD$ for males and females.

7.6 Research Question 1: Are childhood experiences of neglect or abuse predictive of adolescent onset depression?

7.6.1 CES-D

Time 2 CES-D subscales were entered as the dependent variables in a series of hierarchical regression models, the structure of which are described in Table 26 below. Time 1 CES-D subscales were entered as covariates, along with gender, parent education, handedness, and age. CTQ variables and CTQ by gender interactions were entered as the independent variables of primary interest.
Table 26

Structure of CES-D by CTQ linear regression models

<table>
<thead>
<tr>
<th>DV</th>
<th>Time 2 CES-D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Time 1 CES-D</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>CTQ Variable</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>CTQ Variable x Gender</td>
</tr>
</tbody>
</table>

7.6.1.1 CTQ Neglect and CES-D

The results of regressions of CTQ Neglect onto CES-D subscale are presented in Table 27. Time 1 CES-D was a strong positive predictor of Time 2 CES-D for all subscales. Gender effects were observed for the Depressed Affect and Somatic subscales, such that female gender predicted increase in these symptoms. For the Interpersonal subscale, greater age predicted a reduction in symptomatology. For Depressed Affect, having parents with Incomplete Secondary School education predicted increase in depressive symptoms, as compared with having parents with Complete Secondary School education.

*Main effects were present in all regressions, such that greater reported levels of childhood neglect predicted increase in depressive symptomatology for all CES-D subscales.*

7.6.1.2 CTQ Abuse and CES-D

The results of regressions of CTQ Abuse onto CES-D subscales are presented in Table 28. Time 1 CES-D was a strong positive predictor of Time 2 CES-D for all subscales. Gender effects were observed for CES-D Total, Depressed Affect and Somatic subscales, such that female gender predicted increase in symptoms. For the Interpersonal subscale, greater age predicted a reduction in symptomatology. For Depressed Affect, having parents with Incomplete Secondary School education predicted increase in depressive symptoms, as compared with having parents with Complete Secondary School education.
Greater reported levels of childhood abuse predicted increase in depressive symptomatology for all CES-D subscales.

An interaction effect for CES-D Total suggested that while CTQ Abuse predicted CES-D Total significantly for both genders, the relationship was particularly strong for females (see Figure 18).

Figure 18. Interaction between gender and CTQ Abuse in predicting CES-D Total symptom change.

An interaction for the relationship between Abuse and Somatic symptoms indicated that the relationship only existed for females, as illustrated in Figure 19.
Figure 19. Interaction between gender and CTQ Abuse in predicting CES-D Somatic symptom change.
Table 27

Result of regressions predicting Time 2 CES-D with covariates, an independent variable of CTQ Neglect, and an interaction term of Neglect and gender

<table>
<thead>
<tr>
<th>Step</th>
<th>Total</th>
<th>Depressed Affect</th>
<th>Somatic</th>
<th>Wellbeing</th>
<th>Interpersonal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R^2 = .195(.137)^a, R^2Δ= .195R^2 = .231(.178), R^2Δ = .126(.066), R^2Δ = .126R^2 = .228(.174), R^2Δ = .228</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F(8,112) = 3.390, p = .002*</td>
<td>F(8,115) = 4.323, p &lt; .001*</td>
<td>F(8,116) = 2.096, p = .042*</td>
<td>F(8,116) = 4.275, p &lt; .001*</td>
<td>F(8,115) = 2.511, p = .015*</td>
</tr>
<tr>
<td>T1 CES-D</td>
<td>β = .372, t = 4.178, p &lt; .001*</td>
<td>β = .319, t = 3.706, p &lt; .001*</td>
<td>β = .305, t = 3.343, p = .001*</td>
<td>β = .466, t = 5.609, p &lt; .001*</td>
<td>β = .254, t = 2.791, p = .006*</td>
</tr>
<tr>
<td>Gender</td>
<td>n.s.</td>
<td>β = .254, t = 3.053, p = .003*</td>
<td>β = .197, t = 2.196, p = .030*</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Handedness</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>ISS v CSS</td>
<td>n.s.</td>
<td>β = .233, t = 1.986, p = .049*n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>CSS v TAFE</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>TAFE v UGrad</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>UGrad v PGrad</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Step 2</td>
<td>R^2 = .388(.338), R^2Δ= .193R^2 = .306(251), R^2Δ = .074R^2 = .234(.174), R^2Δ = .108R^2 = .501(462), R^2Δ = .274</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F(1,111) = 34.923, p &lt; .001*</td>
<td>F(1,114) = 12.225, p = .001*</td>
<td>F(1,115) = 16.199, p &lt; .001*</td>
<td>F(1,115) = 63.085, p &lt; .001*</td>
<td>F(1,114) = 11.765, p = .001*</td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td>β = .454, t = 5.910, p &lt; .001*</td>
<td>β = .277, t = 3.496, p = .001*</td>
<td>β = .333, t = 4.025, p &lt; .001*</td>
<td>β = .542, t = 7.493, p &lt; .001*</td>
<td>β = .288, t = 3.430, p = .001*</td>
</tr>
<tr>
<td></td>
<td>Step 3</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

^aR^2(Adjusted R^2)^  
^bMales = 0, Females = 1  
^cISS = Incomplete Secondary School, CSS = Complete Secondary School, UGrad = Undergraduate Degree, PGrad = Postgraduate Degree  
*Significant at α=.05
### Table 28

Result of regressions predicting Time 2 CES-D with covariates, an independent variable of CTQ Abuse, and an interaction term of Abuse and gender

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Depressed Affect</th>
<th>Somatic</th>
<th>Wellbeing</th>
<th>Interpersonal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² = .203(.147) a,  R²Δ = .203R² = .223(.169), R²Δ = .223R² = .147(.087), R²Δ = .147R² = .228(.174), R²Δ = .228R² = .149(.089), R²Δ = .149</td>
<td>.203(.147)</td>
<td>.203R² = .223(.169)</td>
<td>.223R² = .147(.087)</td>
<td>.223R² = .228(.174)</td>
<td>.228R² = .149(.089)</td>
</tr>
<tr>
<td>F(8,114) = 3.634, p = .001*</td>
<td>F(8,115) = 4.135, p &lt; .001*</td>
<td>F(8,113) = 2.442, p = .018*</td>
<td>F(8,116) = 4.275, p &lt; .001*</td>
<td>F(8,115) = 2.511, p = .015*</td>
<td></td>
</tr>
<tr>
<td><strong>T1 CES-D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .384, t = 4.418, p &lt; .001*</td>
<td>β = .285, t = 3.295, p = .001*</td>
<td>β = .318, t = 3.494, p = .001*</td>
<td>β = .466, t = 5.609, p &lt; .001*</td>
<td>β = .254, t = 2.791, p &lt; .001*</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong> b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .198, t = 2.332, p = .021*</td>
<td>β = .275, t = 3.299, p = .011*</td>
<td>β = .233, t = 2.589, p = .011*</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS v CSS c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .230, t = 1.953, p = .053</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSS v TAFE</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE v UGrad</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGrad v PGrad</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² = .466(.424), R²Δ = .263R² = .342(.387), R²Δ = .320(.265), R²Δ = .172R² = .402(.356), R²Δ = .175R² = .293(.238), R²Δ = .145</td>
<td>.466(.424)</td>
<td>.263R² = .342(.387)</td>
<td>.320(.265)</td>
<td>.172R² = .402(.356)</td>
<td>.175R² = .293(.238)</td>
</tr>
<tr>
<td>F(1,113) = 55.715, p &lt; .001*</td>
<td>F(1,114) = 41.761, p &lt; .001*</td>
<td>F(1,112) = 28.393, p &lt; .001*</td>
<td>F(1,115) = 33.641, p &lt; .001*</td>
<td>F(1,114) = 23.331, p &lt; .001*</td>
<td></td>
</tr>
<tr>
<td><strong>CTQ Abuse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .581, t = 7.464, p &lt; .001*</td>
<td>β = .499, t = 6.462, p &lt; .001*</td>
<td>β = .453, t = 5.329, p &lt; .001*</td>
<td>β = .448, t = 5.800, p &lt; .001*</td>
<td>β = .409, t = 4.830, p &lt; .001*</td>
<td></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² = .487(.441), R²Δ = .021</td>
<td>.487(.441)</td>
<td>R²Δ = .021</td>
<td>.487(.441)</td>
<td>.369(.312), R²Δ = .049</td>
<td>n.s.</td>
</tr>
<tr>
<td>F(1,112) = 4.480, p = .037*</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td>β = .244, t = 2.117, p = .037*n.s.</td>
<td>β = .041, t = 2.932, p = .004*n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² = .295(.198), R²Δ = .141</td>
<td>.295(.198)</td>
<td>R²Δ = .141</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>F(1,58) = 11.582, p = .001*</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>CTQ Abuse Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .391, t = 3.403, p = .001*n.s.</td>
<td>β = .103, t = .823, p = .414</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² = .682(.628), R²Δ = .268</td>
<td>.682(.628)</td>
<td>R²Δ = .268</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>F(1,47) = 39.679, p &lt; .001*n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>CTQ Abuse Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β = .637, t = 6.299, p &lt; .001*n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

---

*Adjusted R²*

* Males = 0, Females = 1

ISS = Incomplete Secondary School, CSS = Complete Secondary School, UGrad = Undergraduate Degree, PGrad = Postgraduate Degree

*Significant at α=.05
7.6.2 KSADS-PL depressive disorders

Two binary logistic regressions were conducted with KSADS-PL Depressive Disorder diagnosis (absent or present) as the outcome variable, and gender, handedness, age and parent education as covariates. The independent variables were CTQ Neglect or Abuse, and a gender by CTQ interaction term.

Table 29

Structure of KSADS-PL depressive disorders by CTQ logistic regression models

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Gender</td>
</tr>
<tr>
<td></td>
<td>Handedness</td>
</tr>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Parent Education</td>
</tr>
<tr>
<td>Step 2</td>
<td>CTQ Variable</td>
</tr>
<tr>
<td>Step 3</td>
<td>CTQ Variable x Gender</td>
</tr>
</tbody>
</table>

7.6.2.1 CTQ Neglect and KSADS-PL depressive disorders

A main effect for CTQ Neglect was observed; greater reported Neglect increased the likelihood of receiving a KSADS-PL diagnosis of depressive disorder at Time 2. Covariates of age and parent education also predicted diagnostic status; older age conferred less likelihood of diagnosis, while having parents with incomplete secondary school education increased the likelihood of diagnosis when compared with having complete secondary school educated parents.
### Table 30

**Results of logistic regression predicting KSADS-PL depressive disorder diagnosis from CTQ Neglect**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>e^β</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS v CSS</td>
<td>-2.352</td>
<td>1.188</td>
<td>3.923</td>
<td>1</td>
<td>.048*</td>
<td>.095</td>
</tr>
<tr>
<td>Age</td>
<td>- .005</td>
<td>.002</td>
<td>5.230</td>
<td>1</td>
<td>.022*</td>
<td>.995</td>
</tr>
<tr>
<td>Neglect</td>
<td>1.860</td>
<td>.854</td>
<td>4.746</td>
<td>1</td>
<td>.029*</td>
<td>6.422</td>
</tr>
</tbody>
</table>

*Significant at α=.05

### 7.6.2.2 Abuse

CTQ Abuse also predicted caseness; greater reported Abuse was associated with increased likelihood of depressive disorder at Time 2. As above, older age conferred less likelihood of diagnosis, while having parents with incomplete secondary school education increased the likelihood of diagnosis when compared with having complete secondary school educated parents.

### Table 31

**Results of logistic regression predicting KSADS-PL depressive disorder diagnosis from CTQ Abuse**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>e^β</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS v CSS</td>
<td>-2.352</td>
<td>1.188</td>
<td>3.923</td>
<td>1</td>
<td>.048*</td>
<td>.095</td>
</tr>
<tr>
<td>Age</td>
<td>- .005</td>
<td>.002</td>
<td>5.230</td>
<td>1</td>
<td>.022*</td>
<td>.995</td>
</tr>
<tr>
<td>Abuse</td>
<td>3.952</td>
<td>1.215</td>
<td>10.583</td>
<td>1</td>
<td>.001*</td>
<td>52.045</td>
</tr>
</tbody>
</table>

*Significant at α=.05

*ISS = Incomplete Secondary School, CSS = Complete Secondary School (Parent Education)*
7.7 Research Question 2: Are childhood neglect and abuse reflected in adolescent neuroanatomy?

Neuroanatomical regions of interest were entered as the dependent variables in a series of hierarchical regression models, the structure of which are described in Table 32 below. Gender, parent education, handedness, and age were entered as covariates, with CTQ scales as independent variables.

Table 32

Structure of region of interest by CTQ linear regression models

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Region of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>CTQ Variable</th>
</tr>
</thead>
</table>

| Step 3            | CTQ Variable x Gender                     |

7.7.1 CTQ Neglect

Predictive relationships were found between three regions of interest (all interacting with gender) and CTQ Neglect. There were no significant predictive relationships between any Step 1 covariates and Neglect scores for any of these three region.

7.7.1.1 Left dorsal paracingulate volume and CTQ Neglect

A significant interaction was found between gender and CTQ Neglect in predicting left dorsal paracingulate volume, such that greater reports of neglect were associated with larger left dorsal paracingulate volumes for females, although the relationship was only observed at a trend level. While the opposite appeared to apply to males, the relationship was not significant (see Table 33 and Figure 20).
Table 33

Results of linear regression predicting left dorsal paracingulate from CTQ Neglect

<table>
<thead>
<tr>
<th>CTQ Neglect x Left Dorsal Paracingulate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 3</strong> R² = .109(.044), R²Δ= .036 F(1,125) = 5.056, p = .026*</td>
</tr>
<tr>
<td>Interaction β= .282, t = 2.249, p = .026*</td>
</tr>
<tr>
<td><strong>Step 2 Male</strong> R² = .146(.055), R²Δ= .019 F(1,65) = 1.419, p = .238</td>
</tr>
<tr>
<td>Neglect Male β= -.145, t = - 1.191, p = .238</td>
</tr>
<tr>
<td><strong>Step 2 Female</strong> R² = .184(.078), R²Δ= .052 F(1,54) = 3.415, p = .070</td>
</tr>
<tr>
<td>Neglect Female β= .247, t = 1.848, p = .070</td>
</tr>
</tbody>
</table>

*R² (Adjusted R²)

*Significant at α=.05

---

**Figure 20.** Interaction between gender and CTQ Neglect in predicting left dorsal paracingulate volume.

### 7.7.1.2 Right rostral cingulate volume and CTQ Neglect

A significant interaction between gender and CTQ Neglect was also observed to predict right rostral cingulate volume. High levels of neglect were predictive of larger right rostral cingulate
volumes for girls. While the opposite appeared to occur for boys, only the relationship for females was significant (see Table 34 and Figure 21).

Table 34

Results of linear regression predicting right rostral cingulate volume from CTQ Neglect

<table>
<thead>
<tr>
<th>CTQ Neglect x Right Rostral Cingulate</th>
<th>Step 3</th>
<th>R² = .069(.002)², R²Δ = .043 F(1,125) = 5.783, p = .018*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction</td>
<td>β = .312, t = 2.405, p = .018*</td>
<td></td>
</tr>
<tr>
<td>Step 2 Male</td>
<td>R² = .061(-.040), R²Δ = .037 F(1,65) = 2.571, p = .114</td>
<td></td>
</tr>
<tr>
<td>Neglect Male</td>
<td>β = -.206, t = -1.603, p = .114</td>
<td></td>
</tr>
<tr>
<td>Step 2 Female</td>
<td>R² = .123(.009), R²Δ = .044 F(1,54) = 2.736, p = .014*</td>
<td></td>
</tr>
<tr>
<td>Neglect Female</td>
<td>β = .225, t = 1.654, p = .014*</td>
<td></td>
</tr>
</tbody>
</table>

*R²(Adjusted R²)

*Significant at α=.05

Figure 21.

Interaction between gender and CTQ Neglect in predicting right rostral cingulate volume.
7.7.1.3 Corpus callosum midlength and CTQ Neglect

A significant interaction between gender and CTQ Neglect predicted corpus callosum midlength (see Table 35 and Figure 22). High levels of neglect were predictive of greater corpus callosum midlength for females only. There was no relationship between childhood neglect and corpus callosum midlength for males.

Table 35

Results of linear regression predicting corpus callosum midlength from CTQ Neglect

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>ΔR²</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>.108</td>
<td>.042</td>
<td>5.855</td>
<td>.017*</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Neglect</td>
<td>-.148</td>
<td>.247</td>
<td>1.363</td>
<td>.247</td>
</tr>
<tr>
<td>Female Neglect</td>
<td>.328</td>
<td>.019</td>
<td>5.840</td>
<td>.019*</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Neglect</td>
<td>.328</td>
<td>.019</td>
<td>5.840</td>
<td>.019*</td>
</tr>
</tbody>
</table>

*Adjusted R² (aR²)

*Significant at α=.05

Figure 22.

Interaction between gender and CTQ Neglect in predicting corpus callosum midlength.
7.7.2 CTQ Abuse

Predictive relationships were found between four regions of interest (all interacting with gender) and CTQ Abuse. There were no significant predictive relationships between any Step 1 covariate and Abuse scores for any of these four regions.

7.7.2.1 Left amygdala volume and CTQ abuse

There was an interaction between CTQ Abuse and gender in predicting left amygdala volume. Separate gender analyses revealed that a significant relationship existed for males only, such that greater reported abuse predicted smaller left amygdala volumes (see Table 36 and Figure 23).

Table 36

<table>
<thead>
<tr>
<th>Results of regression predicting left amygdala volume from CTQ Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTQ Abuse x Left Amygdala</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
<tr>
<td>Interaction</td>
</tr>
<tr>
<td><strong>Step 2 Male</strong></td>
</tr>
<tr>
<td>Abuse Male</td>
</tr>
<tr>
<td><strong>Step 2 Female</strong></td>
</tr>
<tr>
<td>Abuse Female</td>
</tr>
</tbody>
</table>

*R2(Adjusted R2)

*Significant at $\alpha=.05$
Corrected for whole brain volume

Figure 23. Interaction between gender and CTQ Abuse in predicting left amygdala volume.

7.7.2.2 Left rostral cingulate volume and CTQ Abuse
A main effect was found whereby greater reported abuse predicted larger left rostral cingulate ACC volumes. Based on a strong trend for an interaction with gender, separate gender analyses were conducted, which revealed that the above relationship was only significant for males (see Table 37 and Figure 24).
### Table 37

**Results of linear regression predicting left rostral cingulate volume from CTQ Abuse**

<table>
<thead>
<tr>
<th></th>
<th>Step 2</th>
<th></th>
<th>Step 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2\Delta$</td>
<td>$F(1,126)$</td>
<td>$p$</td>
</tr>
<tr>
<td><strong>Region of Interest</strong></td>
<td>.109</td>
<td>.029</td>
<td>4.033</td>
<td>.047*</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>.175</td>
<td></td>
<td>2.008</td>
<td>.047*</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td>.134</td>
<td>.024</td>
<td>3.500</td>
<td>.064</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>-.259</td>
<td></td>
<td>-1.871</td>
<td>.064</td>
</tr>
<tr>
<td><strong>Abuse Male</strong></td>
<td>.176</td>
<td>.074</td>
<td>5.807</td>
<td>.019*</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>.277</td>
<td></td>
<td>2.410</td>
<td>.019*</td>
</tr>
<tr>
<td><strong>Abuse Female</strong></td>
<td>.158</td>
<td>.002</td>
<td>.100</td>
<td>.753</td>
</tr>
<tr>
<td><strong>β</strong></td>
<td>.042</td>
<td></td>
<td>.317</td>
<td>.753</td>
</tr>
</tbody>
</table>

*Significant at $\alpha=.05$

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted $R^2$</strong></td>
<td>$R_2^*$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 24.** Interaction between gender and CTQ Abuse in predicting left rostral cingulate volume.

*Corrected for whole brain volume*
7.7.2.3 Left dorsal cingulate volume and CTQ Abuse

An interaction between CTQ Abuse and gender was found to predict left dorsal cingulate volume. Separate analyses for males and females indicated that for males only, higher levels of reported abuse predicted larger left dorsal cingulate volumes (see Table 38 and Figure 25).

Table 38

Results of linear regression predicting left dorsal cingulate volume from CTQ Abuse

<table>
<thead>
<tr>
<th>CTQ Abuse x Left Dorsal Cingulate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 3</strong> R² = .114(.050)⁹, R²Δ = .034, F(1,124) = 4.739, p = .031*</td>
<td></td>
</tr>
<tr>
<td>Interaction β = -.337, t = -2.177, p = .031*</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Male</strong> R² = .244(.163), R²Δ = .057, F(1,65) = 4.910, p = .030*</td>
<td></td>
</tr>
<tr>
<td>Abuse Male β = .242, t = 2.216, p = .030*</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Female</strong> R² = .082(-.039), R²Δ = .012, F(1,53) = .712, p = .402</td>
<td></td>
</tr>
<tr>
<td>Abuse Female β = -.119, t = -.844, p = .402</td>
<td></td>
</tr>
</tbody>
</table>

⁹R²(Adjusted R²)
*Significant at α=.05

*Corrected for whole brain volume

Figure 25. Interaction between gender and CTQ Abuse in predicting left dorsal cingulate volume.
7.7.2.4 Corpus callosum midlength and CTQ Abuse

A main effect was found whereby greater levels of reported abuse predicted greater corpus callosum midlength. A gender interaction was also significant; separate analyses for males and females revealed that the above relationship was only significant for females (see Table 39 and Figure 26.).

Table 39

Results of linear regression predicting corpus callosum midlength from CTQ Abuse

<table>
<thead>
<tr>
<th>CTQ Abuse x Corpus Callosum Midlength</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>R² = .095(.037)², R²Δ = .057, F(1,125) = 7.940, p = .006*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest</td>
<td>β = .250, t = 2.818, p = .006*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>R² = .127(.064), R²Δ = .033, F(1,124) = 4.629, p = .033*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>β = .287, t = 2.151, p = .033*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Male</td>
<td>R² = .051(-.051), R²Δ = .000, F(1,65) = .027, p = .870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse Male</td>
<td>β = .020, t = .164, p = .870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Female</td>
<td>R² = .256(.158), R²Δ = .188, F(1,53) = 13.386, p = .001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse Female</td>
<td>β = .646, t = 3.659, p = .001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²R²(Adjusted R²)

*Significant at α=.05

Table 39

<table>
<thead>
<tr>
<th>CTQ Abuse x Corpus Callosum Midlength</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>R² = .095(.037)², R²Δ = .057, F(1,125) = 7.940, p = .006*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest</td>
<td>β = .250, t = 2.818, p = .006*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>R² = .127(.064), R²Δ = .033, F(1,124) = 4.629, p = .033*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>β = .287, t = 2.151, p = .033*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Male</td>
<td>R² = .051(-.051), R²Δ = .000, F(1,65) = .027, p = .870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse Male</td>
<td>β = .020, t = .164, p = .870</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Female</td>
<td>R² = .256(.158), R²Δ = .188, F(1,53) = 13.386, p = .001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abuse Female</td>
<td>β = .646, t = 3.659, p = .001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*R²(Adjusted R²)

*Significant at α=.05

Figure 26. Interaction between gender and CTQ Abuse in predicting corpus callosum midlength.
7.8 Research Question 3: What neuroanatomical correlates of depressive symptomatology can be observed prior to onset?

A series of hierarchical linear regressions was conducted, using Time 2 CES-D scales as the independent variables. The corresponding Time 1 questionnaire data was entered in Step 1 so that in subsequent analyses, influence of Time 1 symptom level was controlled for, making the dependent variable in effect a measure of symptom change between the two time points. Gender, handedness, parent education and age at scan were entered as covariates, with neuroanatomical regions of interest and interactions with gender as the independent variables.

Table 40

Structure of CES-D by region of interest linear regressions

<table>
<thead>
<tr>
<th>DV</th>
<th>Time 2 CES-D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Time 1 CES-D</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>Region of Interest</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>Region of Interest x Gender</td>
</tr>
</tbody>
</table>

7.8.1 CES-D Total

One region of interest predicted CES-D Total symptom change.

7.8.1.1 Right rostral cingulate volume and CES-D Total

There was a positive relationship between CES-D Total symptom change and right rostral cingulate volume. Larger right rostral cingulate volume predicted increase in CES-D Total depressive symptoms from Time 1 to Time 2. Time 1 CES-D Total scores also strongly predicted Time 2 scores, and female gender predicted an increase in CES-D Total score. Regression results are given in Table 41 below.
Table 41

Results of linear regression predicting CES-D Total symptom change from right rostral cingulate volume

<table>
<thead>
<tr>
<th>CES-D Total x Right Rostral Cingulate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Time 1 CES-D</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
</tr>
<tr>
<td><strong>Region of Interest</strong></td>
</tr>
</tbody>
</table>

---

Figure 27. Right rostral cingulate volume and CES-D Total residual score for males and females.

7.8.2 CES-D Depressed Affect

Two regions of interest predicted change in CES-D Depressed Affect scores, the right hippocampus and left ventral cingulate.

---

This marginal finding was interpreted as significant, given the exploratory nature of this research.
In each of these regressions, Time 2 CES-D Depressed Affect was strongly predicted by Time 1 CES-D Depressed Affect. Female gender also predicted increased CES-D Depressed Affect. Finally, level of parental education predicted increase in CES-D Depressed Affect; having TAFE educated parents predicted symptom increase, as compared with undergraduate parent education.

7.8.2.1 Right hippocampus volume and CES-D Depressed Affect

A significant gender by right hippocampus interaction was found in predicting CES-D Depressed Affect symptom change. Separate gender analyses revealed that a significant predictive relationship existed only for females, such that smaller right hippocampi predicted increase in CES-D Depressed Affect.

Table 42

Results of linear regression predicting CES-D Depressed Affect symptom change from right hippocampus volume

<table>
<thead>
<tr>
<th>CES-D Depressed Affect x Right Hippocampus</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Time 1 Depressed Affect</td>
<td>β = .307, t = 3.599, p &lt; .001*</td>
<td>Gender (b)</td>
<td>β = .300, t = 3.568, p = .001*</td>
</tr>
<tr>
<td></td>
<td>TAFE v UGrad (c)</td>
<td>β = -.236, t = -2.288, p = .024*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 3</td>
<td>R² = .289(.225), R²Δ = .034, F(1,110) = 5.237, p = .024*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest Male</td>
<td>β &lt; .001, t = -.003, p = .997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest Female</td>
<td>β = -.251, t = -2.271, p = .028*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Male</td>
<td>R² = .077(-.053), R²Δ &lt; .001, F(1,57) &lt; .001, p = .997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest Male</td>
<td>β &lt; .001, t = -.003, p = .997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest Female</td>
<td>β = -.251, t = -2.271, p = .028*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Adjusted R²
\(b\) Males = 0, Females = 1
\(c\) UGrad = Undergraduate Degree

*Significant at \(\alpha=.05\)
Figure 28. Interaction between gender and right hippocampus volume in predicting CES-D Depressed Affect symptom change.

7.8.2.2 Left ventral cingulate volume and CES-D Depressed Affect

A significant gender by left ventral cingulate volume interaction was found in predicting CES-D Depressed Affect symptom change. Separate gender analyses revealed that a significant predictive relationship existed for females, such that larger left ventral cingulate predicted increase in CES-D Depressed Affect.
Table 43

Results of linear regression predicting CES-D Depressed Affect symptom change from left ventral cingulate volume

<table>
<thead>
<tr>
<th>CES-D Depressed Affect x Left Ventral Cingulate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
</tr>
<tr>
<td>Time 1 Depressed Affect</td>
<td>(R^2 = .218(.163), R^2_\Delta = .218, F(8,114) = 3.972, p &lt; .001^*)</td>
</tr>
<tr>
<td>Gender</td>
<td>(\hat{\beta} = .271, t = 3.091, p = .003^*)</td>
</tr>
<tr>
<td>TAFE v UGrad</td>
<td>(\hat{\beta} = .280, t = 3.331, p = .001^*)</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
</tr>
<tr>
<td>Time 2 Depressed Affect</td>
<td>(\hat{\beta} = .111(-.014), R^2_\Delta = .032, F(1,57) = 2.065, p = .156)</td>
</tr>
<tr>
<td>Region of Interest Male</td>
<td>(\hat{\beta} = -.186, t = -1.437, p = .156)</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td></td>
</tr>
<tr>
<td>Time 3 Depressed Affect</td>
<td>(\hat{\beta} = .226, t = 1.973, p = .054)</td>
</tr>
</tbody>
</table>

\(^a_{R^2}(Adjusted R^2)\)

\(^b_{Males = 0, Females = 1}\)

\(^c_{UGrad = Undergraduate Degree}\)

\(^*_{Significant at \alpha=.05}\)

*Corrected for whole brain volume

Figure 29. Interaction between gender and left ventral cingulate volume in predicting CES-D Depressed Affect symptom change.

\(^3_{This marginal finding was interpreted as significant, given the exploratory nature of this research.}\)
7.8.3 CES-D Somatic

Two volumetric measures were also found to predict CES-D Somatic symptom change; left ventral cingulate, and right orbitofrontal cortex (within which right lateral orbitofrontal cortex was found to account for much of the relationship). In each of these analyses, Time 2 CES-D Somatic score was positively predicted by Time 1 score.

7.8.3.1 Left ventral cingulate volume and CES-D Somatic

A main effect for left ventral cingulate indicated that smaller volumes predicted greater increase in Somatic symptoms.

Table 44

Results of linear regression predicting CES-D Somatic symptom change from left ventral cingulate volume

<table>
<thead>
<tr>
<th>CES-D Somatic x Left Ventral Cingulate</th>
<th>Step 1</th>
<th>R² = .168(.108), R²Δ = .168 F(8,111) = 2.801, p = .007*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1 Somatic</td>
<td>β = .360, t = 3.987, p &lt; .001*</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>R² = .199(.133), R²Δ = .031 F(1,110) = 4.266, p = .041*</td>
<td></td>
</tr>
<tr>
<td>Region of Interest</td>
<td>β = -.182, t = -2.065, p = .041*</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

*R² (Adjusted R²)
*S*Significant at α=.05

This finding, that increase in Somatic symptoms was predicted by reduction in left ventral cingulate, appeared to be in direct contradiction with the finding that increase in Depressed Affect was predicted by enlargement in the left ventral cingulate, in females. In order to clarify the nature of this finding, separate analyses for females and males were conducted. These analyses showed that the main effect was driven by a pattern in males such that larger left cingulate volume in males was associated with Somatic symptom decrease.
Additional results of linear regression predicting CES-D Somatic symptom change from left ventral cingulate volume, divided by gender

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2 R²</td>
<td>.318 (.220)</td>
<td>.494 (.244)</td>
</tr>
<tr>
<td>Step 2 R² Δ</td>
<td>.081</td>
<td>.000</td>
</tr>
<tr>
<td>F(1,56)</td>
<td>6.614</td>
<td>0.021</td>
</tr>
<tr>
<td>p</td>
<td>.013*</td>
<td>.887</td>
</tr>
<tr>
<td>Region of Interest Male β</td>
<td>- .642, t = -2.572, p = .013*</td>
<td>.045, t = .143, p = .887</td>
</tr>
</tbody>
</table>

*R² (Adjusted R²)

*Significant at α=.05

Figure 30. Left ventral cingulate volume predicting CES-D Somatic symptom change, divided by gender.
This was the only finding which appeared to indicate that the volume of a structure specifically predicted decrease of depressive symptoms. In order to further explore this, a hierarchical linear regression was conducted with Somatic symptoms at Time 1 as the dependent variable, and gender, handedness, parent education, left ventral cingulate and the volume x gender interaction term as predictors. A null finding from this analysis indicated that left ventral cingulate volume did not predict Somatic symptoms at Time 1.

Table 46

Results of linear regression predicting CES-D Somatic symptoms at Time 1 from left ventral cingulate volume

<table>
<thead>
<tr>
<th>CES-D Somatic Time 1 x Left Ventral Cingulate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>(R^2 = .141(.089)^a), (R^2\Delta = .141) (F(7,115) = 2.703, p = .012^*)</td>
</tr>
<tr>
<td>Gender</td>
<td>(\beta = -.244, t = -2.785, p = .006^*)</td>
</tr>
<tr>
<td>Step 2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Step 3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

\(R^2(Adjusted R^2)\)

*Significant at \(\alpha=0.05\)

7.8.3.2 Right orbitofrontal cortex volume and CES-D Somatic

There was an interaction between right orbitofrontal cortex and gender in predicting CES-D Somatic symptom change. Separate gender analyses revealed that a relationship existed only for females, such that larger right orbitofrontal cortex volume predicted increase in somatic symptoms. Right lateral and medial orbitofrontal cortex were entered separately as independent variables; only right lateral orbitofrontal cortex showed a relationship with CES-D Somatic Symptoms, at a trend level. For females only, larger right lateral orbitofrontal cortex was associated with increase in somatic symptoms.
Results of linear regressions predicting CES-D Somatic symptom change from right orbitofrontal cortex (OFC) and right lateral orbitofrontal cortex volumes

<table>
<thead>
<tr>
<th>CES-D Somatic</th>
<th>Right OFC</th>
<th>Right Lateral OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>$R^2 = .167(.108)^a$, $R^2\Delta = .167$</td>
<td>$R^2 = .160(.101)$, $R^2\Delta = .160$</td>
</tr>
<tr>
<td></td>
<td>$F(8,113) = 2.827$, $p = .007^*$</td>
<td>$F(8,114) = 2.720$, $p = .009^*$</td>
</tr>
<tr>
<td><strong>Time 1 Somatic</strong></td>
<td>$\beta = .350, t = 3.919, p &lt; .001^*$</td>
<td>$\beta = .337, t = 3.776, p &lt; .001^*$</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>$R^2 = .206(.134)$, $R^2\Delta = .039$</td>
<td>$R^2 = .195(.123)$, $R^2\Delta = .033$</td>
</tr>
<tr>
<td></td>
<td>$F(1,111) = 5.431$, $p = .022^*$</td>
<td>$F(1,112) = 4.630$, $p = .034^*$</td>
</tr>
<tr>
<td><strong>Interaction</strong></td>
<td>$\beta = .260, t = 2.330, p = .022^*$</td>
<td>$\beta = .234, t = 2.152, p = .034^*$</td>
</tr>
<tr>
<td><strong>Step 2 Male</strong></td>
<td>$R^2 = .198(.087)$, $R^2\Delta = .029$</td>
<td>$R^2 = .187(.075)$, $R^2\Delta = .018$</td>
</tr>
<tr>
<td></td>
<td>$F(1,58) = 2.097$, $p = .153$</td>
<td>$F(1,58) = 1.291$, $p = .260$</td>
</tr>
<tr>
<td><strong>Region of Interest Male</strong></td>
<td>$\beta = -.173, t = -1.448, p = .153$</td>
<td>$\beta = -.138, t = -1.136, p = .260$</td>
</tr>
<tr>
<td><strong>Step 2 Female</strong></td>
<td>$R^2 = .336(.221)$, $R^2\Delta = .061$</td>
<td>$R^2 = .312(.194)$, $R^2\Delta = .053$</td>
</tr>
<tr>
<td></td>
<td>$F(1,46) = 4.214$, $p = .046^*$</td>
<td>$F(1,47) = 3.615$, $p = .063$</td>
</tr>
<tr>
<td><strong>Region of Interest Female</strong></td>
<td>$\beta = .255, t = 2.053, p = .046^*$</td>
<td>$\beta = .234, t = 1.901, p = .063$</td>
</tr>
</tbody>
</table>

$^aR^2$ (Adjusted $R^2$)

*Significant at $\alpha=.05$

Figure 31. Interaction between gender and right orbitofrontal cortex volume in predicting CES-D Somatic symptom change.
7.8.4 CES-D Wellbeing

Six regions of interest were found to predict CES-D Wellbeing symptom change. In all cases, Time 1 CES-D Wellbeing positively predicted Time 2 CES-D Wellbeing. No other Step 1 variable was found to predict Wellbeing.

7.8.4.1 Right hippocampus volume and CES-D Wellbeing

There was an interaction between gender and right hippocampus volume in predicting CES-D Wellbeing symptom change, however separate analyses for males and females revealed no predictive relationship between right hippocampus and Wellbeing in either group.

Table 48

Results of linear regression predicting CES-D Wellbeing symptom change from right hippocampus volume

<table>
<thead>
<tr>
<th>CES-D Wellbeing x Right Hippocampus</th>
<th>Step 1</th>
<th>$R^2 = .247(.194)^2$, $R^2\Delta = .247$, $F(8,114) = 4.680$, $p &lt; .001^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1 Wellbeing</td>
<td>$\beta = .478$, $t = 5.773$, $p &lt; .001^*$</td>
</tr>
<tr>
<td></td>
<td>Step 3</td>
<td>$R^2 = .281(.217)$, $R^2\Delta = .029$, $F(1,112) = 4.508$, $p = .036^*$</td>
</tr>
<tr>
<td></td>
<td>Interaction</td>
<td>$\beta = -.217$, $t = -2.123$, $p = .036^*$</td>
</tr>
<tr>
<td></td>
<td>Step 2 Male</td>
<td>$R^2 = .309(.215)$, $R^2\Delta = .034$, $F(1,59) = 2.901$, $p = .094$</td>
</tr>
<tr>
<td></td>
<td>Wellbeing Male</td>
<td>$\beta = .205$, $t = 1.703$, $p = .094$</td>
</tr>
<tr>
<td></td>
<td>Step 2 Female</td>
<td>$R^2 = .311(.196)$, $R^2\Delta &lt; .001$, $F(1,48) = .025$, $p = .876$</td>
</tr>
<tr>
<td></td>
<td>Wellbeing Female</td>
<td>$\beta = .020$, $t = .157$, $p = .876$</td>
</tr>
</tbody>
</table>

$^aR^2$ (Adjusted $R^2$)

*Significant at $\alpha = .05$
Corrected for whole brain volume

Figure 32. Interaction between gender and right hippocampus volume in predicting CES-D Wellbeing symptom change.

7.8.4.2 Left dorsal paracingulate volume and CES-D Wellbeing
There was an interaction between gender and left dorsal paracingulate volume in predicting CES-D Wellbeing symptom change. Separate regressions for males and females revealed that for females only, larger left dorsal paracingulate volume was associated with increase in Wellbeing symptoms.
Table 49

Results of linear regression predicting CES-D Wellbeing symptom change from left dorsal paracingulate volume

<table>
<thead>
<tr>
<th>CES-D Wellbeing x Left Dorsal Paracingulate</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>$R^2 = .228(.174)^a$, $R^2 \Delta = .228$, $F(8,116) = 4.275$, $p &lt; .001^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 Wellbeing</td>
<td>$\beta = .466, t = 5.609, p &lt; .001^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>$R^2 = .264(.200), R^2 \Delta = .031, F(1,114) = 4.798, p = .031^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>$\beta = .233, t = 2.191, p = .031^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Male</td>
<td>$R^2 = .276(.177), R^2 \Delta = .001, F(1,59) = .048, p = .827$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wellbeing Male</td>
<td>$\beta = -.026, t = -.220, p = .827$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2 Female</td>
<td>$R^2 = .387(.284), R^2 \Delta = .076, F(1,48) = 5.963 p = .018^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wellbeing Female</td>
<td>$\beta = .302, t = 2.442, p = .018^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^aR^2$ (Adjusted $R^2$)

*Significant at $\alpha=.05$

Figure 33. Interaction between gender and left dorsal paracingulate volume in predicting CES-D Wellbeing symptom change.

*Corrected for whole brain volume
7.8.4.3 Left dorsal cingulate volume and CES-D Wellbeing

A main effect was indicated, whereby smaller left dorsal cingulate was associated with increase in Wellbeing symptoms.

Table 50

Results of linear regression predicting CES-D Wellbeing Symptom change from left dorsal cingulate volume

<table>
<thead>
<tr>
<th>Step</th>
<th>$R^2$</th>
<th>$R^2\Delta$</th>
<th>$F_{(8,116)}$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>.228(.174)</td>
<td>.228,</td>
<td>4.275,</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Time 1 Wellbeing</td>
<td>$\beta = .466$, t = 5.609, p &lt; .001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>.257(.199)</td>
<td>.029,</td>
<td>4.548,</td>
<td>.035*</td>
</tr>
<tr>
<td>Region of Interest</td>
<td>$\beta = -.178$, t = -2.133, p = .035*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a corrected for whole brain volume

**Figure 34.** Main effect of left dorsal cingulate volume in predicting CES-D Wellbeing symptom change.
7.8.4.4 Right rostral cingulate volume and CES-D Wellbeing

A main effect for right rostral cingulate indicated that larger volumes were associated with greater Wellbeing symptom change. As there was also a significant interaction between right rostral cingulate and gender, separate analyses were conducted for males and females. The relationship only reached significance in females.

Table 51

Results of linear regression predicting CES-D Wellbeing symptom change from right rostral cingulate

<table>
<thead>
<tr>
<th>CES-D Wellbeing x Right Rostral Cingulate</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td>$R^2 = .228(.174)$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$R^2\Delta = .228$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(8,116) = 4.275$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1 Wellbeing</td>
<td>$\beta = .466$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = 5.609$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>$R^2 = .257(.199)$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$R^2\Delta = .029$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(1,115) = 4.488$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .036^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region of Interest</td>
<td>$\beta = .173$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = 2.118$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .036^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>$R^2 = .287(.225)$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$R^2\Delta = .031$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(1,114) = 4.886$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .029^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>$\beta = .241$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = 2.210$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .029^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Male</strong></td>
<td>$R^2 = .275(.177)$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$R^2\Delta = .000$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(1,59) = .024$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .878$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wellbeing Male</td>
<td>$\beta = .018$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = .154$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .878$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step 2 Female</strong></td>
<td>$R^2 = .399(.299)$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$R^2\Delta = .089$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(1,48) = 7.099$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .010^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wellbeing Female</td>
<td>$\beta = .321$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$t = 2.664$,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = .010^*$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*R' (Adjusted R')

*Significant at $\alpha = .05$
Figure 35. Main effect of right rostral cingulate volume in predicting CES-D Wellbeing symptom change

7.8.4.5 Corpus callosum midlength and CES-D Wellbeing
A main effect was found, such that greater corpus callosum midlength was associated with increase in CES-D Wellbeing symptoms.

Table 52

Results of linear regression predicting CES-D Wellbeing symptom change from corpus callosum midlength

<table>
<thead>
<tr>
<th>CES-D Wellbeing x Corpus Callosum Midlength</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
</tr>
<tr>
<td>Time 1 Wellbeing</td>
<td>( \beta = .476, t = 5.678, p &lt; .001^* )</td>
</tr>
<tr>
<td>Region of Interest</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
</tr>
<tr>
<td>( R^2 = .284(.227), R^2\Delta = .049, F(1,113) = 7.792, p = .006^* )</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\text{Significant at } \alpha=0.05\)
Figure 36. Main effect of corpus callosum midlength in predicting CES-D Wellbeing symptom change.

7.8.5 CES-D Interpersonal
No neuroanatomical regions of interest emerged as predictors of CES-D Interpersonal symptom change.

7.8.6 KSADS-PL depressive disorders
A series of binary logistic regressions were conducted with the presence or absence of a KSADS-PL depressive disorder as the outcome, gender, handedness, age and parent education as covariates, and region of interest and a region by gender interaction term as independent variables. Three neuroanatomical structures were found to have a predictive relationship with case-level depressive disorder. Age and parent education also predicted outcome in each of these models; increase in age reduced the likelihood of depression diagnosis, and having parents with
incomplete secondary school education increased the likelihood of diagnosis (as compared to having parents with complete secondary school education).

Table 53

Structure of region of interest by KSADS-PL depressive disorder logistic regression models

<table>
<thead>
<tr>
<th>DV</th>
<th>KSADS-PL Depressive Disorder (Present/Absent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Gender</td>
</tr>
<tr>
<td>Handedness</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Parent Education</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>Step 3</td>
<td>Region of Interest x Gender</td>
</tr>
</tbody>
</table>

7.8.6.1 Whole brain volume and KSADS-PL depressive disorders

Whole brain volume was found to predict KSADS-PL depression diagnosis; larger whole brain grey and white matter volume decreased the likelihood of case-level depression.

Table 54

Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from whole brain volume

<table>
<thead>
<tr>
<th></th>
<th>Overall Model Evaluation</th>
<th>Goodness of fit</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>df</td>
<td>p</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td>20.328</td>
<td>7</td>
<td>.005*</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td>6.833</td>
<td>1</td>
<td>.009*</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>27.161</td>
<td>8</td>
<td>.001*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictors</th>
<th>$\beta$</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>e^$\theta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.005</td>
<td>0.002</td>
<td>5.230</td>
<td>1</td>
<td>.022*</td>
<td>.995</td>
</tr>
<tr>
<td>ISS v CSS$^a$</td>
<td>-2.352</td>
<td>1.188</td>
<td>3.923</td>
<td>1</td>
<td>.048*</td>
<td>.095</td>
</tr>
<tr>
<td>Whole brain volume</td>
<td>-9.14E-06</td>
<td>3.75E-06</td>
<td>5.924</td>
<td>1</td>
<td>.015*</td>
<td>&lt;1.000</td>
</tr>
</tbody>
</table>

$^a$Significant at $\alpha=.05$

$^a$ISS = Incomplete Secondary School, CSS = Complete Secondary School (Parent Education)
7.8.6.2 Right rostral paracingulate volume and KSADS-PL depressive disorders

A main effect indicated that smaller right rostral paracingulate volume was associated with greater likelihood of case-level depression.

Table 55

Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from right rostral paracingulate volume

<table>
<thead>
<tr>
<th>Overall Model Evaluation</th>
<th>Goodness of fit</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ² df p</td>
<td>-2LL Cox-Snell R² Nagelkerke R²</td>
</tr>
<tr>
<td>Model 1</td>
<td>20.328 7 .005*</td>
<td>78.443 .138 .268</td>
</tr>
<tr>
<td>Step 2</td>
<td>4.234 1 .040*</td>
<td>- - -</td>
</tr>
<tr>
<td>Model 2</td>
<td>24.562 8 .002*</td>
<td>74.209 .164 .320</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>SE</th>
<th>Wald df p</th>
<th>e^β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-.005</td>
<td>.002</td>
<td>5.230 1 .022*</td>
<td>.995</td>
</tr>
<tr>
<td>ISS v CSS</td>
<td>-2.352</td>
<td>1.188</td>
<td>3.923 1 .048*</td>
<td>.095</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>-3.808</td>
<td>1.207</td>
<td>9.950 1 .002*</td>
<td>.022</td>
</tr>
</tbody>
</table>

*Significant at α=.05

7.8.6.3 Right ventral paracingulate volume and KSADS-PL depressive disorders

A main effect for right ventral paracingulate volume indicated that larger structure volumes were associated with increased likelihood of case-level depressive illness.
Table 56

Results of logistic regression predicting KSADS-PL depressive disorders diagnosis from right ventral paracingulate volume

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>e^β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-.005</td>
<td>.002</td>
<td>5.022</td>
<td>1</td>
<td>.025*</td>
<td>.995</td>
</tr>
<tr>
<td>ISS v CSS</td>
<td>-2.375</td>
<td>1.186</td>
<td>4.008</td>
<td>1</td>
<td>.045*</td>
<td>.093</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>2.160</td>
<td>2.517</td>
<td>6.071</td>
<td>1</td>
<td>.014*</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Significant at α=.05

ISS = Incomplete Secondary School, CSS = Complete Secondary School (Parent Education)
### 7.9 Summary of Research Question 2 and 3 findings

Table 57 summarises the major findings from Research Question 2 (Are childhood neglect and abuse reflected in adolescent neuroanatomy?) and Research Question 3 (What neuroanatomical correlates of depressive symptomatology can be observed prior to onset?).

Table 57

*Summary of predictive relationships between CTQ Neglect/Abuse and neuroanatomical regions of interest, and between neuroanatomical regions of interest and CES-D and KSADS-PL measures of depression*

<table>
<thead>
<tr>
<th></th>
<th>CTQ Neglect</th>
<th>CTQ Abuse</th>
<th>CES-D Total</th>
<th>CES-D Depressed Affect</th>
<th>CES-D Somatic</th>
<th>CES-D Wellbeing</th>
<th>KSADS-PL Depressive Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td>Both -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>Males +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>(Females +)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>Males +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Ventral Cingulate</td>
<td>Females +</td>
<td>Both -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>Males -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>Females +</td>
<td>Both +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Females +</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>Both -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>Both +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>Females -</td>
<td>Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>Females +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>Females +</td>
<td>Females +</td>
<td>Both +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.10 Research Question 4: Do neuroanatomical features mediate relationships between early life adversity and adolescent onset depression?

7.10.1 Mediation models
A simple mediation model (depicted in Figure 37) proposes that the relationship between an initial variable (X) and an outcome variable (Y) is at least partially accounted for by relationships between the initial variable and a mediating variable (M) and between the mediating variable and the outcome variable. The unmediated relationship between X and Y is known as the total effect, denoted as pathway c. The relationship between X and M is denoted as pathway a, and the relationship between M and Y as pathway b. In mediation analysis, after the effect of the mediator variable has been accounted for, any remaining relationship between X and Y is known as the direct effect, or pathway c'. The amount of mediation is defined as the reduction of the effect of the initial variable on the outcome when the mediator variable is included in the analysis.

\[ X = \text{Initial variable, } Y = \text{Outcome variable, } M = \text{Mediating Variable, } c = \text{Total effect, } c' = \text{Direct effect.} \]

Figure 37. A simple mediation model.
A mediation model was specified in the present research which posits childhood adverse experiences (neglect or abuse) as the initial variable, and depressive symptomatology as the
The mediator variable is proposed to be any neuroanatomical structure whose volume was related (in the same direction) to the initial and outcome variables (see Figure 38).

Baron and Kenny (1986) and Judd and Kenny (1981) outline four steps in establishing mediation:

**Step 1: Demonstrate that the initial variable is correlated with the outcome.**

More recent models suggest that this step is not necessary for establishing mediation, particularly in longitudinal research (MacKinnon, Fairchild & Fritz, 2007). Therefore both relationships predicted under Research Question 1 (Are childhood experiences of neglect or abuse predictive of adolescent onset depression?) will be included in mediation analysis.

**Step 2: Show that the initial variable is correlated with the mediator.**

Any relationships revealed in the analyses under Research Question 2 (Are childhood neglect and abuse reflected in adolescent neuroanatomy?) will be considered for inclusion.

**Step 3: Show that the mediator affects the outcome variable.**

The mediator variable and the outcome variable may be correlated because both are predicted by the initial variable. In order to demonstrate an independent relationship between $M$ and $Y$, $X$
must be entered as a covariate in regression analyses. For this reason, any significant relationships discovered under Research Question 3 (What neuroanatomical correlates of depressive symptomatology can be observed prior to onset?) will be re-analysed with the inclusion of the relevant CTQ scale as a covariate before being considered for inclusion in a mediation model.

*Step 4: To establish that M completely mediates the X-Y relationship, the effect of X on Y controlling for M (path c') should be zero.*

This step is only required if a full mediation model is specified. Mediation will be measured using Sobel test calculations available through Preacher and Leonardelli’s (2001) Interactive Calculation Tool for Mediation Tests. This is an online tool that, using $a$, $b$, and the standard errors of each, calculates the critical ratio as a test of whether the indirect effect of $X$ on $Y$ via $M$ is significantly different from zero. As recommended by Preacher and Leonardelli (2001), and Baron and Kenny (1986), the Aroian version of the Sobel test will be used.

Three mediation models were specified based on Steps 1-3 outlined above. For each of these models, one or more of the pathways was significant only for females, therefore all pathways were reanalysed using only female data. To test each model, a subset of female cases containing data for all three variables was used, in order to ensure the same sample was analysed for each of the three regressions. Each regression was then performed and the resulting beta weights were used to calculate the Aroian statistic (regression analyses are included as Appendix 14). In the figures below, standardised beta weights are provided for ease of interpretation – these differ from those found in the regressions under Research Questions 1-3 due to the smaller sample sizes.

7.10.1.1 CTQ Abuse, corpus callosum midlength, and CES-D Wellbeing

A model was specified in which, for females only, corpus callosum midlength was predicted to mediate the relationship between CTQ Abuse and CES-D Wellbeing. In the reanalysis of predictive relationships between each of the variables (using the smaller, female-only subsample) all relationships retained significance at the $\alpha=.05$ level. As is requisite for a mediation model, the relationship between the mediator variable (corpus callosum midlength) and the outcome variable (CES-D Wellbeing) remained significant when the initial variable (CTQ Abuse) was included as a covariate, and the strength of the relationship between CTQ Abuse and CES-D Wellbeing was lessened when corpus callosum midlength was included in the analysis.
However, the mediation model did not reach statistical significance, with an Aroian statistic of 1.840 ($p = .066$).

![Diagram of mediation model](image)

*Significant at $\alpha=.05$, **Significant at $\alpha=.001$

Aroian = 1.840, $p = .066$

Figure 39. Model testing whether corpus callosum midlength mediated the relationship between CTQ Abuse and CES-D Wellbeing.

7.10.1.2 CTQ Neglect, corpus callosum midlength, and CES-D Wellbeing

For females only, corpus callosum midlength was predicted to mediate the relationship between CTQ Neglect and CES-D Wellbeing. In regressions using the smaller, female-only subsample, relationships between CTQ Neglect and CES-D Wellbeing, and between corpus callosum midlength and CES-D Wellbeing retained significance at the $\alpha=.05$ level. The relationship between CTQ Neglect and corpus callosum midlength was reduced to a weak trend ($p = .097$). The relationship between the mediator variable (corpus callosum midlength) and the outcome variable (CES-D Wellbeing) remained significant when the initial variable (CTQ Neglect) was included as a covariate, and the strength of the relationship between CTQ Neglect and CES-D
Wellbeing was lessened when corpus callosum midlength was included in the analysis. However, the difference between the total effect of CTQ Neglect on CES-D Wellbeing and the direct effect once corpus callosum midlength was accounted for was not statistically significant.

Figure 40. Model testing whether corpus callosum midlength mediated the relationship between CTQ Neglect and CES-D Wellbeing.

7.10.1.3 CTQ Neglect, right rostral cingulate volume, and CES-D Wellbeing

The final mediation model tested whether right rostral cingulate volume mediated the relationship between CTQ Neglect and CES-D Wellbeing. In the reanalyses using the smaller, female-only subsample the relationships between CTQ Neglect and CES-D Wellbeing, and between right rostral cingulate volume and CES-D Wellbeing retained significance at the $\alpha=.05$ level. However, CTQ Neglect no longer predicted right rostral cingulate volume. The relationship between right rostral cingulate volume and CES-D Wellbeing remained significant when CTQ Neglect was included as a covariate, and the strength of the relationship between CTQ Neglect and CES-D Wellbeing was lessened when right rostral cingulate was included in
the analysis. However, the difference between the total effect of CTQ Neglect on CES-D Wellbeing and the direct effect once right rostral cingulate volume was accounted for was not statistically significant.

*Aroian = .0912, p = .302

*Significant at \( \alpha = .05 \),  **Significant at \( \alpha = .001 \)

*Figure 41. Model testing whether corpus callosum midlength mediated the relationship between CTQ Neglect and CES-D Wellbeing.*
Chapter 8: Discussion

The results detailed in Chapter 7 are discussed and elaborated upon in the following sections, organised according to the four Research Questions around which this thesis was structured. Following the consideration of each Research Question, this final chapter addresses some implications of the findings for the broader theories considered in the introductory chapters, highlights some remaining unanswered questions, as well as outlining the strengths and limitations of the current thesis and implications for future research.

Before discussing each of the Research Questions, below is a consideration of basic patterns observed in two of the cornerstones of the research design – childhood maltreatment and change in depressive symptoms from early to mid-adolescence.

8.1 Prevalence of neglect and abuse

There was a low level of neglect and abuse in the sample; this was not unexpected, given the participants were not selected on the basis of any indications of maltreatment. There was no difference in the amount of neglect reported by girls and boys, however girls reported experiencing more abuse than boys. There have been some previous findings that females are more likely to experience emotional abuse (Arnow et al., 2011) and robust findings that girls are more vulnerable to sexual abuse (Gilbert et al., 2009) – however, sexual abuse items from the CTQ were not included in the Abuse variable, and other research has failed to find gender differences in non-sexual forms of abuse (Stith, 2009). There were no relationships between CTQ Neglect or Abuse and the demographic variables measured (FSIQ, age, or parent education).

8.2 Prevalence of depressive symptoms

The findings for the CES-D were somewhat surprising. The literature on emergence of depression in adolescence suggested that a rise in CES-D scores from early to mid-adolescence could be expected. Instead, there was no rise in score on any subscale, or in the total score. In fact, depression symptom severity reduced from Time 1 to Time 2 on both the Depressed Affect and Wellbeing subscales. Re-examining the information presented in Chapter 1 on the Great Smoky Mountains study (Angold & Costello, 2006) revealed that while the overall pattern was for a distinct rise in depression scores, large fluctuations in early adolescence were evident in the
average depression scores, including a rise and then sharp drop, before the more consistent pattern of rising scores emerged in mid-adolescence. It is possible that the lack of a strong increase in depression symptomatology in this sample reflects the participants’ relatively young age, slightly preceding the strong incline in depressive symptomatology expected.

Given the considerable body of evidence showing the divergence of depression prevalence between girls and boys in adolescence, it was also surprising that there were few gender differences in the incidence of depressive symptoms in this sample. In early adolescence, boys showed higher levels of Somatic symptoms, and the only gender difference in mid-adolescence was the higher level of Depressed Affect reported by girls.

Even less consistent with expectations was the finding that for all scales except Interpersonal\(^4\), significant symptom *reduction* was noted between Time 1 and Time 2. A paradoxical finding in many studies of self-rated adolescent onset depression is that while (for girls at least) cross-sectional studies tend to find an increase in depressive symptomatology during adolescence (W. E. Craighead, Smucker, L. W. Craighead & Ilardi, 1998; Finch, Saylor & Edwards, 1985; Hecht et al., 1998), longitudinal studies often find a decline in self-reported depression scale scores (e.g., Angold, Erkanli, Loeber & Costello, 1996; Burks, Dodge & Price, 1995; Cole, Peeke, Martin, Truglio & Sroczyński, 1998; Devine, Kempton & Forehand, 1994). Twenge and Nolen-Hoeksema (2002) suggest that this may be due to measurement effects, rather than to a true decline in symptoms, particularly as longitudinal studies using clinical diagnosis more consistently find increases in depressive symptomatology during adolescence – as was the case with the KSADS-PL diagnoses in this sample.

The CES-D is designed to measure current depressive symptoms, and in its initial validation demonstrated only moderate test-retest reliability (between .4 and .7 depending on the time between administrations; Radloff, 1977). The validation also showed that the test-retest reliability was substantially reduced by the occurrence of significant life events before one or both of the

\(^4\) A note on the Interpersonal subscale: Symptom change on the Interpersonal subscale of the CES-D was not predicted by any brain structure variables, nor by female gender. It was also the only scale that did not show an overall reduction in scores from Time 1 to Time 2. In her validation of the original CES-D with adolescents, Radloff (1991) commented that responses to the Interpersonal items may reflect normative adolescent concerns with peer relationships in this population, and noted that the scores on the Interpersonal subscale were somewhat elevated in a normal sample of adolescents. This suggests that in adolescent groups, the Interpersonal subscale may be less specific to depressive symptoms as opposed to more developmentally normative worries and concerns, and possibly explains the lack of findings for Interpersonal symptom change in this sample.
administrations. While there are advantages to using a scale that is sensitive to current depressive symptoms, this may also have lead to greater variability in the scores related to adolescents’ current circumstances and more generally to the emotional lability characteristic of adolescence.

The nature of symptom change over time was clarified by the analysis of residuals (predicting Time 2 score based on Time 1 score), which revealed that males and females showed distinct patterns of symptom change. While males showed a negative pattern of residuals on all CES-D scales, females showed the opposite – in other words, for girls, Time 2 CES-D scale scores were higher than predicted based on their Time 1 scores. The final hierarchical regression models demonstrated that once the covariates of handedness, age, and parent education were accounted for, female gender predicted increases in Depressed Affect and Somatic symptoms.

The pattern of findings from KSADS-PL interviews supported the impression from the CES-D residuals, that for females at least, there was an increase in depression from Time 1 to Time 2. By nature of the sample selection, no participant had case level depression at Time 1. By Time 2, 16 adolescents met diagnostic criteria for probable, definite or in remission diagnosis of past or current depressive disorder, and the majority of these (11) were girls. Overall, 10.5% of the sample were experiencing a current depressive illness at Time 2 – this figure is higher than point prevalence rates of major depression generally reported amongst adolescents, which tend to be around 3-5%, indicating that this was indeed a risk-enriched sample (Haarasilta, Marttunen, Kaprio & Aro, 2001; Oldehinkel, Wittchen & Schuster, 1999; Lewinsohn et al., 1998; Lewinsohn, Hops, Roberts, Seeley & Andrews, 1993).

Therefore, overall the findings supported previous research indicating that during adolescence, a gap in prevalence of depression emerges between males and females. The prospective, longitudinal design of this study meant that challenges to the validity of the gender gap from potential artefacts such as proclivity for help-seeking, or negative recall bias in women, were minimised.

8.3 Research Question 1: Are childhood experiences of neglect or abuse predictive of adolescent onset depression?

The relationships between childhood maltreatment and depression are already well established (Kessler et al., 2010; Gilbert et al., 2009) and were not the major focus of this thesis, so they will not be dealt with in great detail here. Briefly however, these findings support previous literature indicating that childhood neglect and abuse are powerful contributors to the development of depression. The findings from the current study strongly indicated that neglect and abuse in
childhood were associated with depression in adolescence. Both childhood neglect and abuse predicted change in depressive symptoms on the CES-D Total score and all CES-D subscales, and predicted the occurrence of case level depression in mid-adolescence.

Neglect accounted for 19.3% of the variance in CES-D Total symptom change. While significant, the amount of variance accounted for by neglect in Depressed Affect (7.4%), Somatic symptoms (10.8%), and Interpersonal symptoms (8%) change was less the 27.4% of variance it contributed to change in scores on Wellbeing. There were no differences between males and females in terms of the relationships between neglect and symptom change on any CES-D scale.

There were some gender differences in the relationships between childhood abuse and depression. The relationship between abuse and CES-D Total symptom change was particularly strong for females, and the relationship between abuse and Somatic symptoms was only evident for females. Abuse accounted for 26.3% of the variance in CES-D Total score change – 14.1% for males and 26.8% for females. Similar percentages of variance in symptom change were accounted for by abuse in the Depressed Affect (20.8%), Somatic (17.2%), Wellbeing (17.5%) and Somatic subscales (14.5%). For the CES-D Total score, abuse accounted for more symptom change variance in females (26.8%) than males (14.1%), although both were significant. For Somatic symptoms, the relationship was only significant for females, among whom abuse accounted for 32.1% of variance in symptom change.

The particularly strong relationship between abuse and depression for girls was interesting, given mixed findings in the past regarding differential effects of maltreatment on males and females. However, given the lack of a rise in depression symptoms in boys overall in the sample, gender differences in all the findings of this thesis should be interpreted cautiously. One potential contributor to the strength of this finding is that females have been suggested to be more sensitive to the interpersonal nature of abuse in the family context. As discussed in Chapter 4, women are thought to show a stronger interpersonal orientation than men, and to attribute more responsibility to themselves for the quality of interpersonal relationships (Nolen-Hoeksema & Jackson, 2001). This may lead to a greater propensity for self-blame and internal attributions for experiences of abuse from a family member (Cutler & Nolen-Hoeksema, 1991), which in turn are related to the development of depression in childhood and adolescence (Feiring et al., 2002).

In summary, the relationships between childhood maltreatment and adolescent depressive symptoms were as predicted. That childhood neglect and abuse form risk factors for the
development of depression in adolescence was an assumption upon which the design of this research was founded – the current findings confirmed that assumption.

8.4 Research Question 2: Are childhood neglect and abuse reflected in adolescent neuroanatomy?

Both neglect and abuse predicted the volumes of multiple brain structures in young adolescents. Overall, the pattern of findings for abuse and neglect demonstrated the necessity of differentiating these two types of childhood maltreatment in neurodevelopmental research. While both neglect and abuse were associated with higher levels of depressive symptoms, the brain structures associated with each were different (with the exception of the corpus callosum) and while neglect affected structures in females only, abuse largely affected structures in males.

Neglect was associated with significant interactions for three structures: left dorsal paracingulate, right rostral cingulate, and corpus callosum midlength. In each case, the interaction revealed a particular relationship between neglect and larger measures on structural features for girls only (although this relationship failed to reach significance for the left dorsal paracingulate).

Abuse was associated with significant interactions in four structures: the left amygdala, left rostral cingulate, left dorsal cingulate, and corpus callosum midlength. In contrast with the findings for neglect, the interactions showed that the findings for abuse largely applied to males, with the exception of corpus callosum midlength. For males only, childhood abuse predicted smaller left amygdalae, and larger left dorsal and left rostral cingulate volumes. As was the case for neglect, abuse also predicted greater corpus callosum midlength for girls.

Some previous findings have indicated that the neurobiological sequelae of maltreatment differed for females and males, and the causes for gender-specific findings are addressed within several of the sections of this thesis discussing individual structures. Some authors have suggested that the male developing brain may be more susceptible to the adverse effects of maltreatment (DeBellis et al., 1999b; DeBellis et al., 2002). Edmiston and colleagues (2011) observed alterations in both males and females related to childhood maltreatment, but noted that neurostructural alterations in girls with histories of maltreatment were focussed in areas related to emotion regulation, whereas in boys, the affected regions were more associated with impulse control. The findings of this thesis, that different types of maltreatment also differentially affected brain structures between girls and boys, adds a further dimension to previous findings, and warrants attention in future research.
In the following sections, each of the brain structures measured (hippocampus, amygdala, anterior cingulate cortex, orbitofrontal cortex, and corpus callosum) is discussed separately, with regards to the findings of this research, theoretical implications, and directions for further research.

8.4.1 Hippocampus

The research reviewed in the introduction suggested that hippocampal reductions observed in adults exposed to childhood maltreatment are due either to disruptions to the adolescent development of the hippocampus, or formed pre-existing risk factors for pathological response to traumatic experiences associated with maltreatment (e.g., Gilbertson et al., 2002; Rao et al., 2010; Dannlowski et al., 2012). Therefore, in the participants for this research, who had no history of depression, and underwent brain scans in early adolescence and therefore before the putative disruption to adolescent hippocampal development would occur, no reductions in hippocampal volume associated with either form of childhood maltreatment were predicted. In accordance with this hypothesis, no such relationships were found.

This aligns with previous findings, that while hippocampal reductions are found in adults with histories of maltreatment, they are not found in children with such histories (e.g., Driessen et al., 2000; Bremner et al., 1997b; DeBellis et al., 1999b; Carrion et al., 2001). Possible explanations for this were reviewed in the introductory chapters and are summarised below:

- Most findings in adults are from samples selected based on diagnosis with a psychiatric disorder (often PTSD, e.g., Bremner et al., 1997b). The smaller hippocampi observed in these samples may reflect not an outcome of childhood maltreatment, but a risk factor for a pathological response to such experiences. Therefore, in children who have histories of maltreatment but who have not yet, and may not ever, develop psychopathology in adulthood, differences in hippocampal volume would not be expected.

- The psychiatric disorders often associated with childhood maltreatment in adult samples may cause stress-related damage to the hippocampus in the form of dendritic atrophy, cell death and/or suppression of adult neurogenesis. Hippocampal reductions observed in adult psychiatric samples with histories of childhood maltreatment (e.g., Bremner et al., 1995; Driessen et al., 2000) may be due to pathophysiological processes of the mental illness, which require time and the development of the disorder before being observable (Teicher et al., 2003).
• Alcohol and/or substance use often associated with psychopathology in adulthood may also contribute to reduction in hippocampal size (Ellason et al., 1996; DeBellis et al., 2000b).

• Stress processes associated with childhood maltreatment may exert a delayed suppression of hippocampal maturation in adolescence (Anderson & Teicher, 2004).

One limitation of the current study is the retrospective self-report measure of childhood maltreatment, which may result in negative recall biases in reporting of early experiences, and is unlikely to capture maltreatment occurring very early in childhood. The hippocampus appears to be most vulnerable to the experience of maltreatment in earlier, rather than later, childhood. Andersen and colleagues (2008) found that hippocampal volume reduction in response to sexual abuse was associated with abuse from 3-5 years of age (and, marginally, from 11-13 years). Rao and colleagues (2010) found that parental nurturance at age four, but not eight, predicted smaller adolescent hippocampal size. The direction of the latter finding is somewhat surprising, and the authors offer multiple potential theories for this, including reflections on timing of adolescent hippocampal synaptic pruning. Regardless, the finding does support the possibility that effects of familial environment on hippocampal development are specific to the early childhood years. Thus it is possible to speculate that the maltreatment most likely to result in hippocampal reductions would perhaps occur too early for adolescents in this sample to remember and report it. However, there are also other research reports which point towards a more substantive interpretation of this null finding.

Anderson and Teicher (2004) examined the effects of early maternal deprivation on synaptic density in rats and found distinct relationships and time courses for the expression of these effects between the hippocampus, the amygdala, and the prefrontal cortex. Relationships between early life stress and synaptic density were evident for both the hippocampus and the amygdala. However the modest reduction in density for the amygdala was observable from an early age and remained fairly consistent across age groups. On the other hand, the reduction in density in the hippocampus only emerged later, as a lack of developmentally normal overproduction of synapses.

Another possibility is that the psychosocial outcomes associated with childhood abuse and perhaps particularly neglect, may have flow-on effects related to hippocampal neurogenesis. Animal research has indicated that greater environmental complexity can increase the number of new neurons in the hippocampus. The production of new hippocampal neurons has been demonstrated in both animals and humans (Eriksson et al., 1998; Gould et al., 1999a). However
the survival of these cells may be dependent on experience. In laboratory animals, adult-generated cells appear to degenerate within 2 weeks of production. The survival of a significant proportion of these new cells was preserved by environmental stimulation in the form of training on hippocampal-dependent tasks (Gould, Tanapat, Beylin, Reeves & Shors, 1999; Ambrogini et al., 2000). Given the poor outcomes for adults with histories of childhood abuse and neglect in terms of work, money, and education (Currie & Widom, 2010), it is possible that the relationship between childhood maltreatment and adult hippocampal degeneration is mediated by experiential impoverishment and associated dampening of hippocampal cell proliferation (perhaps in addition to outright negative and stressful experiences and substance abuse which may cause direct damage to both existing and new hippocampal cells; DeBellis et al., 2000b).

In conclusion, as predicted, there was no relationship between self-reported childhood neglect or abuse and hippocampal volume in early adolescence. Hippocampal reductions have previously been observed in adults exposed to childhood maltreatment; the current finding supports theories that these are either due to disruptions to adolescent development of the hippocampus, or form pre-existing risk factors for pathological responses to traumatic experiences associated with maltreatment. However, it is possible that maltreatment earlier in childhood is specifically associated with hippocampal reductions; the self-report of maltreatment in this study meant that very early maltreatment could not be detected. Future research accessing multiple sources of reporting on maltreatment would be more likely to detect effects of early maltreatment. Longitudinal follow-up of this and other samples into late adolescence and adulthood is likely to provide insight into whether the development of the hippocampus is affected during adolescence and whether alterations are measurable in adulthood.

8.4.2 Amygdala

An emerging body of work suggests that amygdala volume alterations associated with childhood adverse experience (in the context of adult psychopathology) tend towards reduction, particularly on the left (Aas et al., 2012; Karl et al., 2006; Edmiston et al., 2011). Therefore it was hypothesised that childhood neglect and/or abuse would be associated with reduced amygdala volumes in this sample. In support of this hypothesis, childhood abuse was found to predict reduced left amygdala volume in boys.

The left amygdala has been particularly implicated in studies of childhood maltreatment and brain structure. Aas and colleagues (2012) found that smaller left amygdalae mediated the relationship between childhood trauma and cognitive deficits in first episode psychosis, and made several suggestions as to what this may reflect. They contrasted their findings with
previous research which had revealed either no relationships between maltreatment and amygdala size in child populations, or enlargement of amygdalae, and suggested that the severe stress associated with childhood trauma had effects on the amygdala later in development, possibly through the stress associated with first episode psychosis. However, the current finding runs counter to this interpretation, suggesting that alterations to the left amygdala in response to childhood maltreatment are observable in a young population of boys, and are not dependent on the occurrence of psychopathology\(^5\).

More broadly, the amygdala’s role in processing negative emotions is thought to be left-lateralised. In functional studies of amygdalar response to emotional stimuli, the left amygdala is activated more often (Baas, Aleman & Kahn, 2004) and particularly in response to negative stimuli (Wager et al., 2003). Left, but not right, amygdala metabolic and functional activity has also been related to plasma cortisol levels in depressed patients (Drevets et al., 2002b). Therefore the left amygdala may be more sensitive to negative experience, and to associated plasma cortisol increases, than the right.

Aas and colleagues (2012) noted that graver childhood trauma was more strongly associated with amygdala volume reduction, and suggested that the development of the amygdala is affected by actions of the HPA axis. Research with individuals with congenital adrenal hyperplasia (CAH) has shed some light on the effects of glucocorticoid concentrations on brain structure. The condition is associated with prenatal glucocorticoid deficiencies, followed in many cases by excess glucocorticoids during childhood as a complication of medical intervention. In a structural MRI study of 27 children with CAH who had received glucocorticoid therapy, amygdala volumes were found to be 20% smaller than those for matched controls. Interestingly (in light of the current finding) the reduced amygdala volume was bilateral in girls, but was significant only on the left for boys (Merke, Fields, Keil, Vaituzis, Chrousos & Giedd, 2003).

One potential explanation for the gender specificity of the current finding, that abuse was associated with left amygdala reduction in boys only, is that the amygdala follows a more protracted schedule of growth in males than in females (Giedd, Castellanos, Rajapakse, Vaituzis & Rapoport, 1997). Therefore, for adverse experiences to affect amygdala development (possibly via the effects of glucocorticoid secretion), for females those experiences may have to occur

\(^5\) It is however worth noting here that anxiety was not measured as part of this research, and paediatric anxiety was not an exclusion criterion for participants. There are some indications that anxiety, either in isolation or comorbid with depression, has effects on amygdala volume (e.g., Bora et al., 2012a, found right amygdala reductions in depression with comorbid anxiety, and DeBellis and colleagues, 2000a, found that children with generalized anxiety disorder had larger right amygdala volumes than controls).
earlier than for males – perhaps early enough to preclude retrospective self-report in many instances (Giedd et al., 1996b). In support of this interpretation, Merke and colleagues (2003) found that normative maturational increases in amygdala volume for boys were observed bilaterally for healthy controls, but only in the right amygdala for boys with CAH, suggesting that high levels of glucocorticoids during childhood may have a specific suppressing effect on the development of the left amygdala in boys.

Sexual dimorphism in the amygdala, which is usually larger in males than females, suggests an effect of androgens on amygdala volume, supported by animal research showing effects on amygdala volume via manipulation of androgen levels. Cooke, Tabibnia and Breedlove (1999) found that in adult rats, amygdala volumes were reduced after castration in males, and increased after androgen administration in females. Reductions in amygdala volume in response to glucocorticoid levels (either due to stress, or from iatrogenic causes) may therefore be in response to the direct effects of glucocorticoids on the amygdala, or due to glucocorticoid suppression of androgens, or a combination of the two.

There were parallels between Aas and colleagues’ (2012) findings on relationships between childhood trauma and brain structures in first episode psychosis, and Merke and colleagues’ (2003) findings on structural alterations in children with CAH. In both cases, structural alterations were observed in the amygdala, but not the hippocampus; the frequent research focus on neurotoxicity in the hippocampus made this somewhat unexpected. Similarly, this thesis found relationships between childhood abuse and amygdala volume, but not hippocampus volume. This may provide evidence that, in childhood at least, excess glucocorticoids do not lead to reduced hippocampal volumes; based on this theory, one would expect to see hippocampal reductions in children with CAH (therefore likely to have experienced excess glucocorticoid levels) and those with histories of childhood maltreatment, assuming such maltreatment resulted in elevated glucocorticoids as a part of the endocrine stress response. In combination with this thesis’ finding that hippocampal volume reductions pre-dated a rise in depressed mood (for girls), this bears relevance for future considerations of neurotoxicity theories of hippocampal reduction.

In conclusion, the current finding, in the context of related research on the effects of excess glucocorticoids on the developing amygdala, suggests that through the repeated induction of the stress endocrine response, childhood maltreatment may hamper normal development of the left amygdala in boys. As with the hippocampus, future research designs which are able to measure earlier maltreatment could shed light on whether disruption to amygdala development differs
between the genders based on the timing of maltreatment. This finding, together with the extant research, also suggests that future studies may focus on whether the different pre-pubertal hormonal environments boys’ and girls’ brains develop within confer distinct vulnerabilities upon exposure to maltreatment.

8.4.3 Anterior cingulate cortex

Adverse rearing environments have been associated with larger dorsal and rostral ACC volumes in primates (Spinelli et al., 2009) and greater childhood parental nurturance was associated with smaller dorsal ACC in adolescents (Rao et al., 2010). In contrast, other research has found that emotional maltreatment was associated with reduced grey matter volume in prefrontal regions which included the dorsal ACC (Edmiston et al., 2011; van Harmelen et al., 2010). Based on the latter findings, it was hypothesised that childhood maltreatment would be associated with reduced dorsal anterior cingulate volume in this sample. This hypothesis was not supported; left dorsal cingulate volume was positively predicted by childhood abuse for boys. This was in direct contrast with the findings of Edmiston and colleagues (2011) and van Harmelen and colleagues (2010), however was consistent with Spinelli and colleagues (2009) and Rao and colleagues (2010). More broadly, the findings were also consistent with primate research demonstrating cellular alterations in the dorsal ACC in response to early life stress (Mathew et al., 2003).

As well as dorsal volume, left rostral cingulate volume was also positively predicted by abuse in boys, while right rostral cingulate volume was positively predicted by neglect in girls. These findings were in contrast with a previous study that found reduced rostral ACC volumes in adults with histories of childhood maltreatment (Treadway et al., 2009).

It was interesting that the alterations in prefrontal areas associated with maltreatment took the form of expansions rather than contractions. The reduced amygdala sizes associated with childhood abuse in this sample were interpreted as reflecting the effects of glucocorticoids associated with stress, in line with research from children with CAH (Merke et al., 2003). Children raised in adverse circumstances do not appear to experience the same blunting of cortisol response to stress as other children typically do between infancy and adolescence. This normative reduction in cortisol responsivity is known as the stress-hyporesponsive period, and is thought to occur in order to protect the developing brain from the neurotoxic action of stress hormones (Gunnar & Cheatham, 2003; de Haan et al., 1998; Gunnar et al., 1997; Nachmias et al., 1996; Tarullo & Gunnar, 2006). Thus it might be expected that other areas with high concentrations of glucocorticoid receptors (e.g., prefrontal areas) would also demonstrate volumetric reductions in children with histories of maltreatment. This then begs the question of
how to interpret the lack of reduction, and even the expansion in prefrontal sites also thought to be vulnerable to glucocorticoid toxicity.

One particularly intriguing argument regarding the influence of childhood adversity on prefrontal inhibitory areas is that early stress may prompt accelerated maturation of such areas, allowing adaptive responses to early extreme stress, but disallowing more complex and protracted maturational processes and thereby restricting long term developmental potential (Teicher, Ito, Glod, Schiffer & Gelbard, 1996). It is possible that the different neurodevelopmental timetables followed by cortical and subcortical structures may mean that higher glucocorticoid concentrations impinge upon the structure of the amygdala, but are adapted to by later developing frontal areas. Future investigation may focus on the neurodevelopmental processes, possibly related to epigenetic mechanisms, by which early stress may alter the development of frontal cortical areas.

It is also notable that in both males and females, the rostral ACC was affected. The rostral ACC has been particularly associated with representation of affective information related to social stimuli (D. M. Pavlovic et al., 2009). Activity in the rostral ACC has been linked with trait extraversion (Johnson et al., 1999) and harm avoidance (Youn et al., 2002), feelings of social exclusion (Somerville et al., 2006) and distress upon hearing infants’ cries (Lorberbaum et al., 2002) as well as positive emotions felt at the sight of loved ones (Bartels & Zeki, 2004). The maltreatment assessed for in this research had a strong interpersonal element, as it occurred in the family context. As discussed in Chapter 5, the quality of attachment to caregivers has been shown to affect stress-reactivity in young children (Nachmias et al., 1996). Chapter 4 also discussed some of the ways in which maltreatment may affect the interpersonal schemas children develop, predisposing them to depressive cognitions (Kaysen et al., 2005; Pollack et al., 2001; Kovacs & Beck, 1978). Therefore it is fitting that an area associated with social cognition should be altered by suboptimal interpersonal environments during development.

Taken together, these findings extend the emerging body of evidence linking early life adversity with mediofrontal structures, and provide support for their inclusion in future research on the neurobiological sequelae of childhood maltreatment.

8.4.4 Orbitofrontal cortex

It was hypothesised that higher reported levels of childhood maltreatment would predict smaller orbitofrontal cortex volumes. This was based on an emerging body of evidence suggesting that childhood maltreatment is associated with reductions in orbitofrontal cortex volumes in
adolescent samples (Rao et al., 2010; Edmiston et al., 2011; Hanson et al., 2010; Andersen et al., 2008), however the current study found no predictive relationships between childhood neglect or abuse and orbitofrontal cortex volumes.

Reduction in orbitofrontal cortex volume associated with abuse or neglect may be restricted to maltreatment at specific developmental stages. For example, Andersen and colleagues (2008) found that experiences of sexual abuse were only associated with prefrontal cortex alterations when the abuse occurred in adolescence. This suggests that prefrontal areas exhibit a particular developmental sensitivity to abuse-related stress during adolescence – a theory made appealing by the dramatic remodelling of frontal areas known to occur during this time. However, the findings of both Rao and colleagues (2010) and Hanson and colleagues (2010) pointed towards maltreatment earlier than adolescence as a predictor of reduced orbitofrontal cortex volume.

It is possible that the relationships reported above reflect the effects certain types of particularly acute maltreatment, for example sexual abuse (Andersen et al., 2008) or physical abuse severe enough to warrant protective intervention (and therefore inclusion in previous samples of maltreated young people; Hanson et al., 2010). Anderson and colleagues (2008) interpreted the specificity of their finding – that only abuse during the adolescent stage predicted prefrontal volume loss – as indicating that stressful experience in adolescence acted directly on the prefrontal cortex, rather than demonstrating the incubation period associated with stress-related alterations to other structures. If their interpretation was correct, it may follow that more intense or acute types of maltreatment would be required than were recorded in this sample for the effect to be observable; future research investigating prefrontal structural neuroanatomy in preadolescent samples selected on the basis of severe maltreatment may provide clarification.

8.4.5 Corpus callosum

Animal studies (Berrebi et al., 1988; Sánchez et al., 1998) have observed smaller corpus callosum volumes in animals reared in adverse or understimulating environmental conditions. Research with humans has also found reductions in the corpus callosum in maltreated children with PTSD (DeBellis et al., 1999b; DeBellis et al., 2002) and other psychiatric conditions (Teicher et al., 1997; Teicher et al., 2004). It was therefore hypothesised that childhood neglect or abuse would predict smaller measurements in midsagittal corpus callosum area. Midsagittal length was included in this study as an exploratory measure. Contrary to the hypothesis, there were no relationships between childhood maltreatment and midsagittal corpus callosal area, however greater corpus callosum midlength in females was predicted by both self-reported neglect and abuse. It was somewhat unexpected that the length of the corpus callosum was only related to
maltreatment in females, as previous research had found that corpus callosum alterations observed in maltreatment-related PTSD were stronger for males (DeBellis et al., 1999b).

It is interesting that length, but not area, was predicted by childhood maltreatment. The corpus callosum is a relatively late-maturing structure, with extensive myelination occurring post-natally (Yakovlov & Lecours, 1967). The hormonal sequelae of early life stress have been found to suppress glial cell division, which is critical for myelination (Lauder, 1983). Therefore the corpus callosum is a reasonable candidate to show volumetric alterations associated with stressful familial environments. Multiple prior findings from both animal and human populations have observed reductions in corpus callosum volumes in association with adverse early life experience (e.g., Teicher et al., 1997; DeBellis et al., 1999b). In light of the fairly substantial body of evidence pointing towards corpus callosum alterations associated with childhood maltreatment, it is possible that the quantification of a single midsagittal corpus callosum area in this thesis was too crude a measurement to detect the subtle, spatially localised alterations often noted in other studies. Given the rostral to caudal sequence of myelination across development (Giedd et al., 1999b; Thompson, Giedd, Woods, MacDonald, Evans & Toga, 2000), it is also likely that maltreatment at different ages may produce specific and localised alterations to corpus callosum subregions, which the current methodology was not targeted to detect. Measurement methods more sensitive to local alterations in callosal morphometry are available (e.g., Adamson et al., 2011) and may be used on these and similar data in the future in order to detect whether more regionally localised alterations to corpus callosum volume are evident in response to familial maltreatment.

No hypothesis regarding corpus callosum midlength was made, and this is not often a focus of enquiry. It seems likely that the increased corpus callosum midlength associated with both neglect and abuse for girls in this thesis reflects either genetic influences, or the effects of very early life conditions, including conditions in utero. This conclusion was reached in light of previous evidence that environmental conditions did not affect the length of the corpus callosum. In a rat study, experimentally induced differences in early environment (via frequency of handling) affected the width, but not the length of the corpus callosum (Berrebi et al., 1988). Similarly, rhesus monkeys reared in isolation showed smaller corpus callosum area, but no difference in length, compared with those reared in natural conditions (Sánchez et al., 1998).

The greatest increases in corpus callosum midlength occur very early in development. Antenatal MR imaging indicates that the corpus callosum grows rapidly in the second trimester, followed by slower growth in the third (Harreld, Bhore, Chason & Twickler, 2011, see Figure 42). A
sonogram study of corpus callosum length in newborn infants (from groups of normal and pre-term births) found that the increase in callosal length associated with gestation slowed after 2 weeks post-delivery in all groups (Anderson, Laurent, Woodward & Inder, 2006).

Figure 42. Comparative regression analysis of foetal corpus callosal length data, reproduced from Harreld and colleagues (2011).

The morphology of the corpus callosum appears to be highly influenced by genetic factors (Oppenheim, Skerry, Tramo & Gazzaniga, 1989; Tramo, Loftus, Stukel, Green, Weaver & Gazzaniga, 1998; Biondi et al., 1998). For example, the area of the corpus callosum was estimated to be 94% heritable in a twin study of healthy young adults (Scamvougeras, Kigar, Jones, Weinberger & Witelson, 2003). With such high degrees of heritability, the scope for contribution of environmental factors to callosal morphology is fairly modest. It is possible to speculate that corpus callosum alterations observed in this sample reflect heritable characteristics, which may themselves contribute to family members’ maltreatment behaviour, however the design of the current study did not allow the exploration of prenatal factors.

Influences during gestation that were related to the later maltreatment may also have contributed to corpus callosum length. Maternal stress has been found to affect infants’ brain development in
utero (Buss, Entringer & Wadhwa, 2012) and may be related to the alterations in corpus callosum length observed in this sample. It is possible that the adverse family conditions reported by maltreated children preceded their birth; in other words, stressful familial contexts such as those marked by physical abuse and frequent conflict may have constituted stressors for the mother during the child’s gestation. The stress hormones associated with these conditions for the mother can alter brain development in utero; animal research has previously shown that prenatal corticosteroids affected white matter development (Dunlop, Archer, Quinlivan, Beazley & Newnham, 1997). Substance use in parents, which is known to be associated with childhood maltreatment, may contribute to impacts on early brain development; for example smaller corpus callosum volumes have been found in babies born of alcoholic mothers (Bookstein, Connor, Huggins, Barr, Pimentel & Streissguth, 2007). The current research did not measure parental substance use; future research including pregnancy and birth histories could contribute to interpreting these findings. Finally, given that the findings were specific to females, future research could explore whether the prenatal hormonal milieu for the female brain differentially influences corpus callosum length development when combined with other prenatal influences related to childhood maltreatment.

In summary, the predicted relationship between childhood maltreatment and corpus callosum area was not observed. However, greater corpus callosum midlength was associated with both neglect and abuse in females. Research on corpus callosum length is relatively sparse; it was suggested that given the very early timing of growth in corpus callosum midlength, these findings may reflect genetic or gestational influences on infant brain development.

8.5 Research Question 3: What neuroanatomical correlates of depressive symptomatology can be observed prior to onset?

The volumes of several brain structures measured in early adolescence, and prior to depression onset, predicted the emergence of depressive symptoms, however there was a great deal of variation between the measures of depression (i.e., the Total CES-D, its four subscales, and KSADS-PL case level diagnosis).

The following structural volumes predicted symptom change on any of the measures: right rostral cingulate (2 measures), right rostral paracingulate, right hippocampus (2), left ventral cingulate (2), right orbitofrontal cortex, left dorsal paracingulate, left dorsal cingulate, right
ventral paracingulate, corpus callosum midlength, and whole brain volume\(^6\) (reduced whole brain volume was associated with KSADS-PL depression for both males and females). Note that the region of interest volumes entered into each regression for this research were corrected for whole brain volume. Thus when it is stated that volumes were “reduced” or “enlarged”, this is in comparison with the predicted size of that structure, based on the whole brain volume. The findings for each structure, and implications of each are discussed below.

8.5.1 Hippocampus

The extant research pointed to two broad interpretations of the reductions in hippocampal size often observed in depressed individuals (e.g., Frodl et al., 2002b; Bremner et al., 2000; Sheline et al., 1996); that alterations are either a marker of vulnerability for depression, or an outcome of pathophysiological processes associated with depression. It was suggested that if the current research found that hippocampal volume in healthy adolescents was not related to subsequent depression onset, this would indicate that the reduced hippocampal volume associated with depression is largely epiphenomenal, potentially a result of cortisol related neurotoxicity. However, if hippocampal reductions prior to depression onset predicted emergence of depressive symptoms, this would support the theory that hippocampal volume is a risk factor for depressive illness. The latter theory was supported, at least in females – reduced right hippocampus volume predicted an increase in Depressed Affect between early and mid-adolescence.

The stress neurotoxicity theory has frequently been cited to explain findings of reduced hippocampal size in adult depression sufferers. This theory posits that high glucocorticoid concentrations in the brains of depressed individuals exert a neurotoxic effect on the hippocampus, a site made particularly vulnerable by its high concentration of glucocorticoid receptors (Sapolsky, 1985). The current finding does not support this theory – the hippocampal reduction observed in early adolescence for girls predated the onset of depression\(^7\).

---

\(^6\) Whole brain volume was not a region of interest in this research, however it is noted here as all analysis was done using volumes corrected for whole brain volume. Therefore comparison of these findings with those of previous research should take into account whether structure sizes were reported relative to whole brain size.

\(^7\) Anxiety was not included in analyses, and was not an exclusion criterion. If changes in the neurochemical milieu associated with childhood anxiety have a neurotoxic or stunting effect on the hippocampus, this may carry into findings on adolescent depression, given the well established aetiological pathway from childhood anxiety to adolescent and adult depression. However, previous literature has not shown a strong relationship between hippocampal volume and anxiety.
Alcohol and drug use in those with depression has also been suggested to contribute to previous findings of hippocampal reduction in adult sufferers (Ellason et al., 1996; DeBellis et al., 2000b). The current finding indicates that the use of alcohol and drugs in individuals with depression (and other conditions associated with reduced hippocampal volume, notably PTSD) cannot fully account for reduction in hippocampal volume. While drug and alcohol use were not included in the current analyses, the young age and non-clinical nature of this sample make it unlikely that there was drug and alcohol use in participants at Time 1 at a level sufficient to affect brain morphometry.

The strongest alternative possibility is that smaller hippocampal volume predisposes individuals to depression. Amico and colleagues (2011) found that healthy adults with a family history of depression had smaller right hippocampi both than healthy adults with no family history of depression, and than depressed adults. In Amico and colleagues’ study, the fact that hippocampi were smaller in those who were healthy but at risk compared with those currently depressed could be interpreted as reflecting a marker of resilience against depression onset. However, the findings of this thesis suggest rather that smaller hippocampi are an indication of vulnerability. Previous findings that recurrence of depression and longer illness duration were associated with smaller hippocampi in adults still need to be accounted for. These findings may indicate that pre-existing smaller hippocampi not only predispose individuals to depression, but also confer vulnerability for longer duration and poorer prognosis (Frodl et al., 2008b; Kronmüller et al., 2008). It is also possible that a common mechanism or genetic factor renders the hippocampus both smaller in people who are likely to experience depression, and more vulnerable to neurotoxic insult once the depression occurs. For example, in a study of hippocampal volumes and tissue integrity, Cho and colleagues (2010) found that patients with a first episode of major depression had smaller hippocampal volumes than controls, but did not show longer hippocampal T2* relaxation times. In contrast, those with recurrent depression did, indicating that microscopic hippocampal tissue injury (indexed by longer T2* relaxation times) might have been induced by stress processes, in combination with a smaller original gross hippocampal volume, perhaps determined by genetic factors. The role of the hippocampus in down-regulating the activity of the HPA axis makes it likely that there would be an interplay between initial hippocampus function, and vulnerability for stress-related damage to hippocampal tissue. A reduced baseline ability of the hippocampus to exert inhibitory control over glucocorticoid release (Herman & Cullinan, 1997) may result in a failure of the negative feedback loop, and therefore greater HPA-axis activity. The resulting higher circulating cortisol levels may then
contribute to cumulative stress-related tissue damage and/or suppression of neurogenesis and cell survival in the hippocampus.

The finding that the pre-existing hippocampal volume reduction occurred only in females was interesting given that volume reductions associated with depression have more consistently been found in men (e.g., Frodl et al., 2002a; Kronmüller et al., 2008; MacMaster & Kusumakar, 2004). This may reflect different causes for hippocampal reduction – the pre-existing reduction found in females in this thesis may reflect genetic factors, while the reductions previously found in males with depression may be influenced by the putative neuroprotective nature of oestrogen in preserving cell proliferation and survival in depressed females’ but not males’ hippocampi. However, this can only be speculation given the current evidence, and the low incidence of depression in the male participants in this research make it difficult to draw strong conclusions from the observed gender differences.

That only the right hippocampus showed any indication of predicting depression was also interesting, given that volumetric reductions of the hippocampus in predicting schizophrenia (Boos, Aleman, Cahn, Hulshoff Pol & Kahn, 2007; Seidman et al., 2002) and reductions observed in already depressed individuals (see Campbell, Marriott, Nahmias & MacQueen, 2004 for a review), have tended to be more left lateralised. There is some evidence however to suggest that smaller right hippocampal volumes predict vulnerability to PTSD (Gilbertson et al., 2002) and right hippocampal reductions were noted by Amico and colleagues (2011) in adults who were healthy but at risk for depression.

Most of the hippocampal reductions associated with childhood maltreatment (largely in the context of mental health issues) have been on the left side (e.g., Bremner et al., 1997b; Stein et al., 1997; Vythilingam et al., 2002; Teicher et al., 2012). It is possible that the different lateralisation between hippocampal reductions that precede psychopathology as compared to those that occur after its onset (or the experience of maltreatment) reflect asymmetries in stress hormone sensitivity between the left and right hippocampus. The effects of glucocorticoids on hippocampal cell health are not direct, but occur through a cascade of responses including activation of N-Methyl-D-aspartate (NMDA) receptors (Armanini, Hutchins, Stein & Sapolsky, 1990). Glucocorticoid effects on both cell death and suppression of neurogenesis have been found be mediated through NMDA related mechanisms. For example, blockade of NMDA receptors prevents stress-induced atrophy of CA3 pyramidal neurons (Magarinos & McEwen, 1995) and enhances the proliferation of granule cell precursors (Gould, Cameron & McEwen, 1994) while NMDA receptor activation inhibits cell proliferation in the dentate gyrus (Cameron,
McEwen & Gould, 1995). Complex asymmetries in NMDA receptor types have been demonstrated between the left and right hippocampus in animal research (Kawakami et al., 2003) pointing to the possibility that the left and right human hippocampus may be differently vulnerable to the effects of stress hormones.

In summary, hippocampal reductions were observed prior to emergence of depressive symptoms in females, supporting the theory that hippocampal volume is a risk factor for depressive illness. In terms of the functional roles of the hippocampus, an obvious symptomatic expression of hippocampal alterations is the impaired declarative learning and memory and diminished cognitive flexibility apparent in patients suffering from depression (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari & Lönnqvist, 2008). The hippocampus’ putative role in preferencing negative information and encouraging withdrawal (Gray & McNaughton, 1996) is thought to contribute to behavioural features of depression, especially in combination with an underfunctioning approach system. It is possible that suboptimal functioning of the hippocampus, in addition to contributing to dysregulation of the HPA axis, may also contribute to behavioural features that are both generative of, and symptomatic of depression – for example, over-dependence on avoidance and withdrawal as a response strategy. Future research combining neurostructural measures and behavioural observations could help to clarify the relationship between premorbid hippocampal reduction and the development of depressive clinical features.

8.5.2 Amygdala

Meta-analyses have found no overall relationship between amygdala volume and depression, (although there were positive findings in both directions, which may have been related to medication status; Hajek et al., 2009; Hamilton et al., 2008; Bora et al., 2012a). Munn and colleagues (2007) found that amygdala size did not differentiate between groups at high and low familial risk for depression. There are emerging, though inconsistent indications that amygdala volume alteration may be a state- rather than trait-level transitory effect directly related to current depression (MacMaster et al., 2008; van Eijndhoven et al., 2009). Therefore, in the current study, it was predicted that there would not be a relationship between amygdala size in early adolescents prior to depression onset, and depressive symptomatology in mid-adolescence. This hypothesis was supported – there was no relationship between amygdala volume at early adolescence, and change in any of the measures of depressive symptoms or case level disorder.

The extant evidence on relationships between amygdala volume and depression is difficult to interpret. In adult populations, enlargements, reductions, and null findings have all been reported.
in association with depression (Hajek et al., 2009). Meta-analyses indicate that medicated depression is associated with larger amygdalae, and unmedicated depression with smaller amygdalae (Hamilton et al., 2008; Bora et al., 2012a). Mixed findings are reported regarding the relationship between clinical features and amygdala volume in adults – more episodes (Kronenberg et al., 2009) and greater severity (Schuhmacher et al., 2012) have been associated with smaller amygdala, but findings are inconsistent.

There have been some indications that volumetric alterations associated with depression are transitory, state-based features. For example, reduced amygdala volume was found in first episode but not recurrent depression in currently medicated acute patients and larger amygdala in recurrent, but not first episode depression was associated with better HPA down-regulation (Schuhmacher et al., 2012). Conversely, enlarged amygdala volume was found by van Eijndhoven and colleagues (2009) in currently depressed, first episode, medication naïve participants compared to both remitted and never depressed groups. However, in contrast with both these findings, Lorenzetti and colleagues (2010) found larger left amygdala volumes in remitted depression compared with never depressed and currently depressed adults. In further argument against amygdala volume as a state-based phenomenon, declines in amygdalar grey matter density in the 3 years following depressive episode were not related to relapse status (Frodl et al., 2008c).

Findings in children and adolescents with depression have yielded no more clarity than those for adults. Inconsistent findings of reduced amygdalar volumes in depression (Caetano et al., 2007; Rosso et al., 2005) are complicated by possible relationships with comorbid anxiety, and the emergence of bipolar disorder. Few investigations of amygdala size as a predisposing factor for depression have been reported, however notably, Munn and colleagues (2007) found no differences in amygdala size between healthy individuals with and without familial risk for depression. Another finding on family history of depression showed that MDD patients without a family history of depression had enlarged right amygdalae compared to both MDD patients with family history and controls without family history (Saleh et al., 2012).

The current finding supports the conclusion that amygdala size does not constitute a pre-existing neurobiological vulnerability for depression, either through aberrant developmental processes or via a genetic predisposition. It follows that size alterations noted in the amygdala following depression onset are related to disease processes, comorbidity, disease compensatory mechanisms, and/or to the effects of pharmacotherapy.
Animal research has demonstrated neuroplasticity and cell generation within the amygdala during adulthood (Carillo, Pinos, Guillamon, Panzica & Collado, 2007), supporting the possibility that adult volumetric alterations are associated with depression. Amygdalar enlargement may involve dendritic and axonal adaptation to hyperactivity in depression (Flavell & Greenberg, 2008), and reduction may relate to the same stress-related neurotoxic processes discussed with regard to hippocampal reductions.

Functional findings regarding amygdala alterations in depression are much more consistent than structural ones. Heightened tonic and reactive activity in the amygdala has been repeatedly associated with depression (e.g., Drevets et al., 2002a; Abercrombie et al., 1998; Neumeister et al., 2006; Davey et al., 2011). It is possible that volumetric alterations in the amygdala are related to other emotional processing characteristics that intersect with both genetic predispositions and functional activation but do not have a direct relationship with depression. For example, carriers of the short allele of the serotonin transporter gene 5-HTTLPR (which has been implicated in emotional responsiveness and is associated with amygdala activation; Munafo, Brown & Hariri, 2008) have been shown to demonstrate enlarged amygdalae (Scherk et al., 2009). Given that the abnormal amygdala functioning associated with depression is not reliably reflected in a similarly consistent neuroanatomical alteration, abnormal amygdala functioning may also reflect suboptimal regulation by neocortical structures found in this and other studies to be structurally associated with depression, such as the orbitofrontal cortex and ACC, and possibly compensatory response to altered function and volume of the hippocampus in depression.

In summary, the current finding – that amygdala volume in healthy early adolescents did not predict change in depressive symptoms – provides evidence that previously observed amygdalar alterations are associated with disease-concurrent processes and guides further research in focussing on what these may constitute.

8.5.3 Anterior cingulate cortex

All three key regions of the ACC – the dorsal, rostral and ventral areas – were implicated in some form of depressive symptom change. The following subregions were found to predict depressive symptom change: on the right, the rostral cingulate and paracingulate, and ventral paracingulate, and on the left the ventral cingulate, and dorsal cingulate and paracingulate.

8.5.3.1 Ventral anterior cingulate cortex

Volumetric reductions in the ventral ACC have been consistently associated with depression in adults (Hajek et al., 2008). However the research reviewed in the introduction yielded too many
contradictory findings on the relationship between ventral ACC volume and illness course to form a hypothesis about whether such volumetric alterations would predate the onset of depression. The current findings echoed the complex nature of previous research reports on this area. Right ventral paracingulate volume positively predicted KSADS-PL case level depression for both genders. Within the CES-D, left ventral cingulate volume positively predicted Depressed Affect for girls, but negatively predicted Somatic symptom change for both genders. Further analysis showed that the negative relationship for Somatic symptoms was driven by the finding for boys, that smaller left ventral cingulate volume predicted a reduction in Somatic symptoms from Time 1 to Time 2.

The ventral ACC is implicated in the experience of both positive and negative affect (B. A. Vogt & Sikes, 2000; Bancaud & Talairach, 1992) and particularly social and affiliative affective responses (A. R. Damasio et al., 2000). As reviewed in Chapter 3, the ventral ACC is strongly implicated in depression in adults – findings have generally indicated that smaller volume, but greater activity, in this region is associated with adult depression (e.g., Hajek et al., 2008; Drevets, 1999). Greater activation in the ventral ACC is also associated with difficulty down-regulating negative mood states (Beauregard et al., 2006) and has been related to depressive status in adolescents (Yang et al., 2009), and reduced activation is associated with recovery from depression (Mayberg et al., 1999).

Volume decreases in ventral ACC associated with adult depression have been found to be specific to individuals with a familial risk for depression, and particularly on the left side (Hajek et al., 2008). In this sense, the present finding was unexpected, in that greater volume of left ventral cingulate in girls predicted increase in Depressed Affect. However, this is a similar pattern to that observed for the right lateral orbitofrontal cortex: in both instances, a frontal structure in which reductions are observed in adult depression was found to be enlarged prior to the onset of symptoms.

Previous research has observed reduced ventral ACC volume early in illness course and has found that volumes were not related to illness severity or duration (Drevets et al., 1997; Hajek et al., 2008). However more recent research found indications that reductions are related to medication status and length of illness (Yücel et al., 2008), as well as severity of illness (Frodl et al., 2008a). In combination with observations that increased left ventral activation is associated with depressive phenomena, these findings, and the current finding that left ventral cingulate was enlarged prior to depression onset, suggest that both increased size and activation of this region forms a risk factor for depression.
Over-activity of the region may also make it vulnerable to disease-related atrophy, reflected in the smaller volumes noted after depression onset. Like the orbitofrontal cortex, the ACC contains high concentrations of glucocorticoid receptors and may exert inhibitory control over the HPA axis; therefore dysfunction of the ventral ACC may not only be caused by excess glucocorticoids, but may contribute to less effective regulation of the neuroendocrinological stress response (Ahima & Harlan, 1990; Diorio, Viau & Meaney, 1993; Pezawas et al., 2005). In support of possible stress-related tissue alterations, post-mortem human research has shown that volumetric reduction in the ventral ACC largely takes the form of reduction in glial cells (Ongür et al., 1998). In experimental animals, glial cell reduction has been shown to be a consequence of repeated stress induction (Radley et al., 2008; Czéh, Simon, Schmelting, Hiemke & Fuchs, 2005; Banasr & Duman, 2007). Functional research also provides some evidence that alterations in ventral ACC function are state-based; for example metabolism in the ventral ACC has repeatedly been found to be elevated in depressed subjects, and declines upon remission in the same subjects (Drevets et al., 1997; Mayberg et al., 2000; Holthoff et al., 2004; Drevets et al., 2002a).

A reversed form of the relationship between larger ventral ACC and depressive symptoms was observed for the boys in this sample. Somatic symptoms were higher at Time 1 for boys than girls, and dropped from Time 1 to Time 2 in boys. A smaller left ventral cingulate volume was found to predict the reduction in Somatic symptoms in boys – this was the only instance in which the volume of a structure appeared to exhibit a protective effect against depressive symptoms, and the only structure to have a relationship with depressive symptoms in boys specifically. It is also noteworthy that reduction in left sided ventral ACC negatively predicted Somatic symptoms in boys, mirroring the finding that increased right-sided lateral orbitofrontal volume predicted increase in Somatic symptoms in girls.

The ventral ACC is thought to play a role in visceromotor control (Freedman, Insel & Smith, 2000), which makes the relationship with Somatic symptoms observed here particularly intriguing. In their overview of the ventral ACC and its relationship with mood disorders, Drevets, Savits and Trimble (2008) reviewed evidence linking the ventromedial prefrontal cortex, including the ventral ACC, to the function of the SNS in depression. Of particular relevance to the current finding was the research reviewed which pointed to the left ventromedial prefrontal cortex as having an inhibitory relationship with its right-sided counterpart, mediating sympathetic autonomic, affective and HPA axis arousal. Disinhibition of the right ventromedial prefrontal cortex via left-sided dysfunction was theorised to contribute to the reduced parasympathetic-sympathetic tone associated with adverse medical outcomes in patients with
depression (Carney, Freedland & Veith, 2005). There is intuitive appeal in the idea that alterations in the left ventral ACC should not only influence risk for depression, but should also be specifically related to a Somatic symptom profile.

Davey, Harrison, Yücel and Allen (2012) found that in depressed adolescents and young adults, there was increased functional connectivity between the ventral ACC and frontal regions that overlapped with areas captured in the lateral orbitofrontal measurement of this research. They suggested that increased cingulo-cortical connectivity was clinically expressed in disturbances in self-reflective and visceromotor processes in depression. The current finding provides a potential structural complement to the functional findings, in that enlargement in both ventral ACC and lateral orbitofrontal regions (albeit differently lateralised) were precursors to an increase in depressive symptoms.

The findings of this thesis, particularly that smaller left sided volume exerted a protective influence for boys, are novel and require replication; their implications are open to debate and should inform future research with young samples, in the choice of ventral ACC as a region of interest, the distinction between cingulate and paracingulate volumes, and in the measurement of depression in ways which allow description of symptom clusters and exploration of differences in symptoms profiles and their neurostructural correlates between girls and boys.

8.5.3.2 Dorsal anterior cingulate cortex

Very little research has focussed on the volume of the dorsal ACC, or on the potential relationship between dorsal ACC structure and depression. Based on preliminary findings in adult depression (Chen et al., 2007; Caetano et al., 2006), it was hypothesised that reduced dorsal ACC volume would predict the onset of depression in adolescence. This hypothesis was partially supported in that reduced left dorsal cingulate volume predicted increased symptoms on the CES-D Wellbeing subscale for both boys and girls. However, complementing this, larger left dorsal paracingulate volume predicted increased symptoms on the same subscale, for girls only. The expansion in paracingulate volume also accounted for more variance in Wellbeing change than did the reduction in cingulate volume (7.6% and 2.9% respectively). It is interesting to note that the expansion in the dorsal paracingulate echoes the findings for the orbitofrontal cortex and ventral ACC – premorbid volumetric expansions in frontal regions usually associated with postmorbid volumetric reductions.

The pairing of reduction in the dorsal cingulate with expansion in the paracingulate means this finding may be interpreted as reflecting altered morphology, rather than altered volume as such.
This observation also adds a further dimension to interrogation of previous findings that dorsal ACC is reduced in association with depression. Separate delineation of cingulate and paracingulate aspects of the ACC was not undertaken in previous studies, and the precise location of previously observed dorsal reductions is not clear. Therefore, in order to clarify whether observed alterations in cingulate portions of the ACC are accompanied by the reverse alterations in the adjacent paracingulate, future research should differentiate between the two, and/or provide spatially localised accounts of volumetric alterations observed in this region.

The dorsal ACC is implicated in a suite of processes that can loosely be grouped as executive functions (Allman, Kakeem, Erwin, Nimchinsky & Hof, 2001), most particularly conflict monitoring (Botvinick et al., 2004). Activation of the dorsal ACC is associated with focussed attention on effortful cognitive tasks (e.g., Raichle et al., 1994) and the dorsal ACC’s contribution to focussed attention is interrupted by state anxiety (Mizuki et al., 1989). Dorsal ACC volume has also been implicated in inhibitory control (Casey et al., 1997). Suppression of the affective regions of the ACC during cognitive tasks, and of cognitive regions during affective processing and experience has been observed (Drevets & Raichle, 1998; Bush et al., 1998; Bush et al., 1999). Thus it is likely that altered functioning in the dorsal ACC may contribute to some of the cognitive difficulties associated with depressive illness, and in particular difficulties in attention and the inhibition of anxious rumination.

If the observed alterations in dorsal ACC structure correspond to sub-optimal functioning, it is also possible that the combination of reduced conflict monitoring capacity, and an associated decrement in decision-making and planning ability may combine with dysfunction in the dorsal ACC’s putative role in conversion of cognitive processes into physical action (B. A. Vogt et al., 1995), to contribute to the avolitional nature of depressive symptoms.

In light of the scarcity of previous volumetric research measuring the dorsal ACC in depression, and particularly in adolescent depression, it is not possible to interpret these findings with certainty. However, the extant literature provides some indications of specific ways in which the dorsal ACC may be related to clinical features of mood disorder, and the present finding should orient future investigation towards this structure in paediatric and adolescent depression.

8.5.3.3 Rostral anterior cingulate cortex

It was hypothesised that reduced rostral ACC volume would predict the onset of depression in adolescence. The current study found the opposite; that larger volumes of the right rostral cingulate predicted symptom increase for both girls and boys, as reflected in the CES-D Total
score, and the CES-D Wellbeing subscale for girls. Complementing this, smaller right rostral paracingulate volume predicted case level depression as measured on the KSADS-PL for both genders.

Overall, findings for the rostral ACC were consistent – enlargement in the right rostral cingulate and a corresponding decrease in the right rostral paracingulate. Given the relative recency of research interest in this area, these findings reinforce the value of separate delineation and inclusion of this region in research on mood disorder. Particularly important is delineation of cingulate and paracingulate divisions, in order to clarify whether reduction in one area corresponds to enlargement in the other, as was the case in these findings and those in the dorsal ACC.

Rostral ACC was the only structure that predicted change in CES-D Total score, and one of only two regions of interest that predicted case-level depression. This suggests that the rostral ACC may have particular relevance to clinical depression. Interestingly, several functional studies have found that rostral activity is associated with treatment response (Mayberg et al., 1997; Müllert et al., 2007; Pizzagalli, 2011; Pizzagalli et al., 2001). Previous meta-analysis also found that the most robust volumetric effect associated with depression was reduction in the rostral ACC, which was more pronounced in those with longer illness durations (Bora et al., 2012a).

The rostral ACC has been particularly associated with representation of reward, and approach motivation and behaviour, especially related to social stimuli (D. M. Pavlovic et al., 2009). Anhedonia, often considered the definitive feature of clinical depression, has been linked with rostral ACC function (Keedwell et al., 2005). This complements previous findings suggesting that the rostral ACC is involved in the subjective experience of pleasure. The current findings lend extra support to these theories in that, as well as predicting change in total CES-D symptoms, rostral ACC also predicted change on the Wellbeing subscale for females. Items on the Wellbeing subscale include “Enjoyed life” and “Felt happy”, indexing the subjective experience of positive affect. There is also an element of social-affective processing in the item “Felt as good as other people”. This suggests that the enlargement in right rostral cingulate has a particular relationship with a reduction in positive affect. The rostral ACC has been implicated in both positive (e.g., Bartels & Zeki, 2004) and negative affect (e.g., Somerville et al., 2006). Given this, and the region’s association with CES-D Total score, it is possible that there is a relationship with negative affect as well. The lateralisation of several findings for this thesis in the right rostral ACC lends support to the idea that this side, similar to other frontocortical areas, may be specialised for negatively valenced affect.
Another potential function of the rostral ACC concerns pain. While the dorsal ACC is more often discussed with regard to the affective experience of pain (Rainville, Duncan, Price, Carrier & Bushnell, 1997; Tölle et al., 1999; Peyron, Laurent & García-Larrea, 2000) there is also evidence that the rostral ACC has its own unique role in pain processing.

Figure 43, reproduced from Eisenberger and Lieberman (2004), maps the location of activity in several functional studies and demonstrates that while the experience of pain appears to be localised in the dorsal ACC, the anticipation of pain is represented in the rostral ACC.

**Figure 43.** Localization of activity in several studies that activated rostral ACC vs. dorsal ACC (reproduced from Eisenberger and Lieberman, 2004).

In the same paper, Eisenberger and Lieberman present evidence for the neural overlap of representation of socio-emotional and physical pain, suggesting that the rostral ACC may have a role in the anticipation of pain from a range of sources, including interpersonal ones. An over-active anticipatory focus on negative events or experiences is characteristic of depression, and is reflected in the Wellbeing scale item “Felt hopeful”. Thus it seems fitting that a larger rostral ACC, particularly on the right, may be associated with the more negative expectation for the future characteristic of depression.
Given the recency of interest in the rostral ACC as distinct from adjacent areas, and the scarcity of volumetric findings in this region, it is too early to present a strong single interpretation of the current results. However, several possibilities emerged from the findings of this thesis, focussing on the rostral ACC’s role in the experience of positive affect and reward approach behaviour, its role in negative affect especially related to social cues, and in particular its link with the anticipation of pain.

8.5.4 Orbitofrontal cortex

A tentative hypothesis was made that some alteration in orbitofrontal cortex volume would predict the emergence of depression. The current study found that larger right orbitofrontal cortex volume was associated with increase in Somatic symptoms, and that this effect was largely accounted for by the lateral portion of the orbitofrontal cortex.

The most frequent finding in depressed adults has been for grey matter reductions in the orbitofrontal cortex (see Arnone et al., 2012, for meta-analysis). However, the current observation accords with Chen and colleagues’ (2008) finding that, before Bonferroni correction, right lateral orbitofrontal cortex total and grey matter volume was greater in depressed adolescents than controls, as well as Najt and colleagues’ (2007) finding of enlarged lateral orbitofrontal cortex volumes in bipolar depression.

That larger right lateral orbitofrontal cortex was associated with depression is reasonable, given its putative role in response inhibition and sensitivity to punishment related information. The right orbitofrontal cortex has been associated with a more active behavioural inhibition system, and chronic prevention (as opposed to promotion) focus (Eddington et al., 2009). The latter was especially the case in depressed individuals, and was particularly associated with the right lateral orbitofrontal cortex. While the medial orbitofrontal cortex is associated with reward learning, the lateral orbitofrontal cortex is associated with inhibition of responses, especially previously rewarded responses (Elliott et al., 2000). There is intuitive appeal in the idea that this may relate to the experience of frustrative non-reward in depression. Over-activity of the right lateral orbitofrontal cortex may contribute to the increased sensitivity to punishment and reduced motivation to pursue previously rewarding activities observed in depression, manifesting behaviourally in withdrawal and avoidance.

In adult samples, bilateral orbitofrontal cortex reductions have been associated with depression (Rajkowska et al., 1999; Lacerda et al., 2004; Bremner et al., 2002; Lai et al., 2000), and it has been suggested that these either relate to excitotoxic damage, or reflect a compensatory alteration.
in response to functional abnormalities in connected regions. The former interpretation seems more likely given the current finding of enlarged right orbitofrontal cortex prior to depression onset, in combination with Bora and colleagues’ (2012b) meta-analysis findings that orbitofrontal cortex reductions were more pronounced in later life depression and unmedicated MDD. The prefrontal cortex may, in primates at least, have a higher concentration of glucocorticoid receptors than the hippocampus (Sánchez, Young, Plotsky & Insel, 2000), rendering it particularly vulnerable to insult via high levels of glucocorticoids.

In many cases of depression, accelerating frequency and increasing context-independence of depressive episodes is observed over the life course, as was discussed in Chapter 1 (Harrington et al., 1997; Weissman et al., 1999). Stress-related cell damage and reduction in orbitofrontal cortex volume in adults with depression may contribute to this pattern. The progressive worsening of depressive illness, and the decoupling of depressive episodes from stressful life events may correspond to limbic hyperactivation, and eventual limbic irritability, in combination with decreasing inhibitory capacity of top-down regulatory structures including the orbitofrontal cortex.

8.5.4.1 The orbitofrontal cortex’s role in emotion regulation

Depression has been associated with deficits in the ability to down-regulate amygdalar activity in response to negative emotional stimuli, and less frequent use of cognitive reappraisal (putatively subserved by the orbitofrontal cortex) as an emotional regulation strategy (Kanske, Heissler, Schönfelder & Wessa, 2012).

Altered functional connectivity between the amygdala and prefrontal regions including the orbitofrontal cortex has been implicated in emotion regulation deficits in depression. Specific emotion regulation strategies have been found to recruit distinct prefrontal regions: reappraisal of a stimulus as less negative or threatening specifically activates the orbitofrontal cortex, whereas cognitive distraction recruits parietal, dorsomedial prefrontal and anterior cingulate areas (Kanske, Heissler, Schönfelder, Bongers & Wessa, 2011; McRae, Hughes, Chopra, Gabrieli, Gross & Ochsner, 2010). Kanske and colleagues (2012) found increased right lateral orbitofrontal cortex activation in people with a history of depression when presented with negative stimuli and asked to use a cognitive reappraisal strategy. These participants used cognitive reappraisal less often in daily life, and less effectively down-regulated amygdalar activity when they used this strategy in the experimental setting. The authors interpreted this, and the hyperactivation observed in the lateral orbitofrontal cortex in depression (Drevets, 2007) as representing a compensatory mechanism for dysregulated amygdalar function. However, given
that the increased orbitofrontal cortex activation did not appear to effectively down-regulate amygdalar activity, the compensatory efficacy of this activation is questionable, and, as noted by the authors, represents a loss of neural efficiency. In other words, according to the compensation theory, people with depression need to recruit greater neural resources when required to regulate negative emotions. The finding of enlarged right lateral orbitofrontal cortex as a predictor of Somatic symptoms suggests an alternative to the compensation interpretation. While enlargement in size and increase in activation are not necessarily analogous, it is likely that they are related. That differences in the right lateral orbitofrontal cortex were observed prior to the onset of depressive symptoms suggests that alterations in this region (perhaps underlying the hyperactivation noted above) are a marker of vulnerability for depression, as opposed to a compensatory emotion regulation mechanism – particularly in combination with this thesis’ finding that there were no alterations to amygdala size predictive of depression.

8.5.4.2 The orbitofrontal cortex and reward

That the right lateral orbitofrontal cortex was positively associated with Somatic symptoms in particular is consistent with previous research implicating the orbitofrontal cortex in regulating approach behaviours. Within the Somatic symptoms subscale were items like “Did not feel like eating” (the orbitofrontal cortex has been implicated in the pleasurable experience of eating; Small, Bender, Veldhuizen, Rudenga, Nachtigal & Felsted, 2007), “Could not get going”, “Everything was an effort” and “Talked less”. All of these items can be interpreted as indicating suppression of approach behaviour or appetitive drive. Within the orbitofrontal cortex function for decision-making in the calibration of risk and reward, the lateral orbitofrontal cortex has been suggested to specialise in suppressing responses that had previously been rewarded. Loss of motivation for previously pleasurable activities is central to depression, and larger size and (previously observed) over-activity of the right lateral orbitofrontal cortex may reflect a pathological suppression of pursuit of rewarding experiences, or in combination with amygdalar over-activity an unbalanced calibration of the risk for punishment associated with reward-driven behaviour, in line with the association between right frontal activity and prevention focus observed by Amodio and colleagues (2004).

In conclusion, the finding that right lateral orbitofrontal cortex enlargement predicted an increase in Somatic symptoms raised some interesting questions and allowed further interpretation of previous findings. In particular, findings of enlarged regulatory prefrontal structures as a predictor of depressive symptoms challenge the utility of maturational disparity theories in explaining depression. These findings do not suggest that depression is predicted by
under-developed prefrontal regulation of negative affect associated with limbic activity during adolescence. Rather, they were interpreted as suggesting an over-regulation of reward pursuit; however further research linking frontal volumes to function, and both to behaviour is needed to substantiate this theory.

8.5.5 Corpus callosum

The literature review showed that both expansions (Walterfang et al., 2009; Wu et al., 1993; MacMaster et al., 2012) and reductions (Lyoo et al., 2002; Sun et al., 2009) in regions of the corpus callosum have been associated with depressive illness, largely in adult samples. There were also preliminary indications that other measures of callosal morphology such as length are associated with depression (Wu et al., 1993; Lacerda et al., 2005; Walterfang et al., 2009c). Given that volumetric research into the corpus callosum in depression is limited, it was not possible to form a hypothesis and callosal measures of midsagittal area and length were entered into the analysis in an exploratory manner. Of these measures, only callosal midlength predicted any change in depressive symptomatology; in both males and females, greater midlength was associated with a rise in symptoms on the CES-D Wellbeing subscale.

The null finding for area may reflect the lack of spatial localisation available using the measurement method chosen in this thesis, and therefore cannot be considered definitive. However, if future findings with healthy adolescents prior to the onset of depression also indicate that there is no alteration in corpus callosum area or volume, this may suggest that alterations to callosal volume previously associated with adolescent depression either occur after onset of symptoms or are markers of a particular subtype of depression not captured with adequate frequency in the current sample. For example, influences of familial risk for depression on callosal morphology were discussed in some previous studies (Frodl et al., 2012; Lacerda et al., 2005). Ritchie and colleagues (2012) examined the neurostructural correlates of childhood maltreatment in elderly persons and found that there were no relationships between corpus callosum size in later life and a history of childhood adversity. However, they did find a relationship between exposure to parental mental illness and greater corpus callosum area. Although it is not possible to draw direct conclusions from this, it is possible that this indexes a genetic contributor to callosal size related to familial risk for depression (although other explanations are also possible, such as compensatory brain development mechanisms over the life span). A small group of studies have begun to further examine commonalities between genetic features and white matter alterations in depression (reviewed in Tham, Woon, Sum, Lee & Sim, 2011).
Three studies (Walterfang et al., 2009a; Lacerda et al., 2005; Wu et al., 1993) have previously noted associations between depression and corpus callosum length, and several other studies have found relationships between length and other forms of psychopathology, however none have ventured much interpretation of these findings. It is worth highlighting prior to the review below that comparison with other findings should take into account methodological differences – many previously reported findings measured corpus callosum length from the anterior-most to posterior-most point on the midsagittal slice. The method used in this thesis identified endpoints which maximised the length produced and followed the curve of the corpus callosum to end at the rostrum, rather than the anterior-most part of the genu.

Wu and colleagues (1993) found that corpus callosum length was greater for depressed women than controls. Lacerda and colleagues (2005) found that greater length was associated with earlier age of onset and longer illness duration in adult major depression, both indicators of poorer prognosis (Lewinsohn et al., 1998; Lewinsohn et al., 1993; Weissman et al., 1999). Walterfang and colleagues (2009c) found no differences in total cross-sectional area or curvature of the corpus callosum between currently depressed, remitted, and never depressed adults but noted a trend for longer corpora callosa in the never depressed group – a contrasting finding to those of Wu and colleagues (1993) and Lacerda and colleagues (2005).

In male autistic children (mean age 10 years), reduced anterior-posterior corpus callosum length has been observed (Vidal et al., 2006). In schizophrenic men, an increase in corpus callosum length was reported (Mathew, Partain, Prakash, Kulkarni, Logan & Wilson, 1985) however conversely Colombo, Bonfanti and Scarone (1994) found that in a group of schizophrenics, corpus callosum midlength was positively associated with the Global Assessment of Functioning (GAF) score and age of onset. They speculated that as higher GAF and later age of onset predicted better outcome, longer corpus callosum may be a marker for better prognosis (in contrast with Lacerda and colleagues’ 2005 finding). Hauser, Dauphinais, Berrettini, DeLisi, Gelernter and Post (1989) compared callosal area, width and length between adults with schizophrenia, bipolar disorder, and controls. The only measure to differentiate between groups was length; participants with bipolar disorder had shorter callosal lengths than controls or schizophrenic patients. Finally, Walterfang and colleagues (2009a) found a trend towards longer callosum midlength in bipolar patients with a family history of affective illness compared to those without (in contrast with Hauser et al., 1989).

In conclusion, the finding that greater corpus callosum midlength was associated with increase in depressive symptoms was somewhat unexpected – however upon closer examination of previous
literature there are indications that a reasonable number of studies have also noted length alterations associated with depression and other forms of psychopathology. As discussed with regard to maltreatment, it is possible that corpus callosum length alterations reflect processes occurring very early in life – even prenatally. Genetic and gestational influences on corpus callosum length have already been mentioned with regard to maltreatment. Kochunov and colleagues (2010) examined genetic contributors to white matter microstructure (measured using diffusion tensor imaging; DTI). They found that whole brain fractional anisotropy was linked to a marker on chromosome 15q25, which is in the region containing the family of MDD2 genes, previously associated with depressive illness (Holmans et al., 2004). Maternal mental illness may create both genetic and gestational conditions (in the form of altered hormonal milieu for the developing foetus), which could be reflected in corpus callosum length. Further research into genetic and very early life influences on corpus callosum length, and the inclusion of length as a variable in more studies of corpus callosum morphology, will help in the interpretation of these findings.

This concludes the discussion of individual structural measures as predictors of depressive symptom change. Before moving on to the final Research Question, it is worth commenting on the implications of these findings for the neurobiological models of affect regulation introduced in Chapter 2.

8.5.6 Relevance to neurobiological models of affect regulation

The findings that both subcortical and prefrontal structures predicted depression are of relevance to interpreting neurobiological models of affect regulation. For example, these findings implicate structures in both the affective and cognitive-regulatory social information processing nodes of Nelson and colleagues’ (2005) model of adolescent depression, suggesting that premorbid and pre-adolescent status of components of both these nodes influence their functioning during adolescence (as implied by the emergence of depressive symptoms).

The larger lateral orbitofrontal cortex observed prior to depression onset may have particular relevance to Davey and colleagues’ (2008) theory on the depressogenic functions enabled by the maturing orbitofrontal cortex in terms of the capacity to represent more distal, and more frustratable, rewards.

Forbes and Dahl (2005) argued that although heightened negative affect is an easily recognised sign of depression, the core of the disorder lies in the reduction of positive affect, which differentiates depression from other psychiatric disorders (Clark & Watson, 1991). This thesis
found alterations in regions associated with the production of both positive (e.g., the rostral ACC) and negative affect (e.g., the amygdala) and the processing of reward (the orbitofrontal cortex). Also of relevance to this is the predominance of the Wellbeing subscale in the positive findings. This subscale consists of items indexing positive affect (e.g., “Felt happy”, “Enjoyed life”) and was the measure of depressive symptoms most frequently predicted by neuroanatomical variables.

The implications of these findings for maturational disparity theories are open to debate, and with a single time-point at which volumetric measures were taken, the scope for contribution to these theories is limited. However, it can be noted that structures associated with both the production and the regulation of affective states were shown to be altered prior to the onset of depression, and very early in adolescence. Where alterations in subcortical structures were presented, they were in the form of reductions. Alterations in cortical structures on the other hand more often took the form of increases in volume. The larger lateral orbitofrontal cortex noted particularly suggests that a simplistic interpretation of maturational disparity describing an overdeveloped limbic system and underdeveloped frontal regulatory system is unlikely to be useful.

8.6 Research Question 4: Do neuroanatomical features mediate relationships between early life adversity and adolescent onset depression?

Structural alterations observed prior to depression onset were investigated as possible neurobiological risk factors, conferred by childhood maltreatment. This was tested through analysis of mediation by brain volumes of the relationship between childhood maltreatment and adolescent depression.

No hypotheses were made regarding mediation analyses, as the results from Research Questions 1, 2 and 3 were required to determine which structures would be analysed under Research Question 4. However it was noted that, according to the hypotheses made under the each of Research Questions 1-3, candidate structures for mediation were concentrated in the prefrontal region – the ACC and the orbitofrontal cortex.

Two neuroanatomical measures were found to be associated with both childhood maltreatment and change in depressive symptoms – corpus callosum midlength and right rostral cingulate volume. However neither was found to mediate the relationship between childhood maltreatment and depressive symptom change. No relationship between maltreatment and orbitofrontal cortex was observed, and therefore this was not considered as a potential mediator.
The rostral anterior cingulate was analysed as a potential mediator for the relationship between neglect and CES-D Wellbeing symptom change, however no mediating effect was found. Relationships between corpus callosum midlength and neglect, abuse, and Wellbeing symptom change were found, and therefore midlength was included in two mediation models. Though neither found a mediating effect, the reduction in the direct relationship between abuse and Wellbeing after inclusion of midlength approached significance, with an Aroian statistic of 1.840 ($p = .066$). The Aroian statistic is relatively conservative (Preacher & Leonardelli, 2001), and the sample size was reduced due to the analysis only of females, therefore it is worth considering corpus callosum midlength in future research involving similar constructs, and testing for mediation where possible.

It is possible that the effects of childhood maltreatment on adolescent mental health are exerted through mechanisms not reflected in structural neuroanatomy. For example, altered functional connectivity between implicated structures, or function of structures affected by implicated regions may act as mediating influences between maltreatment and adolescent depression. Clearly there are multiple interacting factors that link the experience of maltreatment to the onset of depression, which were not reflected in the neuroanatomical measures taken in this research. This was demonstrated in the finding that, while both neglect and abuse predicted increase in depressive symptoms for both genders, neglect only affected structures in girls, and abuse mainly affected structures in boys.

However, some constraints associated with this research should also be considered in interpreting the results. In each instance, the mediation models used data only from the females in the sample, reducing sample size considerably. There was also a low level of childhood maltreatment in the sample, and a small number of participants experiencing depressive symptoms at Time 2. The combination of a halved sample size, and the low numbers of children experiencing both maltreatment and depression mean that null findings for the mediation analysis should not be conclusively interpreted as demonstrating absence of any mediating influence of neuroanatomical variables.

Having considered the findings under each of the four Research Questions, the final sections address strengths and limitations of the research, and recommend foci for future investigation.
8.7 Strengths and limitations

8.7.1 Design
The design of this research was a multi-method (questionnaire, interview, neuroimaging), prospective longitudinal investigation of childhood neglect and abuse, structural neuroanatomy, and adolescent onset depressive symptomatology. The study was prospective in that a group of adolescents without significant depressive symptomatology were selected as participants, received MRI scans before the onset of any depressive illness, and were followed up two to three years later with the aim of identifying experiential and biological contributors to the onset of depression. Repeated measurement of symptomatology at the entrance to adolescence, and then in mid-adolescence, allowed for characterisation of change in symptoms, capturing movement towards case-level symptomatology and distinguishing between adolescent onset depression and pre-existing illness. This facilitated greater specificity of interpretations of observations prior to disease onset and allowed for significant contributions to previous literature, particularly in describing with confidence whether structural alterations associated with depression preceded illness onset.

The research design also allowed for developmental specificity in choosing a cohort with a relatively tight age range in a specific phase of life – tracking a group of participants from very early adolescence into the middle of adolescence and capturing information about young people at the entrance to a period of marked vulnerability for psychopathology.

The research was strongly empirical, and contained a mixture of exploratory and confirmatory elements, however it was guided overall by the acknowledgement that the neurobiological study of developmental psychopathology, particularly related to childhood maltreatment, is a recent endeavour. This attitude informed certain decisions – for example the choice to test for relationships between all variables of interest, despite the presence of hypotheses for some and not others, and the decision not to apply corrections for multiple comparisons to any data analyses performed. It is also of note that the treatment of outliers affected the significance of findings in several cases. The interpretations of findings are put forward with the intention that relationships found and interpretations offered may form the basis for future experimental work, including work on the continued longitudinal follow-up of this sample.

8.7.2 Sample selection
The choice of a psychiatrically healthy sample at Time 1 (early adolescence) was integral to the validity of interpretations about the relationships between neuroanatomical variables and the
onset of depression, and these relationships were the core focus of the thesis. However, choosing a healthy sample precluded adolescents with existing psychopathology related to maltreatment. This may have lead to either a lower prevalence of maltreatment in the sample, or a sample biased towards resilience after maltreatment.

The level of parent education was higher in the sample than the general population, with a bachelor degree the modal level of educational attainment. The adolescents also had a slightly higher than average mean FSIQ (although still within the normal range), and there was a positive relationship between parent education and child FSIQ. Consistent with the literature showing that children of less well educated parents are at greater risk for depression, the adolescent children of parents with lower levels of education in this sample endorsed higher levels of depressive symptoms – although in the hierarchical regression models, once other covariates were accounted for, this was confined to Depressed Affect. Thus the high education level of the parents may have worked against the attempt to risk-enrich the sample.

8.7.3 Interpreting gender interactions for depressive symptoms

Where gender interactions were noted in relationships between neuroanatomical volumes and depressive symptomatology, significant relationships were always specific to females. There was far less depressive symptomatology observed in the males in this sample compared to females; depressive symptomatology in fact reduced from Time 1 to Time 2 for males, and only 6.8% of male participants received a case level diagnosis of depression at Time 2, compared to 17.5% of the females. This imbalance of depressive symptomatology between genders limits the conclusions that can be drawn from the preponderance of female-only effects observed. It is possible that similar structure-symptom relationships exist in males to those observed in females, however the prevalence of depression in the males in this sample may have been too low to detect them. Future research could include a greater proportion of males to increase the likelihood of obtaining an adequate sample size of boys. Future longitudinal research with this population may also yield more information as the number of boys experiencing depression is likely to increase.

8.7.4 Measurement of maltreatment

While the design was prospective with regard to the onset of depressive illness, childhood neglect and abuse were measured retrospectively at the second time point. This potentially introduced systematic error, in terms of likelihood of participation of families with adverse experiences, social acceptability biases in reporting of adverse childhood environment, and potential relationships between experience of depressive symptoms and recall bias for negative
childhood experiences. This measurement technique reflected the pragmatic limitations of a PhD thesis rather than a theoretical principal.

Retrospective reports of childhood experience cannot provide evidence of the direction of relationships between maltreatment and neuroanatomy. It is possible for example that behavioural characteristics associated with individual differences in brain structure may render some children more vulnerable to experiencing maltreatment. Alternatively, as an endophenotype, altered brain structures may be one manifestation of heritable characteristics which may contribute to family members’ maltreatment behaviour. Thus the alterations in brain structure may be present in parents and children, and may be contributing factors for abusive or neglectful behaviour, rather than results of these experiences for the children (Teicher, Tomoda & Andersen, 2006). Exploration of genetic and epigenetic influences which may link parental characteristics, experience of maltreatment, brain morphology and incidence of depression would be a valuable extension of research with this and other samples.

Overall, there was a low base rate of all types of maltreatment measured – this was expected given the construction of a healthy sample. The extremely low rate of sexual abuse meant that sexual abuse scale items were not included in either of the maltreatment variables used in regression modelling. Sexual abuse is a strong predictor of depression (Putnam, 2003) and the exclusion of these data may have limited the results.

Despite the multiple limitations identified with the measurement of childhood adverse experiences, this variable was still considered worth exploration given the emerging nature of research into childhood maltreatment and brain development, and the known difficulties measuring childhood maltreatment in all protocols, and this portion of the study was conducted with hypothesis generation for future research in mind.

8.7.5 Potential confounds of the relationship between maltreatment and brain structure
There were several potential influences on brain structure which were not measured, but which could be confounded with risk for maltreatment and/or depression. Future research on this and similar samples would benefit from measuring gestational and birth factors (e.g., pre-term birth, maternal stress, maternal substance use) and parental mental health in order to disentangle the potential contributors of these from the experiences of childhood maltreatment and genetic versus environmental contributors to both depression and brain development.
8.7.6 Measurement of depressive symptoms

The use of multiple measures of depression was a strength of this research. There were remarkably few commonalities in association between brain structures and the different subtypes of depressive symptoms measured, and little agreement in findings between case level depression and depressive symptom change. The need for this kind of specificity in depressive symptom measurement was well articulated in the 2003 strategic plan for mood disorder research from the National Institute of Mental Health:

Advances in depression research and treatment development are highly dependent on the quality of research procedures to measure, assess, or classify the pathology and its expressed symptomatology. A major challenge for the future will be to build a more neurobiologically plausible scheme for characterizing the heterogeneity of depression based on the location and nature of the abnormality in particular circuitry. Though undoubtedly ambitious, such an effort will lead to considerably more consistent findings at the biological level and also will enable us to more rigorously characterize different forms of depression. National Institute of Mental Health, 2003, p. 93

The current research was able to contribute to this goal through the measurement and analysis of separate depressive symptom types. For example, a particular relationship between Somatic symptom change and orbitofrontal/ventral anterior cingulate regions emerged, and was suggested to relate to these areas’ putative functions in visceromotor control (Freedman et al., 2000), SNS regulation (Drevets et al., 2008) and appetitive drive (e.g., Small et al., 2007). Change on the Wellbeing subscale, on the other hand, was predicted by multiple structural volumes, lending neurobiological support to Forbes and Dahl’s (2005) assertion that alteration in positive affect forms the basis of depressive illness. Findings such as these demonstrate that there is marked variability in the relationships between different brain structures and types of depressive symptoms and highlight the need for dimensional measures of symptom profiles in future research into neurobiological correlates of depression.

8.8 Foci for future research

Specific implications for future research were discussed for each region of interest under the relevant structure headings. The following sections concern broader factors which were beyond the scope of this thesis, but which are likely to affect and interact with the variables measured.
8.8.1 Puberty

As reviewed in the introduction, pubertal development has been related to level of depression in girls, even when age and pubertal timing are controlled for (Angold et al., 1998; Patton et al., 1996). Angold and colleagues (1999) provided strong evidence implicating oestrogen in the development of depression in adolescent girls. The onset of puberty has been shown to affect structural properties of multiple brain regions (Peper et al., 2009) making it an important covariate for future studies of brain morphology in adolescence.

8.8.1.1 Pubertal development and the diathesis for affective disorder in girls

Hormonal changes at puberty are thought to catalyse the development of depression in some women. Oestrogen in particular is recognised as playing an important role in mediating females’ sensitivity to stress. The withdrawal of oestrogen prior to menstruation may be analogous to the physiologic effects of anxiolytic withdrawal, creating a greater sensitivity to the anxiogenic and depressogenic effects of negative life events. At the onset of puberty for males, on the other hand, the increase of testosterone has been found to protect against depression and anxiety, although it tends to increase aggressive and risk-taking behaviours (Seeman, 1997).

The cyclical release and withdrawal of oestrogen is thought to form a biological kindling which increases stress reactivity of at-risk individuals to negative life events. The interaction of hormonal change and other risk factors such as childhood adverse experiences may therefore create a vulnerability diathesis upon which social influences may act as a catalyst to generate gender difference in rates of depression (Allen, Barrett, Sheeber & Davis, 2006).

In support of the putative interaction between pubertal oestrogen changes and negative life events, while pubertal oestrogen level rise accounted for 4% of variance in increased negative affect reported by adolescent girls, the joint contributions of oestrogen rise and negative life events accounted for 17% of the variance (Brooks-Gunn & Warren, 1989). It would appear that the onset of puberty sensitises young women to the stress of negative life events, and possibly desensitises young men, via the protective influence of testosterone. Accordingly, after the onset of puberty, the relationship between stress and negative affect strengthens for young women, and declines almost to elimination in young men (Angold et al., 1999).

8.8.1.2 Pubertal timing

Pubertal timing may be affected by childhood stress (Ellis, 2004), and has long been implicated as an influence on adolescent depression, particularly in girls. In combination with the effects of puberty onset on brain structure (Peper et al., 2009) this makes pubertal timing a potential
contributor to relationships between childhood stress, brain development and adolescent depression.

While there are some variations, research generally indicates that girls who mature earlier than their peers are at greater risk for a range of adverse outcomes during adolescence (Burt, McGue, DeMartre, Krueger & Iacono, 2006; Obeidallah, Brennan, Brooks-Gunn & Earls, 2004; Dick, Rose, Viken & Kaprio, 2000; Prokopcekova, 1998; Tschann, Adler, Irwin, Millstein, Turner & Kegeles, 1994; Kaltiala-Heino, Kosunen & Rimpela, 2003; Natsuaki, Biehl & Ge, 2009; Graber, Lewinsohn, Seeley & Brooks-Gunn, 1997; Kaltiala-Heino, Marttunen, Rantanen & Rimpelä, 2003; Ge, Conger & Elder, 1996).

A large scale prospective study found that early puberty was associated with at least one adverse outcome during mid adolescence on all domains measured: crime, substance use, school/peer problems, home problems, sexual behaviour, and psychiatric functioning (Copeland, Shanahan, Miller, Costello, Angold & Maughan, 2010). However, almost all of these problems had attenuated by the time the participants were young adults; only depression persisted. It is unclear what could cause the maintenance of depression as compared with other adverse outcomes – it is possible that the premature exposure of a developing brain to the organizing effects of gonadal steroids may alter an individual’s developmental trajectory, and perhaps canalize certain behavioural and emotional patterns of responding (Sisk & Foster, 2004). Brain structures associated with intense emotional experience and motivation tend to mature earlier than those involved with self-regulation, and early influence on these areas may explain why depression persisted into young adulthood for this group.

The discussion above highlights the strong intersection between pubertal factors and risk for depression, particularly in girls. In future research, the use of hormonal measurements to assess stage and timing of puberty would improve the specificity of findings relating brain structure to depression, and such measurement has since commenced with this sample. In addition, future research that can longitudinally measure brain development, pubertal development, and life experiences in parallel would allow examination of whether early experience and pubertal development can indeed have a prematurely organising effect on the developing brain.

8.8.1.3 Interpersonal stressors: a mediator between pubertal processes and depression in females
It has been suggested that the relationship between pubertal hormone changes and depression in females is mediated by negative life events. The precipitants of early episodes of depression are usually social events (Cyranowski et al., 2000; Hankin & Abranson, 2001; Rudolph, Hammen,
Burge, Lindberg, Herzberg & Daley, 2000). The correspondence between the findings of a specific association between interpersonal stress and risk for depression on the one hand, and the evidence of increased affiliative proclivities amongst females, (both as compared to males, and after menarche) on the other, led Cyranowski and colleagues (2000) to examine potential biological substrates for female affiliative behaviour. Non-human mammal research has strongly implicated the hypothalamic neuropeptide oxytocin in affiliative and care-giving behaviours (Depue & Lenzenweger, 2001). Oxytocin transmission is thought to be regulated by oestrogen and progesterone levels, giving rise to the idea of a hormonally driven pubertal increase in affiliative proclivity for females (Cyranowski et al., 2000). This potential connection between pubertal development and an increase in biologically controlled sensitivity to social stressors allows for a synthesis of psychosocial, biological and stress-response precipitants to adolescent onset depression, with the important caveat that the role of oxytocin in human female affiliative behaviour is yet to be fully understood. Although the formation of affiliative networks is in itself a protective factor against depression, the increased desire and need for these relationships may mean that affiliative failures form potent stressors for girls.

The changes in depression scale scores from Time 1 to Time 2 in this sample did not follow the broader epidemiological pattern of increased depression in girls as clearly as expected. One possible reason for this was that the CES-D has been shown to be sensitive to life-events shortly prior to administration (Radloff, 1977). Given the heightened volatility of interpersonal relationships during adolescence, and the research reviewed above which indicates that pubertal processes render girls particularly vulnerable to negative outcomes from interpersonal difficulties, measurements of both puberty and peer processes are highly suitable for inclusion in future psychobiological research on the development of depression in adolescent girls.

As demonstrated by the sections above, multiple aspects of puberty including biological and psychosocial factors are likely to interact in the generation of risk for adolescent onset depression. While the construction of an early adolescent sample within a narrow age range was a strength of the current research design, greater specificity of assessment regarding the physiological processes of puberty could be achieved by hormonal measures, and will assist future research in parsing and understanding the contributions of biological and psychosocial factors to the development of depression.

There was another aspect of the current research design which would also benefit in future from more specifically pinpointing the developmental stage at which it occurred – the timing of childhood maltreatment, as considered below.
8.8.2 Developmental timing of maltreatment

While it is generally thought that earlier and more prolonged childhood maltreatment is associated with greater effects on neurodevelopment, it has also been suggested that individual neuroanatomical regions become particularly susceptible to the effects of stress at differing times, according to their own schedules of development, leading to windows of vulnerability, or sensitive periods. In their review, “Stress, sensitive periods and maturational events in the adolescent brain”, Andersen and Teicher (2008) outline developmental factors germane to the study of adolescent onset depression. They discuss the possibility that early windows of vulnerability exist, during which depressogenic environmental influences may have particular potency, and suggest that this may account for some of the variability in types of psychopathology associated with childhood maltreatment. As discussed in Chapter 2, different maturational trajectories for synaptic arborisation and pruning, connectivity and myelination are observed between genders, between individuals, and between structures within the brain. Environmental stressors may interact with unfolding neurodevelopmental schedules in timing (i.e., during windows of rapid development) and quality (i.e., interactions between the nature of stressors – social, affective, etc. – and the functions of developing brain structures and networks) to produce particular vulnerability to certain environmental stressors and more protracted and permanent neurodevelopmental implications of these experiences. Particularly compelling, though preliminary, evidence for sensitive periods for the neurodevelopmental and depressogenic impacts of early life adversity comes from Andersen and colleagues’ (2008) study into the effects of childhood sexual abuse on morphometry. They found that sexual abuse at age 3-5 years (and, marginally, at 11-13 years) was uniquely associated with reduction in hippocampal volume in young women. Abuse at 9–10 years old was associated with reduced callosal area, while abuse at 14-16 years was associated with reduction in frontal grey matter. They also noted that depressive symptoms in young adulthood were specifically associated with abuse at 3–5 years, while symptoms related to PTSD were uniquely associated with abuse at 9-10 years. Andersen and Teicher (2008) compared findings from this study with preclinical studies with rats and found analogous patterns of alteration in synaptic density corresponding with early and late maternal separation. For both the women who participated in Andersen colleagues’ study (2008) and the rats studied by Andersen and Teicher (2004) and Leussis and colleagues (2008), early stressors were associated with hippocampal alterations, while later (adolescent) stressors were associated with prefrontal cortex alterations. The timing of stressors may impact on the maturation of an individual structure that is in a crucial developmental stage, and may also spur a cascade of alterations in structures whose development is influenced by affected structures. For
example, the prefrontal cortex, with its protracted post-natal development, is affected by the functioning of limbic and striatal systems, which may contribute to the temporal pattern of findings described above.

Puberty and adolescence represent a time of marked functional and anatomical brain development, altered hormonal milieu and sensitivity to pubertal hormones, and new psychosocial opportunities and pressures associated with puberty and adolescence, as discussed in Chapter 2. As highlighted by Andersen and Teicher (2008), neurodevelopmental processes specific to adolescence may trigger or consolidate the expression of underlying vulnerabilities and predispositions. In other words, specific idiosyncratic aetiological predisposing factors (such as genetic makeup and childhood experiences) may interact with universal phenomena (such as pubertal processes). This may factor into the observation that there is often a time-lag (or incubation period) between the adverse experiences of childhood and the depressive sequelae which emerge in adolescence (e.g., Widom et al., 2007a).

Family environment may be conceptualised as a slow-working, iterative influence that may shape the individual’s style of affective response and the neural substrates of this over many years, meaning that an overall rating of adverse experiences across a long time period still has value as a predictive measure. However, different kinds of emotional, cognitive, and neurobiological development occur at various stages of maturation. Ideally the ages of adverse experiences would be included in analyses and this is an area which could be addressed in future research.

As well as the timing of maltreatment, there is also scope for more investigation into the effects of different types of maltreatment on brain development and risk for depression, as discussed in the next section.

8.8.3 Differential effects of different types of maltreatment

This thesis divided maltreatment into neglect and abuse, as dictated by the factor analysis of CTQ responses. This was an important part of the research design and allowed for the demonstration of a different profile of neuroanatomical correlates for each of the maltreatment types, which also differentially affected boys and girls. However, this resulted in the merging of physical and emotional maltreatment in analyses. While physical maltreatment is the subject of more research output, emotional maltreatment is increasingly being recognised as a problem both of high prevalence (Australian Institute of Health and Welfare, 2011) and of powerful influence on children’s emotional development. Given the evidence reviewed in Chapter 4 on development of negative schemas about the self, maltreatment that involves attacks on the
child’s worth and self-identity is likely to be highly precipitant of negative outcomes (Glaser, 2002). Teicher and colleagues (2006a) found that emotional maltreatment was more closely associated with poor psychiatric outcomes than was physical abuse. The US Adverse Childhood Experiences study found that emotional abuse was associated with the highest risk for developing depression in adulthood (Chapman et al., 2004). Verbal abuse has also been found to be a risk factor for several personality disorders, independent of any risk conferred by other types of maltreatment and adversity (Johnson, Cohen, Smailes, Skodol, Brown & Oldham, 2001). Given that emotional abuse \(^8\) is the most frequently substantiated form of abuse in Australia (AIHW, 2011), the effects of such experiences on brain development and mental health are of particular importance; future research could focus on disentangling the particular effects of emotional maltreatment on brain development and wellbeing.

Having discussed several possibilities to improve the measurement of maltreatment, the final section will briefly describe some of the avenues for further exploration of neurobiological correlates of childhood maltreatment and adolescent depression.

### 8.8.4 Comorbidity and parental mental health

It is a limitation of this research that comorbid mental health conditions and substance use in the participants were not considered in the analyses, and neither were parental mental health and substance use. This was necessary to define a realistic scope for the research design, however it is possible that co-morbidity with other disorders may have driven some of the brain differences observed (e.g. the potential confound of amygdala reductions in depression with comorbid anxiety conditions, Bora et al., 2012a; DeBellis et al., 2000a). Drug and alcohol use in both mothers during pregnancy, and children themselves, have been found to have effects on brain development (e.g. Bookstein et al., 2007; Squeglia, Jacobus, & Tapert, 2009). Measurement of parental substance use (especially during pregnancy) and analysis of any comorbid mental health conditions or substance use in participants would be a valuable addition to future research.

### 8.8.5 Measurement of stress hormones

Throughout the literature review and interpretation of findings, a strong emphasis on potential causes and outcomes of disruption to the HPA axis associated with both childhood maltreatment and depression emerged. A key process implicated in much of the research discussed throughout was the alteration to cell and synaptic survival and proliferation associated with increased stress hormone concentrations. Many interpretations of these and previous

---

\(^8\) Defined by AIFS as inappropriate verbal or symbolic acts such as rejecting, isolating, terrorising, corrupting, denigrating and belittling (Holzer & Bromfield, 2010).
findings rested on assumptions about the role of cortisol in volumetric alterations. In order to
test whether these assumptions are accurate, one valuable extension of this research would be to
directly measure stress hormone levels in association with the other variables that this thesis focussed on. For similar reasons, measurement of the pituitary gland would have been a suitable
addition to this research – data on pituitary volumes was not available for inclusion in this thesis,
but has since been analysed and published (Whittle et al., 2012).

8.8.6 Next steps in interpreting structural volumetric findings
The technology available to pursue understanding of neurostructural development has advanced
since this research was initiated, and image acquisition at a higher resolution than was used for
this study will benefit future work with this and other samples. While considerable theoretical
clarity can be achieved from examining simple volumetric measures of brain structures, there are
limitations in this approach for understanding network models of affect regulation. Psychopathologies of affect dysregulation are not likely to result solely from discrete structural
abnormalities, a proposition supported by the rarity of localised legion studies reporting clear
mood disorder sequelae. Viewing affective disorders from a systems level would allow the
incorporation of pathways, or neural circuits, into theoretical models, including measures of
cohesiveness of connectivity between structures, covariance in size of linked structures, and
dysregulating effects of system failure on other linked, but functionally distinct, systems.

Two neural circuits are thought to underlie affective regulation, the ventral and dorsal systems.
The ventral system includes the amygdala, ventromedial orbitofrontal cortex, and ventral ACC,
and is involved in rapid evaluation of the affective significance of stimuli, and corresponding
production of affective states. Dysfunction within the ventral system is thought to result in a
reduction in constraint, and the associated psychopathological symptoms including inability to
suppress negative affect, and maladaptive impulsivity (Bremner et al., 2002; Ghashghaei &

The dorsal system includes the hippocampus, ventrolateral orbitofrontal cortex and dorsal ACC
and suberves a more cognitive form of affective process, including executive control of
affective states. Dysfunction within this system has been associated with increased activity of the
ventral system, resulting in higher negative affect levels, and the psychopathological symptoms
associated with high levels of negative affect (Ghashghaei & Barbas, 2002; Mayberg, 2003; Price,
1999). The anterior ACC is thought to connect the two (Mayberg, 2003). The evidence from this
thesis implicated structures in both the dorsal and ventral systems, suggesting the involvement of
both in the aetiology of depression.
The magnitude of maturation in these two circuits at adolescence is likely to have important implications for an individual’s affect regulation capacity, and thus understanding of the morphometry of the structures themselves should be complemented by quantification of the white matter microstructure connecting them. The use of diffusion tensor imaging, which enables the measurement of white matter connectivity between structures, in future research will allow exploration of the connectivity within these neural circuits and elucidate any relationship between the cohesiveness of these circuits and the emergence of mental illness during adolescence.

8.9 Conclusion
This thesis examined predictive relationships between childhood maltreatment, structural neuroanatomical features in early adolescence, and depressive symptoms in mid-adolescence.

The examination of relationships between maltreatment in childhood and structural neuroanatomical features in a healthy adolescent sample allowed for new insight into the implications of childhood adverse experience for brain development, and assisted in parsing early experiential effects from later psychopathological processes, often indistinguishable in previous studies. This research also allowed for differentiation between neglect and abuse in terms of their influences on brain development and depression. This included the finding that these two types of maltreatment affected males and females differently, with male neuroanatomical volumes predicted only by abuse, and female volumes largely by neglect.

The prospective longitudinal research design allowed for contribution to theoretical debate about the timing of structural alterations previously associated with depression – specifically, whether observed alterations formed risk factors for depression, or whether they were outcomes of disease-related processes. Vulnerability biomarkers for depression suggested by the current findings included corpus callosum midlength, hippocampal volume, and the volumes of orbitofrontal and medial prefrontal regions.

A particularly interesting pattern that emerged from the findings was for premorbid volumetric expansions in frontal regions usually associated with postmorbid volumetric reductions. Enlargement of prefrontal structures (often conceptualised as serving regulatory functions) as predictors of depressive symptoms was inconsistent with maturational disparity theories for explaining adolescent depression, and the possibility that these enlargements instead corresponded to pathological over-regulation of reward pursuit was suggested.
Finally, various implications for future research highlighted by this study were examined. For example, greater specificity of measurement will assist researchers to understand the intersection of external influences on brain development and depression with unfolding developmental processes during childhood, and onset of puberty in adolescence.

It is hoped that these findings contribute to identifying and understanding the links between experiential and biological predisposing factors for depression. In turn, this will assist in better understanding the mechanisms of depressive illness, identifying those most at risk, and designing effective treatments.
References


**Additional references not included in the text:**


Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex, 6*, 215-25.


segmentation equally detect hippocampal volume differences in acute depression. *Neuroimage, 45*(1), 29-37.


the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences, 93*, 1619-1623.


Appendix 1. Sample of communications with participants and families

Affective Dysregulation and risk for psychopathology: Part 2: The neuroanatomical and neurocognitive correlates of three affective temperamental dimensions in adolescents at risk for the development of psychopathology

Participant Information

Dear Participant,

Thanks for all your great help in being a part of the ‘ORYGEN Adolescent Emotional Development Study’. You have been great in filling out the survey at school and at answering some tough questions about yourself and how you have been feeling when we visited you (or for some of you, spoke over the phone). All of your help is going a really long way to understanding why some people your age have some problems with how they are feeling. You might also remember that you are one of a smaller number of kids your age from the study selected to take part a few more times.

What will I have to do for this part of the study?
In this next part of the study, we will be trying to understand how the way the brain looks and works can help our moods. We will be asking you to come along to visit us at one of the places that we work, the Austin Hospital. Here we will be asking you to have a brain scan. It is a bit like an x-ray if you have had one! All you really have to do is to lie in the scanner, a long tube-like machine that takes pictures of your brain (but from the outside), for about 30 minutes. We will have some headphones for you to listen to music whilst the pictures are being taken, or you can even watch a video on a screen at your feet! We will also be asking you to do some do some thinking tasks, some of which will be on a computer – these will take about 40 minutes. These won’t be like school; some kids find them quite fun.

What will happen to my results?
All of your answers to the cognitive tasks will be kept private – this means we don’t tell anyone what you have answered, like teachers at school. The pictures of your brain will also kept private, unless we find some problems (which is very unlikely!), in which case we would let your mum or dad know. And if you have any problems with any of the tasks, or if you want to talk to someone about what you did, the researcher will be happy to help you out.

What if I don’t want to take part in the study?
If at any time during this part of the study you would like to finish, you can. You might find it a bit noisy inside the scanner (when the scanner is on it makes a loud hummm noise), and if you get scared or feel uncomfortable, all you have to do is push a button inside the scanner to make it stop and let us
know you want to come out. And like last time, if you don’t want to do it at all, you don’t have to.

What if I feel nervous about going in the scanner?
If you do feel a bit nervous about being inside the scanner, we can arrange for you to have a look at a pretend scanner before you do the real thing, just so you can see what it will be like. You can talk to your parent or carer, or any of us, about this.

What do I do to take part?
And again, like other times, you will only be able to take part in this study if one of your parents (or the person who cares for you at home) says you can. They will then need to sign a form. You will be asked to sign an agreement form too if you take part. Your parent or carer will also be asked to come with you to the hospital.

Thanks again for your help!

Associate Professor Nick Allen,
ORYGEN Youth Health.

Contacts

Dr. Melissa O’Shea
Project Manager
9342 2800

Dr. Murat Yucel
Neuropsychologist
8345 1303 / 9388 1633
Consent form for persons participating in research projects


Name of participant:  
Address:  
Phone contact:  
Next of kin:  
OPTIONAL: Please provide the name and contact details of someone who will know how to contact you if you move within the next few years:  

Name of chief investigator(s):  
Name of Project Manager: Dr. Melissa O'Shea / Dr. Murat Yucel

1. I (consent/ do not consent) to my child, named above, participating in the above project, the details of which were found in the accompanying information sheet. (Please circle consent status)

2. In my consenting to my child participating in the above study, I acknowledge that:
   a) the researcher or his assistant will administer an MRI scan and a series of cognitive tasks to my child. These procedures will take place at the Brain Research Institute at the Austin Hospital and I can attend with my child if I wish;
   b) the possible effects of the brain scan and cognitive tasks have been explained to me to my satisfaction;
   c) I have been informed that I am free to withdraw my child from the project at any time and in this case, any data supplied by my child will be withdrawn and destroyed;
   d) the project is for the purpose of research;
   e) I have been informed that the confidentiality of the information that my child provides will be protected.

Signature  
Date  

(Parent/Guardian)
Affective Dysregulation and risk for psychopathology: Part 2: The neuroanatomical and neurocognitive correlates of three affective temperamental dimensions in adolescents at risk for the development of psychopathology

PARENT INFORMATION SHEET

Principal Investigator: Assoc. Professor Nick Allen
Project Manager: Dr. Melissa O’Shea

Study Overview.

By now, you and your child have become important participants in the ‘The ORYGEN Adolescent Emotional Development Study.’ Your child’s involvement in the school survey and your family’s involvement in the more detailed home assessment have been fantastic efforts. As you know, this study is investigating how young people regulate their moods and emotions and how difficulties in this area may well be related to problems that are highly common in adolescence such as depression, anxiety and substance use problems.

As we noted when your child participated earlier this year, your child has been selected to take part in the more intensive and most exciting aspect of this project. This aspect of the project allows us to investigate more about how young people regulate their moods, in particular the biological bases of this process. This has not been done in a study of this kind before.

The purpose of this stage of the project is to better understand the relationship between the brain and emotion. We are interested in finding out whether teenagers with different emotional profiles have differences in brain structure (i.e., the size of different brain structures) and function (i.e., blood flow in different brain structures). For example, we are interested in finding out whether individuals who tend to regularly experience negative emotions have differences in brain structure compared to individuals who tend to regularly experience positive emotions. Further, past research has shown that in various mental disorders, there are abnormalities in brain regions that are known to be involved in emotional processing. A second purpose of this project is to examine whether there is a relationship between the brain, one’s emotional profile, and future development of mental disorder.

In this phase of the study, we will be asking that members of our smaller sample attend one session at the Brain Research Institute, Austin and Repatriation Medical Centre, Heidelberg, for the administration of a brain scan (Magnetic Resonance Imaging: MRI) and to take part in some cognitive testing. The MRI is a safe and non-invasive procedure that lasts around 20 minutes and provides us with excellent
information about brain structure and function in regards to how young people regulate their moods. The cognitive tests allow us to investigate in more detail the functioning of areas of the brain related to emotional regulation.

Once again, selection in this phase of the project is not a specific indicator of level of risk for anxiety and/or depression or other mental health or neurological concerns.

Details of this phase of the study are provided below.

**Purposes and Benefits**

Whilst there will be no direct benefit to your child in participating in this study, ‘The ORYGEN Adolescent Emotional Development Study’ the knowledge gained from this phase of the study will help advance our understanding of the neurobiological basis of emotion and individual differences in emotional temperaments. From this research we might also gain insight into the risk factors for mental disorders, thereby providing a basis for future research into early intervention.

**Scanning and Cognitive Testing procedure**

If you agree to your child participating in this phase of the study, they will attend one session at the Brain Research Institute, Austin and Repatriation Medical Centre, Heidelberg. For your child’s comfort, you are asked to accompany them for the session. Transport can be arranged if needed. During this session they will be asked to lie on a table inside a Magnetic Resonance Imaging (MRI) scanner for approximately 30 minutes. During this time the scanner will acquire information about brain anatomy. All of the scanning conducted in the MRI machine will be non-invasive and safe. However, it can be quite noisy and to minimize discomfort in regards to this, your child will be issued with headphones through which they will be able to listen to their choice of music. They don’t need to do anything except relax. One important aspect of the procedure is that your child needs to remain relatively still during the scan. This will be made easier by foam cushioning and velcro bands which will be used to help keep their head relatively still during scanning. While the cushions and bands help to keep the head still, they should be comfortable. Moreover, we will be able to see and communicate with you and your child during the scanning. If your child is becoming uncomfortable or having difficulty concentrating during the session, we can stop the scanning and if desired, continue at another time. They can also request that the scanning be stopped at any time by pushing on a button.

Included with this letter is an MRI information sheet, which describes in a bit more detail the scanning procedure, and what your child must do to prepare for the session. You are asked to read this information sheet carefully, and discuss the scanning procedure with your child. If your child, or yourself, are worried about the procedure or what it entails, we are happy to organize an induction session for your child at the Royal Children’s hospital, where they can visit a mock scanner and familiarize themselves with the equipment before actually having the scan at the Austin Hospital. Please let one of us know whether you would like your child to attend an induction session before signing the consent form.

During the visit to the Austin Hospital, they will also be asked to participate in a number of cognitive tests. These types of tests examine concentration, attention, and
planning skills and have all been well tolerated by young people taking part in similar studies here and overseas. These tasks help us to explore functions of the brain that relate to emotional regulation. Some kids also find them quite fun to complete! They will not receive any scores for these tests; they will just be encouraged to do their best.

Altogether, this phase of the study should take about one and a half hours to complete and you will be recompensed for this time.

Possible risks
The MRI procedure has no known health risks associated with its administration and does not involve exposure to any ionizing radiation. However, participants are instructed not to take metal objects into the scanner. Moreover, parents are advised to let research staff know if their child has any metal implants (i.e., a metal plate or pin) or has been involved in an accident in which metal may have become lodged in any area of their bodies (e.g., eyes).

Whilst the procedure involved in this study is not a full clinical examination, images collected from this assessment will be examined for any unusual features. If the unlikely event that unusual brain features are detected, participants will be referred for a full clinical evaluation and the MRI data will be made available to the treating clinician with participant consent. Parents of these young people will be fully informed of these processes if further investigation is required.

Participation
As in previous stages of this project, before your child participates in this study, you will be asked to provide written consent. By signing the consent form, you are also indicating that you fully understand the conditions of this particular study. Your child will also be asked to confirm their wish to participate prior to the study being conducted. It is important to know that participation in this study is entirely voluntary. Moreover, participation in this phase does not mean that you are required to take part in any other phase of the research, you can make you mind up about that at the time.

In order to recompense you for the time and cost involved in transporting your child to take part in this study, and the time taken for participation, all families taking part will receive $100 to cover these costs.

Confidentiality
Any information collected by the researchers is strictly confidential. All of the information provided by you and your child will be stored securely at ORYGEN Youth Health. The data derived from this study will be used in conjunction with data collected from other sub-projects associated with the ORYGEN Adolescent Emotional Developmental Study, which your child has already participated in. The combined data set will help us to gain a rich understanding of the mechanisms underlying emotional temperament.

Within the limits of the law (i.e., unless we find evidence of any offence that must be reported to authorities by law), we will keep all information confidential and will not provide information about any individual participants to anyone. Participants have already been given a numerical identifier and all subsequent data will be stored in locked files and will be identified using these numerical identifiers, not the names of the parents and students participating in the study or any other identifying information.
Only investigators and a small number of the research staff working on the study will have access to the raw data. Parents will not have direct access to information provided by their child in the survey. The results of the project will only be reported in ways that do not identify individual participants. Moreover, all data provided by you and your child will be destroyed 5 years after the date of the last publication based on this study. Paper copies will be shredded and computer files will be deleted.

**Maintaining Contact**

Once again, this is a longitudinal study and it is likely that we will ask your child to participate in other projects within this phase of the study of which your child is an integral participant. To help us keep in touch with you and your child, we will periodically ask you to confirm your current address or to provide a change of address. Again, if we don’t have an alternative contact such as a relative not living with you or a close friend who we could contact if you have moved from your current address and we cannot get in touch with you, we will ask you to provide one.

**Concerns**

If you or your child has any concerns about how this study is conducted you can contact the Executive Officer, Human Research Ethics at the University of Melbourne. They may be contacted on 8344 2073 (fax: 9347 6739).

**Contacting us**

If you have any questions about this phase of the study or would like to know more about it, please call us here at ORYGEN Youth Health on 9342 2800 and ask for our project manager, Dr. Melissa O’Shea or alternatively, Dr. Murat Yucel (Neuropsychologist) (83451303 / 93881633).
Approval to participate in a research project

PROJECT TITLE: The ORYGEN Adolescent Emotional Development Study – Neuropsychological Testing Phase

Name of participant:
Name of investigator(s): Associate Professor Nicholas Allen, Dr. Murat Yucei, Sarah Whittle

Name of Project Manager: Dr. Melissa O’Shea

After talking about the study with my parents (or guardian), I (agree / do not agree) to take part in this project.

(Please circle)

In taking part, I understand that:

(a) I will have to visit the Brain Research Institute (BRI) and lie inside a scanner for about 30 minutes while pictures are taken of my brain. I will also be required to do some thinking tasks, some of which will be on a computer.

(b) I can stop taking part in the study at any time (including stopping the scanning at any stage when inside the scanner);

(c) the study is just for research;

(d) any results from the scanning or the thinking tasks will be kept private, except that if during scanning you find anything unusual you will let my parents (or guardians) know.

Signature ______________________ Date ____________________
Dear Student,

Thanks for coming in to visit us and taking part in ‘The ORYGEN Adolescent Emotional Development Study’ – Neuropsychological Testing Phase.

We realise that being inside a brain scanner can sometimes be scary, especially because of the loud noise. But we hope that you didn’t find it too uncomfortable.

We also hope you enjoyed doing the thinking tasks. We realise that some of them made you concentrate pretty hard!

If you have any concerns or would like to talk to someone about your experience inside the scanner or about any of the thinking tasks you did, you might want to talk to:

- Your parents or guardians
- A teacher
- A doctor

You might also like to talk to someone involved in our study. You can contact Melissa O’Shea, or myself on 9342 2800.

Thanks once again,
Nick.

Associate Professor Nick Allen

ORYGEN Youth Health
Appendix 2. Independent samples t-test comparing those with present and absent data from T1 CES-D on T2 Questionnaire measures

<table>
<thead>
<tr>
<th>T1 CES-D</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
<th>Mean diff</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 CES-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>125</td>
<td>3.372</td>
<td>0.248</td>
<td>0.022</td>
<td>0.250</td>
<td>134</td>
<td>0.803</td>
<td>0.019</td>
<td>0.077</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>3.353</td>
<td>0.215</td>
<td>0.065</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 CES-D Depressed Affect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>125</td>
<td>2.161</td>
<td>0.282</td>
<td>0.025</td>
<td>0.345</td>
<td>134</td>
<td>0.731</td>
<td>0.030</td>
<td>0.087</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>2.131</td>
<td>0.229</td>
<td>0.069</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 CES-D Somatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>125</td>
<td>2.420</td>
<td>0.269</td>
<td>0.024</td>
<td>0.148</td>
<td>134</td>
<td>0.882</td>
<td>0.012</td>
<td>0.084</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>2.407</td>
<td>0.262</td>
<td>0.079</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 CES-D Wellbeing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>125</td>
<td>1.804</td>
<td>0.352</td>
<td>0.032</td>
<td>0.510</td>
<td>134</td>
<td>0.611</td>
<td>0.056</td>
<td>0.110</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>1.747</td>
<td>0.329</td>
<td>0.099</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 CES-D Interpersonal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>125</td>
<td>2.880</td>
<td>1.286</td>
<td>0.115</td>
<td>-0.523</td>
<td>134</td>
<td>0.602</td>
<td>-0.211</td>
<td>0.403</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>3.091</td>
<td>1.221</td>
<td>0.368</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>126</td>
<td>-0.011</td>
<td>0.318</td>
<td>0.028</td>
<td>-1.374</td>
<td>135</td>
<td>0.172</td>
<td>-0.139</td>
<td>0.101</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>0.128</td>
<td>0.375</td>
<td>0.113</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTQ Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>126</td>
<td>2.899</td>
<td>0.225</td>
<td>0.020</td>
<td>-1.364</td>
<td>135</td>
<td>0.175</td>
<td>-0.100</td>
<td>0.073</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>2.999</td>
<td>0.312</td>
<td>0.094</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 KSADS Depressive Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>126</td>
<td>0.119</td>
<td>0.325</td>
<td>0.029</td>
<td>0.277</td>
<td>135</td>
<td>0.782</td>
<td>0.028</td>
<td>0.102</td>
</tr>
<tr>
<td>Missing</td>
<td>11</td>
<td>0.091</td>
<td>0.302</td>
<td>0.091</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 3. CES-D distribution and transformations

<table>
<thead>
<tr>
<th></th>
<th>Skewness(SE)</th>
<th>Kurtosis(SE)</th>
<th>Shapiro-Wilk</th>
<th>p</th>
<th>Transform</th>
<th>Skewness(SE)</th>
<th>Kurtosis(SE)</th>
<th>Shapiro-Wilk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 Total</strong></td>
<td>1.388(.215)</td>
<td>3.981(.427)</td>
<td>.867</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.821(.216)</td>
<td>0.656(.428)</td>
<td>.959</td>
<td>.001</td>
</tr>
<tr>
<td><strong>T2 Total</strong></td>
<td>1.562(.208)</td>
<td>2.989(.413)</td>
<td>.867</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.818(.208)</td>
<td>0.508(.413)</td>
<td>.949</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T1 Depressed Affect</strong></td>
<td>1.987(.216)</td>
<td>4.152(.428)</td>
<td>.751</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>1.208(.216)</td>
<td>0.728(.428)</td>
<td>.830</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T1 Wellbeing</strong></td>
<td>0.759(.216)</td>
<td>0.447(.428)</td>
<td>.932</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.048(.216)</td>
<td>-0.817(.428)</td>
<td>.948</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T1 Somatic</strong></td>
<td>1.166(.216)</td>
<td>1.748(.428)</td>
<td>.918</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.335(.216)</td>
<td>-0.214(.428)</td>
<td>.975</td>
<td>.019</td>
</tr>
<tr>
<td><strong>T1 Interpersonal</strong></td>
<td>1.418(.216)</td>
<td>1.116(.428)</td>
<td>.723</td>
<td>&lt;.001</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>T2 Depressed Affect</strong></td>
<td>2.143(.208)</td>
<td>4.669(.413)</td>
<td>.691</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>1.498(.208)</td>
<td>1.632(.413)</td>
<td>.769</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T2 Wellbeing</strong></td>
<td>1.246(.208)</td>
<td>1.567(.413)</td>
<td>.859</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.533(.208)</td>
<td>-0.597(.413)</td>
<td>.914</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T2 Somatic</strong></td>
<td>1.193(.208)</td>
<td>2.035(.413)</td>
<td>.912</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>.344(.208)</td>
<td>0.095(.413)</td>
<td>.972</td>
<td>.010</td>
</tr>
<tr>
<td><strong>T2 Interpersonal</strong></td>
<td>1.664(.208)</td>
<td>2.753(.413)</td>
<td>.717</td>
<td>&lt;.001</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Appendix 4. CTQ distribution and transformations

<table>
<thead>
<tr>
<th></th>
<th>Skewness(SE)</th>
<th>Kurtosis(SE)</th>
<th>Shapiro-Wilk</th>
<th>p</th>
<th>Transform</th>
<th>Skewness(SE)</th>
<th>Kurtosis(SE)</th>
<th>Shapiro-Wilk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td>2.367(.207)</td>
<td>7.875(.411)</td>
<td>0.744</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>1.314(.207)</td>
<td>1.663(.411)</td>
<td>0.847</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neglect</td>
<td>1.292(.207)</td>
<td>1.542(.411)</td>
<td>0.873</td>
<td>&lt;.001</td>
<td>Ln</td>
<td>0.325(.207)</td>
<td>.415(.411)</td>
<td>0.941</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
## Appendix 5. Region of interest distributions and transformations

<table>
<thead>
<tr>
<th>Region</th>
<th>Skewness (SE)</th>
<th>Kurtosis (SE)</th>
<th>Shapiro-Wilk</th>
<th>P</th>
<th>Transform</th>
<th>Skewness(SE)</th>
<th>Kurtosis(SE)</th>
<th>Shapiro-Wilk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume (Grey and White)</td>
<td>.047(.207)</td>
<td>-.229(.411)</td>
<td>.994</td>
<td>0.838</td>
<td>N/A</td>
<td>-.012(.207)</td>
<td>-.931(.411)</td>
<td>.077</td>
<td>.058</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>.213(.207)</td>
<td>.122(.411)</td>
<td>.989</td>
<td>0.364</td>
<td>N/A</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>.546(.207)</td>
<td>.625(.411)</td>
<td>.973</td>
<td>0.012</td>
<td>N/A</td>
<td>.359(.207)</td>
<td>-.216(.411)</td>
<td>.072</td>
<td>.097</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>.400(.207)</td>
<td>.322(.411)</td>
<td>.985</td>
<td>0.179</td>
<td>N/A</td>
<td>-.333(.211)</td>
<td>-.329(.419)</td>
<td>.063</td>
<td>.200</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>.453(.207)</td>
<td>.807(.411)</td>
<td>.984</td>
<td>0.144</td>
<td>N/A</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>.472(.207)</td>
<td>-.683(.411)</td>
<td>.958</td>
<td>&lt;0.001</td>
<td>Power (.55)</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>.245(.207)</td>
<td>-.1065(.411)</td>
<td>.941</td>
<td>&lt;0.001</td>
<td>None</td>
<td>-.198(.207)</td>
<td>-.871(.411)</td>
<td>.097</td>
<td>.004</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>.548(.207)</td>
<td>-.234(.411)</td>
<td>.970</td>
<td>0.006</td>
<td>Power (.66)</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>.157(.207)</td>
<td>-.651(.411)</td>
<td>.985</td>
<td>0.181</td>
<td>N/A</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Left Ventral Cingulate</td>
<td>1.124(.209)</td>
<td>.828(.414)</td>
<td>.902</td>
<td>&lt;0.001</td>
<td>Power (.10)</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Left Ventral Paracingulate</td>
<td>.643(.208)</td>
<td>-.254(.413)</td>
<td>.946</td>
<td>&lt;0.001</td>
<td>Power (.66)</td>
<td>-.333(.211)</td>
<td>-.329(.419)</td>
<td>.063</td>
<td>.200</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>.091(.207)</td>
<td>-.571(.411)</td>
<td>.987</td>
<td>0.275</td>
<td>N/A</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>.706(.207)</td>
<td>-.792(.411)</td>
<td>.890</td>
<td>&lt;0.001</td>
<td>Ln</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>-.049(.207)</td>
<td>-.348(.411)</td>
<td>.992</td>
<td>0.647</td>
<td>N/A</td>
<td>-.125(.207)</td>
<td>-.117(.411)</td>
<td>.041</td>
<td>.200</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>.431(.207)</td>
<td>-.174(.411)</td>
<td>.978</td>
<td>0.034</td>
<td>Ln</td>
<td>-.333(.211)</td>
<td>-.329(.419)</td>
<td>.063</td>
<td>.200</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>.662(.207)</td>
<td>.317(.411)</td>
<td>.955</td>
<td>&lt;0.001</td>
<td>Power (.66)</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>1.198(.211)</td>
<td>1.120(.419)</td>
<td>.880</td>
<td>&lt;0.001</td>
<td>Ln4G10</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>-.444(.207)</td>
<td>1.460(.411)</td>
<td>.983</td>
<td>0.118</td>
<td>N/A</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>-.724(.207)</td>
<td>1.573(.411)</td>
<td>.971</td>
<td>0.007</td>
<td>Power (.12)</td>
<td>-.127(.207)</td>
<td>.410(.411)</td>
<td>.074</td>
<td>.073</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>-.05(.207)</td>
<td>.528(.411)</td>
<td>.993</td>
<td>0.758</td>
<td>N/A</td>
<td>-.205(.207)</td>
<td>.427(.411)</td>
<td>.052</td>
<td>.200</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td>-.644(.207)</td>
<td>1.397(.411)</td>
<td>.971</td>
<td>0.007</td>
<td>Power (.12)</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>-.362(.207)</td>
<td>.766(.411)</td>
<td>.991</td>
<td>0.576</td>
<td>N/A</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td>-.678(.207)</td>
<td>1.274(.411)</td>
<td>.965</td>
<td>0.002</td>
<td>Power (1.33)</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>.920(.209)</td>
<td>3.505(.414)</td>
<td>.956</td>
<td>&lt;0.001</td>
<td>N/A</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>.106(.209)</td>
<td>.501(.414)</td>
<td>.993</td>
<td>0.757</td>
<td>N/A</td>
<td>-.078(.207)</td>
<td>.550(.411)</td>
<td>.037</td>
<td>.200</td>
</tr>
</tbody>
</table>

### Shapiro-Wilk Test
- Shapiro-Wilk test is used to check for normal distribution of data.
- Values close to 1 indicate a normal distribution.
- Values significantly different from 1 indicate a non-normal distribution.

### Kurtosis
- Kurtosis is a measure of the 'tailedness' of the distribution.
- A value of 3 indicates a normal distribution.
- Values significantly different from 3 indicate a distribution with heavier or lighter tails.

### Transformations
- Ln: Natural log transformation.
- Ln: Logarithmic transformation.
- Lg10: Log base 10 transformation.
- Power: Power transformation.
- Transformations are applied to normalize the data when necessary.

350
### Appendix 6. CES-D and parent education

*ANOVA Table, T1 CES-D by parent education*

<table>
<thead>
<tr>
<th>CES-D Scale</th>
<th>Parent Education</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 Total</strong></td>
<td>Incomplete High School</td>
<td>22</td>
<td>37.093</td>
<td>10.545</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete High School</td>
<td>15</td>
<td>29.867</td>
<td>4.941</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE</td>
<td>22</td>
<td>30.445</td>
<td>7.758</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor Degree</td>
<td>52</td>
<td>31.674</td>
<td>12.399</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Graduate</td>
<td>16</td>
<td>29.326</td>
<td>7.955</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>127</td>
<td>31.891</td>
<td>10.367</td>
<td>1.942</td>
<td>0.108</td>
</tr>
<tr>
<td><strong>T1 Depressed Affect</strong></td>
<td>Incomplete High School</td>
<td>22</td>
<td>12.447</td>
<td>4.861</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete High School</td>
<td>15</td>
<td>8.533</td>
<td>1.767</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE</td>
<td>22</td>
<td>9.400</td>
<td>3.886</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor Degree</td>
<td>51</td>
<td>9.918</td>
<td>4.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Graduate</td>
<td>16</td>
<td>9.563</td>
<td>4.320</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>126</td>
<td>10.059</td>
<td>4.248</td>
<td>2.542</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>T1 Wellbeing</strong></td>
<td>Incomplete High School</td>
<td>22</td>
<td>7.970</td>
<td>2.731</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete High School</td>
<td>15</td>
<td>6.200</td>
<td>2.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE</td>
<td>22</td>
<td>6.818</td>
<td>2.239</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor Degree</td>
<td>51</td>
<td>7.307</td>
<td>2.511</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Graduate</td>
<td>16</td>
<td>6.813</td>
<td>2.689</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>126</td>
<td>7.143</td>
<td>2.498</td>
<td>1.371</td>
<td>0.248</td>
</tr>
<tr>
<td><strong>T1 Somatic</strong></td>
<td>Incomplete High School</td>
<td>22</td>
<td>13.349</td>
<td>3.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete High School</td>
<td>15</td>
<td>12.133</td>
<td>2.748</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE</td>
<td>22</td>
<td>11.636</td>
<td>3.458</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor Degree</td>
<td>51</td>
<td>12.036</td>
<td>4.459</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Graduate</td>
<td>16</td>
<td>10.625</td>
<td>3.138</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>126</td>
<td>12.028</td>
<td>3.841</td>
<td>1.254</td>
<td>0.292</td>
</tr>
<tr>
<td><strong>T1 Interpersonal</strong></td>
<td>Incomplete High School</td>
<td>22</td>
<td>3.591</td>
<td>1.843</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete High School</td>
<td>15</td>
<td>3.000</td>
<td>1.464</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAFE</td>
<td>22</td>
<td>2.546</td>
<td>1.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bachelor Degree</td>
<td>51</td>
<td>3.392</td>
<td>1.801</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-Graduate</td>
<td>16</td>
<td>2.375</td>
<td>0.619</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>126</td>
<td>3.103</td>
<td>1.594</td>
<td>2.582</td>
<td>0.041</td>
</tr>
</tbody>
</table>
**ANOVA Table, T2 CES-D by Parent Education**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T2 Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete High School</td>
<td>21</td>
<td>33.531</td>
<td>10.995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete High School</td>
<td>19</td>
<td>27.003</td>
<td>4.603</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>23</td>
<td>29.783</td>
<td>6.274</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor Degree</td>
<td>56</td>
<td>30.291</td>
<td>7.712</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Graduate</td>
<td>17</td>
<td>28.588</td>
<td>10.411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>30.033</td>
<td>8.229</td>
<td>1.784</td>
<td>0.136</td>
</tr>
<tr>
<td><strong>T2 Depressed Affect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete High School</td>
<td>21</td>
<td>10.571</td>
<td>4.632</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete High School</td>
<td>19</td>
<td>7.579</td>
<td>1.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>23</td>
<td>8.522</td>
<td>2.150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor Degree</td>
<td>56</td>
<td>9.161</td>
<td>2.833</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Graduate</td>
<td>17</td>
<td>9.118</td>
<td>3.638</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>9.044</td>
<td>3.103</td>
<td>2.638</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>T2 Wellbeing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete High School</td>
<td>21</td>
<td>7.143</td>
<td>2.798</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete High School</td>
<td>19</td>
<td>6.474</td>
<td>2.318</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>23</td>
<td>6.261</td>
<td>1.959</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor Degree</td>
<td>56</td>
<td>6.310</td>
<td>2.212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Graduate</td>
<td>17</td>
<td>6.235</td>
<td>3.580</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>6.444</td>
<td>2.472</td>
<td>0.516</td>
<td>0.724</td>
</tr>
<tr>
<td><strong>T2 Somatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete High School</td>
<td>21</td>
<td>12.810</td>
<td>4.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete High School</td>
<td>19</td>
<td>10.377</td>
<td>2.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>23</td>
<td>11.870</td>
<td>2.616</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor Degree</td>
<td>56</td>
<td>11.839</td>
<td>3.577</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Graduate</td>
<td>17</td>
<td>10.706</td>
<td>3.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>11.648</td>
<td>3.311</td>
<td>1.804</td>
<td>0.132</td>
</tr>
<tr>
<td><strong>T2 Interpersonal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete High School</td>
<td>21</td>
<td>3.000</td>
<td>1.581</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete High School</td>
<td>19</td>
<td>2.579</td>
<td>0.769</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>23</td>
<td>3.130</td>
<td>1.604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor Degree</td>
<td>56</td>
<td>2.982</td>
<td>1.228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Graduate</td>
<td>17</td>
<td>2.529</td>
<td>0.943</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>2.897</td>
<td>1.278</td>
<td>0.932</td>
<td>0.448</td>
</tr>
</tbody>
</table>
## Appendix 7. CTQ four-factor structure

<table>
<thead>
<tr>
<th>Item</th>
<th>Factor</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. People in my family looked out for each other.</td>
<td>Emotional Neglect</td>
<td>.763</td>
<td>.325</td>
<td>.103</td>
<td>.117</td>
</tr>
<tr>
<td>19. People in my family felt close to each other.</td>
<td>Emotional Neglect</td>
<td>.759</td>
<td>.238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. My family was a source of strength and support.</td>
<td>Emotional Neglect</td>
<td>.753</td>
<td>.284</td>
<td>.181</td>
<td></td>
</tr>
<tr>
<td>7. I felt loved.</td>
<td>Emotional Neglect</td>
<td>.709</td>
<td>.275</td>
<td>.140</td>
<td>.150</td>
</tr>
<tr>
<td>5. There was someone in my family who helped me feel that I was</td>
<td>Emotional Neglect</td>
<td>.626</td>
<td>.184</td>
<td></td>
<td>.164</td>
</tr>
<tr>
<td>important or special.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I knew that there was someone to take care of me and protect me.</td>
<td>Physical Neglect</td>
<td>.576</td>
<td>.102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I didn’t have enough to eat.</td>
<td>Physical Neglect</td>
<td>.380</td>
<td>.239</td>
<td>-.186</td>
<td></td>
</tr>
<tr>
<td>26. There was someone to take me to the doctor if I needed it.</td>
<td>Physical Neglect</td>
<td>.377</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I had to wear dirty clothes.</td>
<td>Physical Neglect</td>
<td>.214</td>
<td></td>
<td>-.111</td>
<td></td>
</tr>
<tr>
<td>14. People in my family said hurtful or insulting things to me.</td>
<td>Emotional Abuse</td>
<td>.164</td>
<td>.734</td>
<td>.253</td>
<td>.152</td>
</tr>
<tr>
<td>25. I believe that I was emotionally abused.</td>
<td>Emotional Abuse</td>
<td>.164</td>
<td>.588</td>
<td>.333</td>
<td></td>
</tr>
<tr>
<td>3. People in my family called me things like &quot;stupid&quot;, &quot;lazy&quot; or</td>
<td>Emotional Abuse</td>
<td>.240</td>
<td>.561</td>
<td>.308</td>
<td></td>
</tr>
<tr>
<td>&quot;ugly&quot;.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. I felt that someone in my family hated me.</td>
<td>Emotional Abuse</td>
<td>.260</td>
<td>.532</td>
<td>.485</td>
<td>.119</td>
</tr>
<tr>
<td>8. I thought that my parents wished I hadn’t been born.</td>
<td>Emotional Abuse</td>
<td>.358</td>
<td>.446</td>
<td>.293</td>
<td>.269</td>
</tr>
<tr>
<td>4. My parents were too drunk or high to take care of the family.</td>
<td>Physical Neglect</td>
<td>.414</td>
<td></td>
<td>-.102</td>
<td></td>
</tr>
<tr>
<td>11. People in my family hit me so hard that it left me with bruises</td>
<td>Physical Abuse</td>
<td>.203</td>
<td>.140</td>
<td>.787</td>
<td></td>
</tr>
<tr>
<td>or marks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. I believe that I was physically abused.</td>
<td>Physical Abuse</td>
<td>.195</td>
<td>.729</td>
<td>.174</td>
<td></td>
</tr>
<tr>
<td>12. I was punished with a belt, a board, a cord, or some other</td>
<td>Physical Abuse</td>
<td>.191</td>
<td>.172</td>
<td>.288</td>
<td>.141</td>
</tr>
<tr>
<td>hard object.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I got hit so hard by someone in my family that I had to see a</td>
<td>Physical Abuse</td>
<td>.207</td>
<td></td>
<td></td>
<td>.941</td>
</tr>
<tr>
<td>doctor or go to the hospital.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I got hit or beaten so badly that it was noticed by someone like</td>
<td>Physical Abuse</td>
<td>.346</td>
<td>.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a teacher, neighbour, or doctor.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Extraction Method: Principal Axis Factoring.*

*Rotation Method: Varimax with Kaiser Normalization.*
Appendix 8. Descriptive statistics for raw region of interest volumes

<table>
<thead>
<tr>
<th>Region</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Whole Brain Volume</td>
<td>137</td>
<td>1302600.000</td>
<td>107695.000</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>137</td>
<td>2928.445</td>
<td>332.552</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>137</td>
<td>2763.730</td>
<td>326.041</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>137</td>
<td>1830.234</td>
<td>273.061</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>137</td>
<td>1896.869</td>
<td>262.624</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>137</td>
<td>2436.285</td>
<td>1376.992</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>137</td>
<td>1727.183</td>
<td>842.196</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>137</td>
<td>2352.672</td>
<td>655.466</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>137</td>
<td>3464.584</td>
<td>1397.716</td>
</tr>
<tr>
<td>Left Ventral Cingulate</td>
<td>135</td>
<td>190.719</td>
<td>129.347</td>
</tr>
<tr>
<td>Left Ventral Paracingulate</td>
<td>136</td>
<td>209.360</td>
<td>145.355</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>137</td>
<td>2899.993</td>
<td>1325.901</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>137</td>
<td>1553.606</td>
<td>751.736</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>137</td>
<td>2641.715</td>
<td>784.228</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>137</td>
<td>3101.445</td>
<td>1275.687</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>137</td>
<td>224.569</td>
<td>126.458</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>132</td>
<td>122.091</td>
<td>102.610</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>137</td>
<td>19514.964</td>
<td>3963.789</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>137</td>
<td>20209.737</td>
<td>3930.001</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal Cortex</td>
<td>137</td>
<td>10264.000</td>
<td>2152.211</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td>137</td>
<td>9250.964</td>
<td>2175.359</td>
</tr>
<tr>
<td>Right Lateral Orbitofrontal Cortex</td>
<td>137</td>
<td>11029.759</td>
<td>2184.500</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td>137</td>
<td>9179.978</td>
<td>2105.876</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>135</td>
<td>756.878</td>
<td>126.088</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>135</td>
<td>101.727</td>
<td>6.560</td>
</tr>
</tbody>
</table>
Appendix 9a. Region of interest correlations
Right Hippocampus
(R Hipp)
Left Hippocampus
(L Hipp)
Right Amygdala
(R Amyg)
Left Amygdala
(L Amyg)
Left Rostral Cingulate
(LRC)
Left Dorsal Paracingulate
(LDP)
Left Dorsal Cingulate
(LDC)
Left Rostral Paracingulate
(LRP)
Left Ventral Cingulate
(LVC)
Left Ventral Paracingulate
(LVP)
Right Rostral Cingulate
(RRC)
Right Dorsal Paracingulate
(RDP)
Right Dorsal Cingulate
(RDC)
Right Rostral Paracingulate
(RRP)
Right Ventral Cingulate
(RVC)
Right Ventral Paracingulate
(RVP)
Left Orbitofrontal Cortex
(L OFC)
Right Orbitofrontal Cortex
(R OFC)
Left Lateral Orbitofrontal Cortex
(LL OFC)
Left Medial Orbitofrontal Cortex
(LM OFC)
Right Lateral Orbitofrontal Cortex
(RL OFC)
Right Medial Orbitofrontal Cortex
(RM OFC)
Corpus Callosum Midlength
(CC Mid)
Corpus Callosum Area
(CC Area)

r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p
r
p

R Hipp
1

L Hipp
.78
0
1

R Am
.17
.05
.18
4
1

L Am
.26
.01
.15
.08
.68
0
1

LRC
.05
.5
.05
.55
-.01
.97
.02
.78
1

LDP
-.01
.91
.03
.74
.07
.41
.07
.40
-.35
.0
1

LDC
.01
.92
.01
.96
-.07
.45
-.05
.55
.35
.0
-.46
0
1

LRP
.06
.47
.04
.63
-.08
.36
-.10
.23
-.27
.01
.42
0
-.12
.16
1

LVC
.03
.69
.04
.62
-.04
.66
.07
.40
.58
.0
-.08
.34
.17
.05
-.22
.01
1

LVP
.11
.19
.11
.20
-.07
.40
-.07
.41
-.29
.0
.17
.05
.02
.86
.46
0
.02
.86
1

RRC
.07
.42
.10
.24
-.08
.35
-.03
.77
.08
.38
.15
.07
-.16
.07
.22
.01
-.08
.33
.05
.58
1

RDP
.01
.89
-.04
.64
.10
.26
-.0
.99
-.03
.70
.13
.13
.1
.24
.15
.07
.07
.40
.24
.0
-.40
.0
1

RDC
.16
.06
.19
.03
-.09
.32
-.06
.46
-.13
.14
.13
.14
-.01
.96
.11
.20
-.06
.49
.13
.14
.49
.0
-.39
.0
1

RRP
-.03
.74
.02
.81
-.01
.92
-.04
.68
.22
.01
.10
.26
.03
.77
.24
.01
.14
.11
.05
.58
-.27
.0
.47
.0
-.25
.0
1

RVC
.13
.14
.17
.05
-.06
.52
.04
.64
.01
.94
.19
.03
-.09
.32
.14
.10
.32
.0
.38
.0
.51
.0
-.07
.43
.29
.0
-.21
.01
1

RVP
.08
.37
.11
.23
-.01
.90
-.06
.51
.07
.44
.18
.04
.07
.44
.10
.27
.28
.0
.08
.39
-.36
.0
.21
.02
.03
.74
.41
.0
-.04
.67
1

L OFC
.18
.04
.15
.08
.12
.16
.16
.07
.12
.16
.11
.20
.14
.10
.11
.22
.28
.0
.29
.0
.05
.54
.11
.21
.11
.21
.07
.42
.41
.0
.19
.03
1

R OFC
.15
.09
.15
.09
.07
.44
.14
.11
.13
.13
.18
.04
.08
.33
.13
.14
.23
.01
.20
.02
.08
.35
.10
.25
.16
.06
.09
.31
.38
.0
.17
.06
.85
.0
1

LL
OFC
.22
.01
.17
.04
.17
.05
.22
.01
.07
.40
-.01
.94
.21
.01
-.05
.57
.16
.06
.18
.03
.02
.83
.10
.24
.10
.23
-.09
.31
.30
.0
.06
.48
.87
.0
.71
.0
1

LM
OFC
.09
.31
.08
.38
.04
.62
.05
.58
.13
.12
.22
.01
.05
.59
.23
.01
.32
.0
.33
.0
.08
.33
.07
.44
.10
.23
.20
.02
.40
.0
.28
.0
.86
.0
.77
.0
.51
.0
1

RL
OFC
.16
.07
.17
.06
.12
.18
.20
.02
.05
.60
.09
.30
.09
.28
.05
.56
.15
.09
.14
.09
.06
.48
.06
.49
.17
.04
-.02
.77
.26
.0
.06
.51
.751
.0
.88
.0
.75
.0
.55
.0
1

RM
OFC
.09
.28
.08
.34
-.0
.97
.03
.71
.183
.03
.22
.009
.06
.48
.18
.041
.25
.0
.20
.02
.08
.35
.11
.21
.11
.21
.18
.04
.39
.0
.25
.01
.72
.0
.85
.0
.47
.0
.79
.0
.49
0
1

CC
Mid
-.16
.06
-.10
.24
-.08
.34
-.01
.93
-.01
.91
.14
.10
-.05
.60
.12
.18
.11
.19
.08
.34
.11
.20
-.05
.58
.05
.55
-.07
.45
.21
.01
-.03
.75
.12
.16
.18
.03
.08
.36
.12
.16
.09
.31
.22
.01
1

355

CC
Area
-.17
.05
-.12
.17
-.01
.95
.07
.42
.0
.80
.19
.02
-.03
.75
.07
.40
.13
.14
.16
.07
.23
.01
-.09
.29
.21
.01
-.21
.015
.38
.0
.01
.89
.14
.12
.17
.05
.11
.20
.13
.13
.06
.48
.23
.01
.56
0
1


## Appendix 9b. Region of interest correlations summary

<table>
<thead>
<tr>
<th>Positive Correlation</th>
<th>Negative Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Hippocampus</td>
<td>Right Dorsal Cingulate</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>Left OFC</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>Left Lateral OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Lateral OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Lateral OFC</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>Left OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>Left Ventral Paracingulate</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Left Ventral Paracingulate</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Ventral Paracingulate</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Left Ventral Cingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Right Ventral Paracingulate</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Lateral OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Left Lateral OFC</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Corpus Callosum Midlength</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Corpus Callosum Midlength</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Right Medial OFC</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Left Medial OFC</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Corpus Callosum Midlength</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>Corpus Callosum Area</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>Left Medial OFC</td>
</tr>
</tbody>
</table>
## Appendix 10. Independent sample t-tests for gender differences on raw, uncorrected region of interest volumes

<table>
<thead>
<tr>
<th>Region</th>
<th>t</th>
<th>df</th>
<th>p</th>
<th>Mean Diff.</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td>6.254</td>
<td>135</td>
<td>&lt;.001*</td>
<td>102045.000</td>
<td>16316.188</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>1.347</td>
<td>135</td>
<td>0.180</td>
<td>76.553</td>
<td>56.838</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>2.271</td>
<td>135</td>
<td>0.025*</td>
<td>125.039</td>
<td>55.056</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>2.413</td>
<td>135</td>
<td>0.017*</td>
<td>111.014</td>
<td>46.001</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>3.706</td>
<td>135</td>
<td>&lt;.001*</td>
<td>159.531</td>
<td>43.050</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>-0.657</td>
<td>135</td>
<td>0.512</td>
<td>-155.457</td>
<td>236.545</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>0.698</td>
<td>135</td>
<td>0.487</td>
<td>100.899</td>
<td>144.647</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>0.225</td>
<td>135</td>
<td>0.822</td>
<td>25.399</td>
<td>112.758</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>0.659</td>
<td>135</td>
<td>0.511</td>
<td>158.211</td>
<td>240.103</td>
</tr>
<tr>
<td>Left Ventral Cingulate</td>
<td>-0.629</td>
<td>133</td>
<td>0.530</td>
<td>-14.069</td>
<td>22.365</td>
</tr>
<tr>
<td>Left Ventral Paracingulate</td>
<td>0.905</td>
<td>134</td>
<td>0.367</td>
<td>22.643</td>
<td>25.013</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>0.504</td>
<td>135</td>
<td>0.615</td>
<td>114.770</td>
<td>227.919</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>0.297</td>
<td>135</td>
<td>0.767</td>
<td>38.413</td>
<td>129.300</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>0.500</td>
<td>135</td>
<td>0.618</td>
<td>67.415</td>
<td>134.808</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>1.670</td>
<td>135</td>
<td>0.097</td>
<td>362.749</td>
<td>217.261</td>
</tr>
<tr>
<td>Right Ventral Cingulate</td>
<td>0.455</td>
<td>135</td>
<td>0.650</td>
<td>9.899</td>
<td>21.742</td>
</tr>
<tr>
<td>Right Ventral Paracingulate</td>
<td>0.920</td>
<td>130</td>
<td>0.359</td>
<td>16.474</td>
<td>17.906</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>2.657</td>
<td>135</td>
<td>0.009*</td>
<td>1766.621</td>
<td>664.840</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>3.114</td>
<td>135</td>
<td>0.002*</td>
<td>2034.119</td>
<td>653.135</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal Cortex</td>
<td>2.847</td>
<td>135</td>
<td>0.005*</td>
<td>1024.062</td>
<td>359.665</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td>2.013</td>
<td>135</td>
<td>0.046*</td>
<td>742.559</td>
<td>368.793</td>
</tr>
<tr>
<td>Right Lateral Orbitofrontal Cortex</td>
<td>3.440</td>
<td>135</td>
<td>0.001*</td>
<td>1239.930</td>
<td>360.394</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td>2.232</td>
<td>135</td>
<td>0.027*</td>
<td>794.189</td>
<td>355.829</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>1.325</td>
<td>133</td>
<td>0.187</td>
<td>28.774</td>
<td>21.715</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>0.527</td>
<td>133</td>
<td>0.599</td>
<td>0.599</td>
<td>1.136</td>
</tr>
</tbody>
</table>
Appendix 11. Correlations between regions of interest and age

<table>
<thead>
<tr>
<th>Region</th>
<th>r</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td>-.010</td>
<td>.912</td>
<td>137</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>.213</td>
<td>.012</td>
<td>137</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>.213</td>
<td>.013</td>
<td>137</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>.173</td>
<td>.043</td>
<td>137</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>.169</td>
<td>.049</td>
<td>137</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>.023</td>
<td>.793</td>
<td>137</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>.114</td>
<td>.186</td>
<td>137</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>-.019</td>
<td>.824</td>
<td>137</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>.046</td>
<td>.596</td>
<td>137</td>
</tr>
<tr>
<td>Left Subgenual Cingulate</td>
<td>.052</td>
<td>.550</td>
<td>135</td>
</tr>
<tr>
<td>Left Subgenual Paracingulate</td>
<td>.132</td>
<td>.125</td>
<td>136</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>.030</td>
<td>.726</td>
<td>137</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>-.016</td>
<td>.856</td>
<td>137</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>.174</td>
<td>.042</td>
<td>137</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>.056</td>
<td>.515</td>
<td>137</td>
</tr>
<tr>
<td>Right Subgenual Cingulate</td>
<td>.131</td>
<td>.128</td>
<td>137</td>
</tr>
<tr>
<td>Right Subgenual Paracingulate</td>
<td>.177</td>
<td>.042</td>
<td>132</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>.058</td>
<td>.498</td>
<td>137</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>.064</td>
<td>.458</td>
<td>137</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal Cortex</td>
<td>.074</td>
<td>.390</td>
<td>137</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td>.033</td>
<td>.701</td>
<td>137</td>
</tr>
<tr>
<td>Right Lateral Orbitofrontal Cortex</td>
<td>.088</td>
<td>.307</td>
<td>137</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td>.028</td>
<td>.746</td>
<td>137</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>-.031</td>
<td>.721</td>
<td>135</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>.055</td>
<td>.524</td>
<td>135</td>
</tr>
</tbody>
</table>
### Appendix 12. Correlations between regions of interest and handedness

<table>
<thead>
<tr>
<th>Region</th>
<th>Handedness</th>
<th>r</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td></td>
<td>.059</td>
<td>.248</td>
<td>133</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td></td>
<td>.130</td>
<td>.135</td>
<td>133</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td></td>
<td>.050</td>
<td>.566</td>
<td>133</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td></td>
<td>.024</td>
<td>.785</td>
<td>133</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td></td>
<td>.064</td>
<td>.462</td>
<td>133</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td></td>
<td>-.041</td>
<td>.638</td>
<td>133</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td></td>
<td>-.019</td>
<td>.832</td>
<td>133</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td></td>
<td>-.038</td>
<td>.668</td>
<td>133</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td></td>
<td>.004</td>
<td>.963</td>
<td>133</td>
</tr>
<tr>
<td>Left Subgenual Cingulate</td>
<td></td>
<td>.064</td>
<td>.470</td>
<td>131</td>
</tr>
<tr>
<td>Left Subgenual Paracingulate</td>
<td></td>
<td>-.107</td>
<td>.222</td>
<td>132</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td></td>
<td>-.018</td>
<td>.835</td>
<td>133</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td></td>
<td>.038</td>
<td>.666</td>
<td>133</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td></td>
<td>-.019</td>
<td>.826</td>
<td>133</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td></td>
<td>-.072</td>
<td>.413</td>
<td>133</td>
</tr>
<tr>
<td>Right Subgenual Cingulate</td>
<td></td>
<td>-.047</td>
<td>.595</td>
<td>133</td>
</tr>
<tr>
<td>Right Subgenual Paracingulate</td>
<td></td>
<td>-.057</td>
<td>.521</td>
<td>128</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td></td>
<td>-.163</td>
<td>.061</td>
<td>133</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td></td>
<td>-.090</td>
<td>.303</td>
<td>133</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal Cortex</td>
<td></td>
<td>-.154</td>
<td>.076</td>
<td>133</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td></td>
<td>-.132</td>
<td>.129</td>
<td>133</td>
</tr>
<tr>
<td>Right Lateral Orbitofrontal Cortex</td>
<td></td>
<td>-.077</td>
<td>.379</td>
<td>133</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td></td>
<td>-.082</td>
<td>.348</td>
<td>133</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td></td>
<td>.137</td>
<td>.117</td>
<td>131</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td></td>
<td>.094</td>
<td>.287</td>
<td>131</td>
</tr>
</tbody>
</table>
### Appendix 13. Correlations between regions of interest and FSIQ

<table>
<thead>
<tr>
<th>Region</th>
<th>r</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Brain Volume</td>
<td>-.072</td>
<td>.403</td>
<td>133</td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>-.019</td>
<td>.826</td>
<td>133</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>-.014</td>
<td>.875</td>
<td>133</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>-.099</td>
<td>.256</td>
<td>133</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-.138</td>
<td>.113</td>
<td>133</td>
</tr>
<tr>
<td>Left Rostral Cingulate</td>
<td>.095</td>
<td>.275</td>
<td>133</td>
</tr>
<tr>
<td>Left Dorsal Paracingulate</td>
<td>-.069</td>
<td>.433</td>
<td>133</td>
</tr>
<tr>
<td>Left Dorsal Cingulate</td>
<td>.054</td>
<td>.536</td>
<td>133</td>
</tr>
<tr>
<td>Left Rostral Paracingulate</td>
<td>-.046</td>
<td>.596</td>
<td>133</td>
</tr>
<tr>
<td>Left Subgenual Cingulate</td>
<td>.008</td>
<td>.931</td>
<td>131</td>
</tr>
<tr>
<td>Left Subgenual Paracingulate</td>
<td>-.059</td>
<td>.499</td>
<td>132</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>-.001</td>
<td>.989</td>
<td>133</td>
</tr>
<tr>
<td>Right Dorsal Paracingulate</td>
<td>.002</td>
<td>.979</td>
<td>133</td>
</tr>
<tr>
<td>Right Dorsal Cingulate</td>
<td>-.004</td>
<td>.960</td>
<td>133</td>
</tr>
<tr>
<td>Right Rostral Paracingulate</td>
<td>-.022</td>
<td>.799</td>
<td>133</td>
</tr>
<tr>
<td>Right Subgenual Cingulate</td>
<td>.042</td>
<td>.628</td>
<td>133</td>
</tr>
<tr>
<td>Right Subgenual Paracingulate</td>
<td>.016</td>
<td>.857</td>
<td>128</td>
</tr>
<tr>
<td>Left Orbitofrontal Cortex</td>
<td>-.145</td>
<td>.095</td>
<td>133</td>
</tr>
<tr>
<td>Right Orbitofrontal Cortex</td>
<td>-.128</td>
<td>.142</td>
<td>133</td>
</tr>
<tr>
<td>Left Lateral Orbitofrontal Cortex</td>
<td>-.179</td>
<td>.089</td>
<td>133</td>
</tr>
<tr>
<td>Left Medial Orbitofrontal Cortex</td>
<td>-.088</td>
<td>.316</td>
<td>133</td>
</tr>
<tr>
<td>Right Lateral Orbitofrontal Cortex</td>
<td>-.158</td>
<td>.070</td>
<td>133</td>
</tr>
<tr>
<td>Right Medial Orbitofrontal Cortex</td>
<td>-.075</td>
<td>.392</td>
<td>133</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>-.064</td>
<td>.467</td>
<td>131</td>
</tr>
<tr>
<td>Corpus Callosum Area</td>
<td>.002</td>
<td>.985</td>
<td>131</td>
</tr>
</tbody>
</table>
Appendix 14. Mediation analyses

CTQ Abuse > Corpus Callosum Midlength (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.214</td>
<td>0.046</td>
<td>-0.074</td>
<td>1.10E+02</td>
<td>0.046</td>
<td>0.384</td>
<td>6</td>
<td>48</td>
<td>0.886</td>
</tr>
<tr>
<td>2</td>
<td>0.408</td>
<td>0.167</td>
<td>0.043</td>
<td>1.03E+02</td>
<td>0.121</td>
<td>6.822</td>
<td>1</td>
<td>47</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Unstandardized Coefficients

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTQ Abuse</td>
<td>177.121</td>
<td>67.811</td>
<td>0.393</td>
<td>2.612</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Corpus Callosum Midlength > CES-D Wellbeing (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.591</td>
<td>0.35</td>
<td>0.253</td>
<td>0.33013</td>
<td>0.35</td>
<td>3.612</td>
<td>7</td>
<td>47</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>0.666</td>
<td>0.443</td>
<td>0.346</td>
<td>0.30881</td>
<td>0.093</td>
<td>7.713</td>
<td>1</td>
<td>46</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Unstandardized Coefficients

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ugrad vs PGrad</td>
<td>-0.311</td>
<td>0.156</td>
<td>-0.256</td>
<td>-1.987</td>
<td>0.053</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.513</td>
<td>0.133</td>
<td>0.482</td>
<td>3.854</td>
<td>0</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>0.001</td>
<td>0</td>
<td>0.314</td>
<td>2.777</td>
<td>0.008</td>
</tr>
</tbody>
</table>
### CTQ Abuse > CES-D Wellbeing (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.591</td>
<td>0.35</td>
<td>0.253</td>
<td>0.33013</td>
<td>0.35</td>
<td>3.612</td>
<td>7</td>
<td>47</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>0.736</td>
<td>0.542</td>
<td>0.463</td>
<td>0.28001</td>
<td>0.192</td>
<td>19.331</td>
<td>1</td>
<td>46</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Unstandardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGrad vs PGrad</td>
<td>-0.311</td>
<td>0.156</td>
<td>-0.256</td>
<td>-1.987</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.513</td>
<td>0.133</td>
<td>0.482</td>
<td>3.854</td>
</tr>
<tr>
<td>CTQ Abuse</td>
<td>0.846</td>
<td>0.192</td>
<td>0.519</td>
<td>4.397</td>
</tr>
</tbody>
</table>

### CTQ Abuse > Corpus Callosum Midlength > CES-D Wellbeing (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.591</td>
<td>0.35</td>
<td>0.253</td>
<td>0.33013</td>
<td>0.35</td>
<td>3.612</td>
<td>7</td>
<td>47</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>0.666</td>
<td>0.443</td>
<td>0.346</td>
<td>0.30881</td>
<td>0.093</td>
<td>7.713</td>
<td>1</td>
<td>46</td>
<td>0.008</td>
</tr>
<tr>
<td>3</td>
<td>0.754</td>
<td>0.569</td>
<td>0.483</td>
<td>0.27466</td>
<td>0.126</td>
<td>13.15</td>
<td>1</td>
<td>45</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Unstandardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGrad vs PGrad</td>
<td>-0.311</td>
<td>0.156</td>
<td>-0.256</td>
<td>-1.987</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.513</td>
<td>0.133</td>
<td>0.482</td>
<td>3.854</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>0.001</td>
<td>0</td>
<td>0.314</td>
<td>2.777</td>
</tr>
<tr>
<td>CTQ Abuse</td>
<td>0.73</td>
<td>0.201</td>
<td>0.448</td>
<td>3.626</td>
</tr>
</tbody>
</table>
### CTQ Neglect > Corpus Callosum Midlength (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>R Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.211</td>
<td>0.045</td>
<td>-0.072</td>
<td>1.12E+02</td>
<td>0.045</td>
<td>0.381</td>
<td>6</td>
<td>49</td>
<td>0.888</td>
</tr>
<tr>
<td>2</td>
<td>0.314</td>
<td>0.098</td>
<td>-0.033</td>
<td>1.10E+02</td>
<td>0.054</td>
<td>2.862</td>
<td>1</td>
<td>48</td>
<td>0.097</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTQ Neglect</td>
<td>79.301</td>
<td>46.879</td>
<td>0.256</td>
<td>1.692</td>
</tr>
</tbody>
</table>

### Corpus Callosum Midlength > CES-D Wellbeing (Females)

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>R Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.569</td>
<td>0.323</td>
<td>0.225</td>
<td>0.33455</td>
<td>0.323</td>
<td>3.279</td>
<td>7</td>
<td>48</td>
<td>0.006</td>
</tr>
<tr>
<td>2</td>
<td>0.622</td>
<td>0.386</td>
<td>0.282</td>
<td>0.32198</td>
<td>0.063</td>
<td>4.822</td>
<td>1</td>
<td>47</td>
<td>0.033</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.494</td>
<td>0.134</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>0.001</td>
<td>0.0</td>
</tr>
</tbody>
</table>
### CTQ Neglect > CES-D Wellbeing

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>Sig. F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.569</td>
<td>0.323</td>
<td>0.225</td>
<td>0.33455</td>
<td>0.323</td>
<td>3.279</td>
<td>0.006</td>
<td>7</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.768</td>
<td>0.59</td>
<td>0.521</td>
<td>0.2631</td>
<td>0.267</td>
<td>30.615</td>
<td></td>
<td>1</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Std. Error</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.494</td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td>0.638</td>
</tr>
</tbody>
</table>

### CTQ Neglect > Corpus Callosum Midlength > CES-D Wellbeing

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>Sig. F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.569</td>
<td>0.323</td>
<td>0.225</td>
<td>0.33455</td>
<td>0.323</td>
<td>3.279</td>
<td>0.006</td>
<td>7</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.622</td>
<td>0.386</td>
<td>0.282</td>
<td>0.32198</td>
<td>0.063</td>
<td>4.822</td>
<td>0.033</td>
<td>1</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.781</td>
<td>0.61</td>
<td>0.534</td>
<td>0.25935</td>
<td>0.224</td>
<td>26.441</td>
<td></td>
<td>1</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Std. Error</td>
</tr>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.494</td>
</tr>
<tr>
<td>Corpus Callosum Midlength</td>
<td>0.001</td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td>0.599</td>
</tr>
</tbody>
</table>
### Neglect > Right Rostral Cingulate

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.346</td>
<td>0.12</td>
<td>0.014</td>
<td>1.28E+03</td>
<td>0.12</td>
<td>1.136</td>
<td>6</td>
<td>50</td>
<td>0.355</td>
</tr>
<tr>
<td>2</td>
<td>0.373</td>
<td>0.139</td>
<td>0.016</td>
<td>1.27E+03</td>
<td>0.019</td>
<td>1.075</td>
<td>1</td>
<td>49</td>
<td>0.305</td>
</tr>
</tbody>
</table>

#### Unstandardized Coefficients

| CTQ Neglect | 562.682 | 542.643 | 0.152 | 1.037 | 0.305 |

#### Standardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.346</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Right Rostral Cingulate > CES-D Wellbeing

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.557</td>
<td>0.31</td>
<td>0.212</td>
<td>0.33436</td>
<td>0.31</td>
<td>3.15</td>
<td>7</td>
<td>49</td>
<td>0.008</td>
</tr>
<tr>
<td>2</td>
<td>0.632</td>
<td>0.399</td>
<td>0.299</td>
<td>0.31531</td>
<td>0.089</td>
<td>7.099</td>
<td>1</td>
<td>48</td>
<td>0.01</td>
</tr>
</tbody>
</table>

#### Unstandardized Coefficients

<table>
<thead>
<tr>
<th>T1 CES-D Wellbeing</th>
<th>0.463</th>
<th>0.13</th>
<th>0.445</th>
<th>3.555</th>
<th>0.001</th>
</tr>
</thead>
</table>

#### Standardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.463</td>
<td>0.13</td>
<td>0.445</td>
<td>3.555</td>
<td>0.001</td>
</tr>
</tbody>
</table>

| Right Rostral Cingulate | 0       | 0     | 0.321 | 2.664 | 0.01  |
### CTQ Neglect > CES-D Wellbeing

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>R Std. Error</th>
<th>of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.557</td>
<td>0.31</td>
<td>0.212</td>
<td>0.33436</td>
<td>0.31</td>
<td>3.15</td>
<td>7</td>
<td>49</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.765</td>
<td>0.586</td>
<td>0.517</td>
<td>0.26182</td>
<td>0.275</td>
<td>31.914</td>
<td>1</td>
<td>48</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table: Unstandardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.463</td>
<td>0.13</td>
<td>0.445</td>
<td>3.555</td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td>0.646</td>
<td>0.114</td>
<td>0.594</td>
<td>5.649</td>
</tr>
</tbody>
</table>

### CTQ Neglect > Right Rostral Cingulate > CES-D Wellbeing

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>R Std. Error</th>
<th>of the Estimate</th>
<th>R Square Change</th>
<th>F Change</th>
<th>df1</th>
<th>df2</th>
<th>Sig. F Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.557</td>
<td>0.31</td>
<td>0.212</td>
<td>0.33436</td>
<td>0.31</td>
<td>3.15</td>
<td>7</td>
<td>49</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.632</td>
<td>0.399</td>
<td>0.299</td>
<td>0.31531</td>
<td>0.089</td>
<td>7.099</td>
<td>1</td>
<td>48</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.792</td>
<td>0.628</td>
<td>0.556</td>
<td>0.25081</td>
<td>0.229</td>
<td>28.861</td>
<td>1</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table: Unstandardized Coefficients

<table>
<thead>
<tr>
<th>B</th>
<th>Std. Error</th>
<th>Beta</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 CES-D Wellbeing</td>
<td>0.463</td>
<td>0.13</td>
<td>0.445</td>
<td>3.555</td>
</tr>
<tr>
<td>Right Rostral Cingulate</td>
<td>0</td>
<td>0</td>
<td>0.321</td>
<td>2.664</td>
</tr>
<tr>
<td>CTQ Neglect</td>
<td>0.599</td>
<td>0.111</td>
<td>0.551</td>
<td>5.372</td>
</tr>
</tbody>
</table>
Author/s: Barrett, Anna

Title: Childhood maltreatment and structural neuroanatomy as risk factors for adolescent onset depression

Date: 2012


Persistent Link: http://hdl.handle.net/11343/38429

File Description: Childhood maltreatment and structural neuroanatomy as risk factors for adolescent onset depression

Terms and Conditions: Copyright in works deposited in Minerva Access is retained by the copyright owner. The work may not be altered without permission from the copyright owner. Readers may only download, print and save electronic copies of whole works for their own personal non-commercial use. Any use that exceeds these limits requires permission from the copyright owner. Attribution is essential when quoting or paraphrasing from these works.