Anxiety, depression and comorbidity: A comparison of cognitive function in young adults

Zane Quinn

B. Psych. (Hons), B. Eng. (Min Proc)

Thesis submitted in fulfilment of the requirements of the degree of

Doctor of Philosophy (Medicine)

College of Medicine and Dentistry

James Cook University

January, 2017

Statement of Access

I, the undersigned author of this work, understand that James Cook University will make this thesis available for use within the University library and via the Australian Digital Thesis network for use elsewhere. I understand that, as an unpublished work, a thesis has significant protection under the Copyright Act.

_____ _____

Zane Quinn Date

Statement of Sources

I declare that this thesis is my own work and has not been submitted in any other form for another degree or diploma at any university or any other institution of tertiary education. I declare that I have stated clearly and fully in the thesis the extent of any collaboration with others. To the best of my knowledge and belief, the thesis contains no material published previously by any other person except where due acknowledgement has been made. Every reasonable effort has been made to gain permission and acknowledge the owners of copyright material. I would be pleased to hear from any copyright owner who has been omitted or incorrectly acknowledged.

_____ _____

Zane Quinn Date

Ethics Declaration

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council (NHMRC) National statement on Ethical Conduct in Human Research, 2007. The proposed research study received human research ethics approval from Townsville Hospital and Health Service (Approvals: HREC/09/QTHS/116) and from James Cook University Human Research Ethics Committee (Approvals H3616, H4913).

_____ _____

Zane Quinn Date

Statement of the Contribution of Others

I recognise the financial and infrastructural contribution of James Cook University through providing me a workstation, access to resources and funding to conduct my research and attend a conference.

I recognise the financial contribution of the Graduate Research School, who awarded Graduate Research Scheme grants for extra equipment that was required.

I recognise the support, guidance and input provided by my supervisory team: Dr Helen Anscomb, Dr David Mitchell and Professor Bernhard Baune.

_____ _____

Zane Quinn Date

Acknowledgements

A huge thank you to the participants not only for giving up a large portion of time but also for participating in what was sometimes a difficult project. A big thank you for those who provided some of the lighter moments, which can make such an exhausting project more enjoyable.

Thank you to my supervisors Dr David Mitchell, Professor Bernhard Baune and Dr Helen Anscomb for the initial idea and for their excellent edits.

This thesis was edited by Elite Editing, and editorial intervention was restricted to Standards D and E of the Australian Standards for Editing Practice.

A big thank you to Dr Grant Sinnamon, Dr Paula Clancy and Darlene Wallace for their expert advice and skills.

To my associated editors, statisticians, formatters and advisors, hopefully I can repay the kindness and expertise you showed me: Gillian Lunn, Pamela Pensini, Todd Quinn, Michael Civiello, Angela Cunliffe, Dr Carla Ewels, Chelsea Muscat, Dr Jacqueline Homel, Ryan Andersen, Trevor Anderson, Dr Meegan Killcullen and Dr Kayla Morris.

Many thanks to the many members of the organisations I have been involved in during my thesis who have made the time enjoyable: Team Orange, Townsville Ultimate Disc, Give Quiche a Chance, Catan Club and Townsville Permaculture Club.

For those slight distractions that can help in the oddest of ways: Noel Gallagher, Russell Brand and to a lesser extent, Jonathan Ross.

And finally, a big thank you to the support of my family: Wendy, Bill, Todd and Tascha.

List of Works

The following is a list of presentations that have arisen directly from this thesis:

Quinn, Z., Mitchell, D., Anscomb, H. & Baune, B. T. (2014). High school subject selection in depression related cognitive tests. Combined Abstracts of 2014 Australian Psychology Conferences. In *49th Annual Conference of the Australian Psychological Society, 30 September–3 October 2014*, Hobart, TAS, Australia.

Quinn, Z., Mitchell, D., Anscomb, H. & Baune, B. T. (2014). Role of social cognition for young adults with recurrent depression. Combined Abstracts of 2014 Australian Psychology Conferences. In *49th Annual Conference of the Australian Psychological Society, 30 September–3 October 2014*, Hobart, TAS, Australia.

Abstract

The holy grail of depression cognition research is to identify cognitive deficits that are not only associated with depression but which may precede depression and play a role in depression onset. Currently, research to identify cognitive deficits for young to middle-aged adults with depression has been mixed, although some studies have shown significant differences between depression and healthy control groups in the executive function (EF) domains of inhibition, updating, set-shifting, planning and verbal learning and memory. The significant relationships between EF and depression are reflected in biological evidence, with biological abnormalities in EF-associated brain areas, such as the dorsal lateral prefrontal cortex (dlPFC) and the orbital frontal cortex (OFC), being found in depression patients. This thesis presents a series of investigations aimed at advancing understanding of the complex relationships among depression, anxiety and cognitive deficits.

Study participants were primarily recruited from first- and second-year psychology classes at James Cook University, Townsville, Australia. The participants were aged between 17 and 35 years and had experienced depressive and or anxiety symptoms. The participants performed a battery of cognitive tests that included social cognition, inhibition, updating, set-shifting, planning and verbal learning and memory. They underwent a series of structured interviews to determine disorder classification and severity. Other information, such as medical history, school subject history and an intelligence measure, was collected. A small group of participants completed a secondary study investigating correlations between cognition and plasma gamma-aminobutyric acid (GABA). These participants also gave a blood sample.

Study 1 compared the cognitive functioning of the depression (including comorbid depression), anxiety disorder only and healthy control groups. No significant

cognitive differences were found among the three groups. It was noted that approximately one-third of the healthy control group had a high susceptibility to future depressive episodes owing to familial depression diagnosis or subclinical symptoms.

Study 2 investigated depression comorbid with anxiety, focusing on the way anxiety interacted with depression. Participants classified as primary depression, in which depression onset was not due to an anxiety disorder or medical condition, were compared to participants termed secondary depression, whose depression was most probably caused by an anxiety disorder. The healthy control group from Study 1 was included in this comparison. The results showed that those with secondary depression committed significantly fewer errors in the set-shifting task than the primary and healthy control groups; however, there were no significant differences between the primary and healthy control groups. In the rationale for comparing primary and secondary depression, it was suggested that as depression onset for secondary depression is due to a non-depressive disorder, there was a higher probability of biological abnormalities playing a role in primary depression than in secondary depression, which may have been reflected in the results.

Study 3 compared measures of cognition between young adults who had experienced only one or two episodes of depression and then no more episodes (i.e., non-recurrent depression) to those who had experienced three or more episodes (recurrent depression). The recurrent group was found to commit significantly more errors in prosody tasks when the statement was read in a sarcastic tone compared to the non-recurrent group.

In depression cognition studies, it is important to have a measure of intelligence to ensure that outliers do not confound the experiment. Intelligence measures based on literacy are more common in depression experiments than numeracy measures. Study 4

investigated the impact of mathematical ability on cognition, comparing students who had achieved at least a grade of 'B' in either advanced mathematics or physics at high school to those who had studied ordinary mathematics. The results showed that the advanced mathematics group committed fewer errors in the set-shifting task and remembered more words in the initial trial of the verbal learning and memory task than the ordinary mathematics group.

Study 5 investigated the relationship between plasma GABA concentration and EF. Plasma GABA concentration, which has been proposed as a biomarker for depression, has been shown to be lower in depression patients, especially those with primary depression. The results showed that for the subgroup primary depression, there was a significant correlation between plasma GABA concentration and the EF tasks of updating and verbal learning and memory, both of which have significant working memory components. This result was replicated with the ordinary mathematics subgroup (from Study 4). *Post hoc* analysis has suggested that deficits in EF in the primary depression subgroup and ordinary mathematics subgroup have a biological basis, because of their significant relationship with plasma GABA concentration.

In conclusion, while no significant differences were found between the disorder groups, depression and anxiety, and the healthy control groups, significant differences were found in the subgroups of depression. Young adults with primary depression made significantly more errors in set-shifting than those with secondary depression, while young adults with recurrent depression made significantly more errors in prosody than those with non-recurrent depression. Young adults in the ordinary mathematics group made significantly more errors in set-shifting than those in the advanced mathematics group. In the GABA cognition study, for the subgroups primary depression and

ordinary mathematics, plasma GABA concentration significantly correlated with updating and verbal learning and memory.

From these results, two depression pathways were proposed. The Prosodic Pathway proposed that deficits in prosody mediate the pathway from anxiety to depression, while the EF Pathway proposed a link between biological abnormalitieis in the PFC to depression onset. Both pathways were recommended as models for future research.

Contents

List of Tables

List of Figures

List of Abbreviations

ABS	Australian Bureau of Statistics
ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
EF Pathway	Executive Function Depression Pathway
BPD	Bipolar Disorder
CATS	Colorado Assessment Tests
CES-D	Centre for Epidemiologic Studies Depression Scale
CT	Beck's Cognitive Theory of Depression
CVLT	California Verbal Learning Test
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EF	Executive function
fMRI	Functional magnetic resonance imaging
FSIQ	Full-scale IQ
GABA	Gamma-aminobutyric acid
$GABA_A$	GABA receptor A
$GABA_B$	GABA receptor B
GAD	Generalised anxiety disorder
HAM-D	Hamilton Depression Severity Scale
MANOVA	Mixed between-within subjects analysis of variance
MDD	Major depressive disorder
MDE	Major depressive episode
MINI	Mini International Neuropsychiatric Interview

MINI PLUS	Mini International Neuropsychiatric Interview English version 5.0.0 Plus
NART	National Adult Reading Test
NHS	National Health Survey
OCD	Obsessive compulsive disorder
OFC	Orbital frontal cortex
cOFC	Caudal orbital frontal cortex
rOFC	Rostral orbital frontal cortex
PD	Panic disorder
PFC	Prefrontal cortex
dlPFC	Dorsal lateral prefrontal cortex
vlPFC	Ventral lateral prefrontal cortex
Prosodic Pathway	Prosodic uncertainty depression pathway
rCBF	Regional cerebral blood flow
REM	Rapid eye movement
SCID-P	Structured Clinic Interview for Diagnostic and Statistical Manual-III-Patient Version
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Scale
SIGH-AD	Structured Interview Guide for the Hamilton Depression and Anxiety Scales
SSRI	Selective serotonin reuptake inhibitor
ToL	Tower of London
ToM	Theory of Mind
USA	United States of America
VST	Victoria Stroop Test

WAIS	Wechsler Adult Intelligence Scale—Third Edition (III), Fourth Edition (IV), Revised version (R)
WCST	Wisconsin Card Sorting Test
WHO	World Health Organisation
WRAT-R	Wide-range Achievement Test—Revised word recognition subtest
WTAR	Wechsler Test of Adult Reading

Introduction

Depression is the leading cause of disability worldwide, with more than 350 million people affected (World Health Organisation (WHO), 2012). According to the National Health Survey (NHS) (2014), 8.9% of Australians experience feelings of depression (10.4% females, 7.4% males). For anxiety-related conditions, the proportion is higher, at 11.2% (13.0% females, 9.4% males), with 5.1% reporting to have both depression and anxiety-related conditions. For the 15 to 24-year age range, approximately 11% of females and 6% of males experience depression, which is similar to the figures for the total population. However, for anxiety, the percentage of females is 18.9%, with males at 7.9% (the latter figure is similar to that for the total population).

Because of the different methodologies used, it is difficult to compare results from the 2014–2015 NHS to the results for previous surveys, which classified depression and anxiety as long-term conditions. However, other studies have demonstrated that the prevalence of depression is increasing, with younger cohorts exhibiting depressive symptoms at an earlier age and demonstrating an increased lifetime risk (for a review, see Hidaka, 2012). For example, among high school students in the United States of America (USA), there was a marked increase in somatic depression symptoms from the 1980s to 2010, with students becoming twice as likely to seek professional mental health advice (Twenge, 2015). Possible explanations for the increase in depression include greater inequality, low levels of social support, intensive individual competitiveness and increased social failure (Hidaka, 2012). Another factor in the increase in depression may be an increase in anxiety, as anxiety is associated with depression (Cummings, Caporino, & Kendall, 2014; Olino, Klein, Lewinsohn, Rohde, & Seeley, 2010). Anxiety in children and college students from the USA increased one standard deviation from the 1950s to the 1990s (Twenge, 2000). The importance of

anxiety is also demonstrated by psychological disability. In Australia, the prevalence of psychological disability almost doubled in the 15 to 24-year-old group, from 1.2% in 2009 to 2.3% in 2012, with an increase in anxiety (not depression) being a significant factor (Australian Bureau of Statistics (ABS), 2012). The aim of this thesis is to investigate cognitive deficits in young adults with depression and or anxiety. This is an important step in determining whether cognitive deficits play a role in the increase of depression and anxiety in society.

Despite this current increase in depression, there has been limited research examining the cognitive deficits of depression in the young adult population (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Grant, Thase, & Sweeney, 2001). This is an important area of investigation, as identifying a pattern of impairment for young adults with depression can enable more effective treatment in the disorder's infancy, provide an aid to early diagnosis and aid in the development of more effective coping skills for clinicians and sufferers alike. In addition it has been shown that early-onset depression (15 years and younger) can result in a more severe, chronic form of depression, associated with greater suicidality, worse social functioning, a greater number of comorbid mental disorders and more psychological scarring (Hammen, Brennan, Keenan-Miller, & Herr, 2008; Rohde, Lewinsohn, & Seeley, 1994). In addition, the study of cognitive deficits in young adults with depression can help to determine the pathophysiology of cognitive deficits in older adults, leading to an improved understanding of the onset, development, symptoms and management of depression.

Previous research concerning cognitive deficits in young adults with depression has provided inconsistent results regarding the existence of cognitive deficits, the effects of comorbid disorders and the effect of the number of depressive episodes (Castaneda,

Tuulio-Henriksson et al., 2008; Snyder, 2013). Significant cognitive differences between depressed and healthy control groups have been found in the executive function (EF) domains of inhibition, updating, set-shifting, planning and verbal learning and memory (Bearden et al., 2006; Fitzgerald et al., 2008; Grant et al., 2001; Harvey et al., 2004; Smith, Muir, & Blackwood, 2006; Stordal et al., 2004). Cognitive deficits seemingly mirror biological abnormalities, with cellular differences, including decreased glial density in the dorsal lateral prefrontal cortex (dlPFC), orbital frontal cortex (OFC) (Rajkowska, Miguel-Hidalgo et al., 1999), and the anterior cingulate cortex (ACC) (Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Öngür, Drevets, & Price, 1998) found between the brain tissue of depressed patients and healthy control tissue. These biological abnormalities represent a possible biological basis for cognitive deficits in depression, as brain activation and lesion studies show that EF is central to the dlPFC, OFC and ACC (Birrell & Brown, 2000; Buckley et al., 2009; Killgore, Gruber, & Yurgelun-Todd, 2007; Owen, Lee, & Williams, 2000; Wagner, Koch, Reichenbach, Sauer, & Schlösser, 2006).

In this research, Study 1 consists of two main comparisons: depression versus healthy control and anxiety disorder only versus healthy control. Other comparisons include the descriptive and cognitive differences between early- and non-early-onset depression, as well as correlations between depression variables, cognitive measures and disorder severity. Study 2 examines the relationship between comorbid depression and anxiety. Comparison groups do not consist of 'depression only' versus comorbid depression, but between primary and secondary depression. Study 3 investigates the relationship between cognition and number of depressive episodes; specifically, whether there are cognitive differences between a young adult who has experienced one or two depressive episodes only, compared to a young adult who continues to

experience depressive episodes (three or more episodes). Study 4 examines cognitive differences in mathematical ability. Finally, Study 5 examines the relationship between plasma gamma-aminobutyric acid (GABA) concentration, a probable biological marker of depression and EF, a probable cognitive marker of depression.

The first five chapters of the thesis incorporate a review of the current literature of each of the studies mentioned above. Chapter 1 reviews the literature of studies investigating cognitive deficits of young to middle-aged adults with either depression or anxiety. This chapter also introduces the differences between cognitive deficits that are clinical 'state' or 'trait' anomalies in nature and investigates possible biological mechanisms that may provide a framework for the relationship between depression and cognition.

Chapter 2 reviews the association between depressive and anxiety disorders; specifically, the way depressive and anxiety disorders interact. Chapters 3 analyses factors involved in depression relapse, which results in a recurrent or chronic form of depression. Chapter 4 examines the relationship between intelligence and cognition. Chapter 5 examines the relationship between systemic blood GABA concentration and depression, as well as the relationship between GABA concentration and cognition. Chapters 6 to 10 test the hypotheses generated from the reviews of the literature mentioned in Chapters 1 to 5. Finally, Chapter 11 summarises the thesis and presents a framework for future research based on two new proposed depression pathways.

Chapter 1: Cognitive Deficits of Young Adults with Depression, Anxiety Disorders

1.1 Introduction to Cognitive Research for Young Adults with Depression and/or Anxiety

Cognitive differences observed between young adults with depression and matched healthy control participants have mostly been in the area of EFs (Castaneda, Tuulio-Henriksson et al., 2008; Grant et al., 2001; Snyder, 2013). As previous research has been limited in the young adult age range, investigations of young to middle-aged adults are included in this review, as well as research regarding cognitive deficits associated with young adults with anxiety disorders. However, owing to the high rate of comorbid depression associated with anxiety disorders, few studies focus on anxiety disorders only. Categories of cognitive deficits (i.e., whether they are clinical state deficits or trait anomalies) are examined and contrasted. Finally, cellular differences in the prefrontal cortex (PFC), which may provide biological evidence for the cognitive deficits associated with depression, are examined.

1.2 Executive Functions (EFs)

The term ‘executive functions’ refers to a group of neurological processes that allow people to respond flexibly and engage in deliberate, goal-directed thought and actions, especially in new or novel situations (Cragg & Gilmore, 2014). EFs are high-level processes that control and regulate lower-level brain functions, including perception and motor responses (Snyder, 2013). EF are distinct from more automatic cognitive processes such as motor, reading and language skills which are overlearned by repetition. High performance in EF allows a person to respond in a flexible manner, break out of habits, plan, prioritise and deal with novel situations (Snyder, 2013).

Although there is debate regarding the domains of EFs, this thesis focuses on the following EFs: set-shifting, updating, planning, inhibition and verbal learning and memory.

1.2.1 Set-shifting

Set-shifting, which is shifting between tasks or mental sets, has been identified as a possible cognitive deficit of young adults with depression (Snyder, 2013). Usually, set-shifting is assessed using the Wisconsin Card Sorting Test (WCST), Trail Making Test B and the attentional set-shifting test (mostly for animal studies). In the WCST, participants have to try to match cards according to a rule. After 10 correct matches, the rule changes (e.g., colour to shape) and participants have to detect the change and identify the new rule (shifting set). Participants commit a perseverative error if they continue to match with the old rule once a rule change has occurred, while a non-perseverative error can occur in a failure to maintain set and efficient errors. 'Failure to maintain set' refers to a participant correctly matching for colour but selecting shape. 'Efficient errors' refer to errors made during a change of rule when the participant is trying to identify the new matching rule (see Section 6.2.2.1.1 for a full explanation of set-shifting tasks).

Grant et al. (2001) found that young to middle-aged adult depression outpatients underperformed in perseverative errors, categories and ability to maintain set, compared to healthy matched controls on the WCST. Grant et al. found no significant differences in other cognitive domains, such as attention, memory and other tests of EF. They suggested that using outpatients (with reduced disorder severity) could account for the non-significance in learning and memory cognitive tests. Deficits in set-shifting in the WCST have also been reported in other depression studies that compared young to middle-aged adult depression groups against control groups (Channon, 1996; Harvey et

al., 2004; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999). Channon (1996) found that a subclinical sample of young adults with moderate to severe depression according to the Beck Depression Inventory (Beck, Steer, & Carbin, 1988) committed more perseverative and non-perseverative errors than healthy matched controls. Merriam et al. (1999) found that young to middle-aged depression inpatients committed more perseverative and non-perseverative errors and completed fewer categories than matched healthy control participants did. Similar to Merriam et al., in terms of type of participants with depression, Harvey et al. (2004) found that young to middle-aged depression inpatients committed more perseverative errors on a modified version of the WCST, but found non-significant differences in non-perseverative errors.

Harvey et al. included a second set-shifting task, Trail Making Test B and found that the depression group took longer to complete the task than the healthy matched controls. Other studies utilising the Trail Making Test B include Smith et al. (2006), who studied young adults with recurrent depression in remission and Uekermann, Abdel-Hamid et al. (2008), who studied middle-aged depression patients. Both of these found that the depression groups took significantly longer to complete the task than the matched healthy control groups.

Lastly, utilising an attentional set-shifting test, Purcell, Maruff, Kyrios and Pantelis (1997) found that young to middle-aged adult patients with depression had more errors in intradimensional and extradimensional shifts and completed fewer stages than matched healthy controls. An ‘intradimensional shift’ refers to shifting within a stimulus group (e.g., from a line to a different type of line), whereas an ‘extradimensional shift’ refers to shifting between stimulus groups (e.g., from line to shape). Overall, the current literature reveals that young to middle-aged adults with

depression demonstrate reduced performance (more errors and longer completion times) in the set-shifting tasks.

Several studies that include set-shifting have shown a non-significant relationship between depression groups and matched healthy control groups. Castaneda, Suvisaari et al. (2008) investigated cognitive differences between young adults with a lifetime history of depression and a matched healthy control group with no history of depression. At the time of testing, most of the depression group's participants were in remission and all demonstrated good psychosocial functioning. No differences in EF, memory or attention and only minor differences in verbal learning were found between these groups. In Fossati, Amar, Raoux, Ergis and Allilaire (1999), young to middle-aged major depressive disorder (MDD) inpatients were compared with a healthy control group in EF tasks. While there were significant differences between the two groups in aspects of EF such as verbal span and verbal fluency, there were no significant differences for the set-shifting task. Hill, Keshavan, Thase and Sweeney (2004) also found no significant differences between the young adult depression patients and a healthy control group in either of the set-shifting measures WCST or Trail Making Test B. Unlike Castaneda, Suvisaari et al. (2008) (n=68), Fossati et al. (1999) and Hill et al. (2004) both used small sample sizes (n= 20 and 14, respectively), which increased the chance of a Type II error, where the lack of a significant effect could be due to small sample sizes (Field, 2013). In addition, Fossati et al. (1999) used an alternative version of the WCST. Stordal et al. (2004) compared a young to middle-aged sample, including both inpatients and outpatients with recurrent depression (n=45), to a healthy control group, finding differences in a wide range of EF tasks such as set-shifting, verbal fluency and inhibition. However, once medication and retarded psychometric speed was adjusted for, the differences in set-shifting were no longer significant.

In summary, studies have shown non-significant differences between the depression and healthy control groups in set-shifting; however, factors such as small sample sizes and the use of alternative tests may account for these findings (Fossati et al., 1999; Hill et al., 2004). Studies by Castaneda, Suvisaari et al. (2008) and Grant et al. (2001) show comparable methodologies with differing results. Thus, there is no obvious factor from the above studies that differentiates studies with significant differences in set-shifting from those with non-significant differences.

1.2.2 Updating, planning and inhibition

Research of other domains of EF, such as updating, planning and inhibition, have also shown mixed results in terms of cognitive deficits observed in young to middle-aged adults. Harvey et al. (2004) tested inpatients and Rose and Ebmeier (2006) tested both inpatients and outpatients. Both studies found that young to middle-aged depression patients performed significantly worse than matched controls on the updating task, N-back. Other studies found no significant differences but this may be due to other factors. Walsh et al. (2007), for example, stated that a lack of significant differences between the depression and healthy control group might be due to the use of outpatients and a ceiling effect for healthy patients.

In a functional magnetic resonance imaging (fMRI) study featuring young to middle-aged depression outpatients with moderate to severe depression, Fitzgerald et al. (2008) found no significant differences in the 2-back task (only one of the three trials was utilised in this experiment). However, while performing the 2-back task, the depression group showed greater brain activation, especially in the right PFC. In the planning task Tower of London (ToL), Fitzgerald et al. (2008) found that depression patients underperformed, compared to healthy control patients, whereas Purcell et al. (1997) showed that although there was no significant differences in performance, the

depression group demonstrated motor slowness. Other studies found no significant differences between similar groups in the ToL task (e.g., Porter, Gallagher, Thompson, & Young, 2003; Stordal et al., 2004). Using fMRI, Fitzgerald et al. (2008) showed that depressed patients displayed greater activation in the right PFC and suggested that depressed patients may recruit greater brain areas to complete the planning task. Stordal et al. (2004) found that depressed patients had reduced performance in the Stroop Test, a measure of inhibition, while Hill et al. (2004) and Smith et al. (2006) found no significant differences between depressed patients and healthy control participants for this task.

As with the set-shifting studies, the study of other forms of EF performance have shown mixed results in young to middle-aged adult depression samples and matched healthy control groups, and these warrant further study. This is highlighted by the evidence that even in studies with non-significant differences between group performance on a task (Fitzgerald et al., 2008), other measures such as increased brain activation (as demonstrated by fMRI) in areas associated with EF may differentiate those with depression from the healthy controls.

1.2.3 Verbal learning and memory

As with updating (N-back task), verbal learning and memory is a measure of EF that contains a large component of working memory (Khosravi Fard, Keelor, Akbarzadeh Bagheban, & Keith, 2016; Owen, McMillan, Laird, & Bullmore, 2005). Bearden et al., (2006) found young to middle aged depression outpatients demonstrated deficits in verbal learning and memory in the California Verbal Learning Test (CVLT) compared to healthy controls. Smith et al., (2006) showed young adult depression patients in remission displayed deficits in Trial 4 (p=.05) and Trial 5 (p=.05) of the CVLT (of five trials in total) compared to a healthy control group. Horan, Pogge,

Borgaro, Stokes and Harvey (1997) also utilizing the CVLT found gender differences were evident when comparing the performance of adolescent depression patients to normative standards for adult depression patients. Horan et al., revealed that depressed adolescent females in their study performed significantly lower in all CVLT variables, while male adolescents recalled significantly fewer words on Trial 5 only of the long-delay free recall.

Wang et al. (2006) and Grant et al. (2001) found no significant differences in verbal learning and memory between patients and healthy controls. However, both cited that participants were only suffering mild to moderate depression, which may have accounted for the lack of deficits. Further, Fossati et al. (1999) found that depression patients did not show deficits in verbal memory but produced fewer words on verbal fluency tasks. In combination, these findings, as per other measures of EF, are inconsistent, although noting gender differences in future studies would be of interest.

1.3 Young Adults with Anxiety Disorder Only

Little research has been directed towards cognitive deficits found in people who suffer from anxiety disorders without depression, with even less in the young adults' age range (Castaneda, Tuulio-Henriksson et al., 2008). As anxiety is often comorbid with depression (Aalto-Setälä, Marttunen, Tuulio-Henriksson, Poiklainen, & Lönnqvist, 2002; Castaneda, Tuulio-Henriksson et al., 2008), obtaining sufficient sample sizes to compare 'anxiety only' with a matched control group is problematic.

Airaksinen, Larsson and Forsell (2005) studied cognitive deficits in adults diagnosed with anxiety disorders, including panic disorder (PD) with or without agoraphobia, social phobia, obsessive compulsive disorder (OCD), generalised anxiety disorder (GAD) and specific phobia. People with PD, social phobia or OCD showed significant deficits on the episodic memory test compared to a healthy control group. In

addition, those with PD or OCD showed deficits in the time taken to complete an EF task. However, once the results for people comorbid with substance abuse were removed from the sample, this was no longer significant. Although other disorders such as GAD showed no significant differences, the total anxiety group exhibited deficits in episodic memory. Other studies involving people diagnosed with PD have identified deficits in divided attention (Lautenbacher, Spernal, & Krieg, 2002), verbal learning and memory (Asmundson, Stein, Larsen, & Walker, 1995) and spatial learning (Boldrini et al., 2005).

In summary, studies into the effects of anxiety on the cognitive domain of EF are scarce within the specific age range of interest (young adults or adolescents). Regarding the cognitive domain of EF, only deficits in verbal learning and memory seem relevant to young adults with an anxiety disorder without depression; however small sample sizes in some studies may have been a factor in the non-significant results for other forms of EF (Airaksinen et al., 2005; Boldrini et al., 2005; Kaplan et al., 2006).

1.4 State or Trait Deficits

Cognitive deficits are thought to be either state deficits, caused by the depressive episode, or trait (deficits) abnormalities, which are not due to the effects of the depressive episode (Castaneda, Tuulio-Henriksson et al., 2008). The identification of deficits that are specifically illness-state dependant (state deficits) may assist in the assessment and clinical management of depression. State deficits could aid in understanding and assessing any cognitive decline due to the progression of the disorder and this can assist clinicians in selecting appropriate treatment regimes. However, trait deficits that likely precede the disorder have an important role in disorder prevention (Castaneda, Tuulio-Henriksson et al., 2008).

Indications that a deficit may be state or trait can be identified by the relationship between the cognitive deficit and disorder severity. Cognitive deficits that can be shown to positively correlate with disorder severity are likely to be state deficits (i.e., these deficits will increase as the disorder severity increases). Conversely, a non-significant relationship between cognitive deficits and disorder severity is an indicator of a trait deficit (Snyder, 2013).

The current literature relating to whether EF deficits are state or trait indicates inconsistent findings. EF domains, such as updating and verbal learning and memory, have been shown to have a significant relationship with disorder severity or other disorder-dependant-type measures. Harvey et al. (2004) found that deficits in the N-back updating test correlated with number of hospitalisations and Rose and Ebmeier (2006) found that deficits in N-back trials correlated with length of time of disorder (2-back and 3-back, $p<.05$), as well as with depression severity (3-back, $p<.05$). However, although the *p* values in Rose and Ebmeier's research were <.05, owing to the large number of correlational comparisions, they were not statistically significant. Porter et al. (2003) found that cognitive deficits in verbal and spatial learning and memory correlated with depression severity, while deficits in sustained attention and other EF tests did not. Other studies that measured deficits in domains of EF, particularly set-shifting (Grant et al., 2001; Harvey et al., 2004; Purcell et al., 1997), inhibition (Harvey et al., 2004) and verbal span, verbal fluency and visuospatial span (Fossati et al., 1999), did not correlate with disorder severity, which suggests that these are trait deficits. Porter at el. (2003) suggested that learning and memory (verbal and spatial) could represent a state deficit while other forms of EF could represent a stable trait marker for depression.

Probable trait deficits can be identified by whether deficits are still present when the depressive disorder is in remission. The most prominent deficits reported despite clinical recovery have included set-shifting (Paradiso, Lamberty, Garvey, & Robinson, 1997; Preiss et al., 2009; Smith et al., 2006), attention (Neu et al., 2005; Paradiso et al., 1997; Preiss et al., 2009; Smith et al., 2006) and verbal learning and memory (Neu et al., 2005; Preiss et al., 2009; Smith et al., 2006). Smith et al. (2006) suggested that these cognitive deficits may not be simply due to mood disturbances mediated by depression, but rather, trait vulnerabilities. Although the above studies did not rule out the idea that aspects of the depressive disorders could contribute to the in-remission cognitive deficits, they did provide evidence of the possible causal role of cognitive deficits in depression relapse.

Familial studies are a further method for demonstrating not only whether a cognitive deficit is state or trait but also whether the offspring of parents with depression are at increased risk of depression onset. Weissman et al. (2006) found in a 20-year longitudinal study that the offspring of a parent with depression had a 3.3 times higher risk of MDD onset compared to the offspring of non-depressed parents. This agreed with a study by Lieb, Isensee, Höfler, Pfister and Wittchen (2002), who in a four-year longitudinal study, found that having one parent with a MDD diagnosis increased the risk of MDD onset by 2.1 times and this increased to 2.3 times if both parents had an MDD diagnosis. This finding was also replicated by Klein et al. (2013) in a 15-years longitudinal study. Klein et al. found that having a depressed parent, being female and having sub-threshold depression were significant predictors of future depression. Although Klein et al. found that gender was a predictor of a future depressive episode, if a male had a depressed parent, they were as likely as a female with a depressed parent to experience a future depressive episode. While there are

possible contributing environmental factors to depression onset, the high concordance rates between parent and child suggest a possible genetic or trait factor in mood disorders.

Familial studies involving cognitive testing have identified the cognitive deficits that may precede the onset of a depression disorder. For example, Mannie, Barnes, Bristow, Harmer and Cowen (2009) showed that adolescents (mean age 18.9 years) with no depression history but with a depressed parent performed worse than healthy matched controls on the Rey Auditory Verbal Learning Test (verbal learning and memory). In a separate study, Mannie, Harmer, Cowen and Norbury (2009) found that although the familial group did not perform differently than the control group on the updating task N-back, the group with a depressed parent showed greater activation of the superior temporal cortex, superior parietal cortex and the lateral occipital cortex during this task. Mannie, Harmer et al. stated that these brain networks supported working memory and that their over-activation compared to the control group could demonstrate a trait vulnerability marker for depression. They noted that there were consistently lower scores for the family history group in the N-back task, despite there being no statistically significant differences. A further study by Mannie, Norbury et al. (2008) showed that while responding to emotionally balanced stimuli, healthy control participants activated the anterior cingulate cortex (ACC), whereas children with a depressed parent did not. These studies have demonstrated that healthy individuals with a familial history of depression show decreased cognitive performance, which may be associated with differences in brain activation. The differences in brain activation may represent a trait anomaly.

Although limited research exists regarding familial studies involving MDD and set-shifting, research on other related disorders have shown interesting results. For

example, Szöke et al. (2006) showed that relatives of both bipolar or schizophrenia patients showed deficits in the set-shifting test Trailing Making Test B compared to healthy controls; however, no differences were found in the WCST. In contrast, Liu, Zhao and Tam (2003) found that relatives of schizophrenia patients performed worse than healthy controls in perseverative and non-perseverative errors in the WCST. These results suggest that owing to either genetic or environmental influences of a parent with a disorder, cognitive deficits in set-shifting represent trait vulnerabilities that may precede depression onset.

Attempting to categorise an area of cognition as definitively state or trait is problematic. Verbal learning and memory has been shown to be a state deficit due to its positive relationship with depression severity (Porter et al., 2003), but also a trait deficit in remission studies (Neu et al., 2005; Preiss et al., 2009; Smith et al., 2006) and familial studies (Mannie, Barnes et al., 2009). Also set-shifting which has demonstrated to be a trait deficit due to a non-significant relationship with severity (Grant et al., 2001; Harvey et al., 2004; Purcell et al., 1997), and in remission studies (Paradiso, Lamberty, Garvey, & Robinson, 1997; Preiss et al., 2009; Smith et al., 2006) there is still some evidence of state-like qualities. A study by Merriam et al. (1999) found that depression severity was moderately correlated with set-shifting, suggesting a state deficit. However, further analysis in Merriam et al. suggested that depression severity only played a role in the initial aspects of the set-shifting test (WCST) and once the general principles were acquired, severity was no longer a factor. Essentially, cognitive deficits that correlate significantly with depression severity can be classified as state deficits; however, that does not preclude them from demonstrating other properties such as being present in disorder remission, which is a trait-like characteristic.

1.5 Biological Differences

Differences in cell biology in the PFC may explain the cognitive differences observed with depression. Previous research had identified the dorsal lateral prefrontal cortex (dlPFC) and the orbital frontal cortex (OFC) as areas of interest for depression studies (Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Biver et al., 1994; Bremner et al., 1997).

Rajkowska, Miguel-Hidalgo et al. (1999) studied brain tissue samples taken from the dlPFC and OFC of deceased people who had depression and matched healthy control tissue. Differences were found in the brain samples of the rostral orbital frontal cortex (rOFC), caudal orbital frontal cortex (cOFC) and the dlPFC. In the rOFC, the depression group was found to have reduced overall cortical thickness and smaller neuronal cell bodies, but increased density of smaller neurons (layer III). In the cOFC, there were no significant differences in cortical thickness but there was a reduction in neuronal size, densities of larger neurons and glial density in large- and medium-sized glial cell nuclei. Differences in the dlPFC were similar to those in the cOFC, with no reduction in the overall cortical thickness but with a reduction in neuronal size, increase in density of the smallest neurons and reduction in glial density.

Glial cells have important metabolic influences on neurons and contribute to synaptic function and neurotransmission (Cotter et al., 2001). Glial cell activity affects several processes, including regulation of extracellular potassium, glucose storage and metabolism and glutamate uptake, which are all important for normal neural activity (Öngür et al., 1998). Rajkowska, Miguel-Hidalgo et al. (1999) suggested that the differences in cell biology, including glial density in the dlPFC, resulted in altered metabolism rates. The abnormalities in the cellular structure in the dlPFC and OFC could be a factor in the reduced performance in EF of people with depression.

Differences have also been found between healthy controls and people with MDD in the ACC and reduced grey matter in the PFC. Cotter et al. (2001) showed that in layer 6 of the supracallosal ACC, MDD participants had a significant reduction in glial cell density and neuronal size compared to healthy controls. Öngür et al. (1998) showed that people with MDD had reduced glial cell density in the subgenual ACC, with the most prominent reduction in the subgroup with familial MDD (although not significantly lower than non-familial MDD). As noted above, glial cells play an important role in many aspects of neural activity. A neuromorphometric study compared a healthy control group to a currently depressed group and showed reduced cortical grey matter volume in the PFC; namely, the dorsal anterolateral PFC, the dorsal medial PFC and the ventrolateral PFC (Salvadore et al., 2011). These studies highlight the biological differences between people with depression and healthy control participants, especially in terms of reduced glial density in the ACC and reduced grey matter volume in the PFC.

Human and animal studies highlight the role of the PFC, most notably the dlPFC and OFC in the performance of set-shifting tasks such as the WCST. Berman, Doran, Pickar and Weinberger (1993) found that performing the WCST led to increased regional cerebral blood flow (rCBF) in the human PFC in the dlPFC and OFC and speculated that activation of the two different areas may represent different aspects of the WCST. Mansouri, Matsumoto and Tanaka (2006) investigated cellular activity in the dlPFC in monkeys while performing a simplified version of the WCST (colour and shape only). One cell's activity was modulated, owing to errors made during a rule change, while for the other cells their activity differed between correct and incorrect responses not related to rule changes. Mansouri et al. suggested that the dlPFC is involved in maintaining the relevant rule across the trials, assessing behavioural

outcomes and monitoring the processes that could lead to success or failure. Buckley et al. (2009), who conducted research with macaque monkeys, found that only lesions to the inferior dlPFC and not the superior dlPFC impaired performance on the WCST. Buckley et al. also found that lesions to the ACC and the OFC affected test performance negatively. These studies have shown that the PFC, particularly the dlPFC and OFC, are not only relevant to set-shifting but individual components of the task may be reflected in specific brain areas.

To examine the specific roles of the dlPFC and OFC, animal lesion studies have been examined, ulitising the attentional set-shifting test. Attentional set-shifting consists of only two types of stimuli, such as lines and shapes. As explained earlier, if the participant is required to shift from a line to a different kind of line (within the same stimulus group), that is known as an intradimensional shift, whereas shifting from a line to a shape (between stimulus groups) is known as an extradimensional shift. Once an intradimensional shift has occurred, if the intradimensional rule changes are reversed, this is known as reverse learning (Chudasama, 2011). Dias, Robbins and Roberts (1996b) lesioned the dlPFC and OFC in three marmoset monkeys and found that compared to the control monkeys, the marmoset monkeys had greater difficulty in performing an extradimensional shift. When reverse learning of an intradimensional shift occurred, the lesioned monkeys committed a greater number of perseverative errors, while there was no significant difference in non-perseverative errors. In a separate study in which the area of lesion was more specific to either the dlPFC or the OFC, Dias, Robbins and Roberts (1996a) demonstrated a double disassociation. Monkeys lesioned in the dlPFC displayed deficits in the shifting set aspect of set-shifting (extradimensional shift) but not in reverse learning, whereas monkeys lesioned in the OFC displayed deficits in reverse learning but not in shifting set. This result was

replicated by Birrell and Brown (2000), who found that rats lesioned in the medial PFC (and not OFC) displayed deficits in shifting set but not in reverse learning, while rats lesioned only in the OFC showed deficits in reverse learning and not in shifting set. This provides evidence for Berman et al.'s (1993) speculation that different sections of the PFC are responsible for different aspects of set-shifting tests, with the dlPFC responsible for shifting set while the OFC is responsible for perseveration.

Performance in other EF tasks also activates different areas of the PFC. For the Stroop task, which measures inhibition, there is a positive correlation between depression severity and activation in the left dlPFC and anterior cingulate gyrus and a negative correlation with activation in the right dlPFC (Killgore et al., 2007). For the N-back task, which measures updating and involves a large working memory component, there was increased activation in the dlPFC, ventral lateral prefrontal cortex (vlPFC) and frontal poles (Owen, McMillan et al., 2005). For a specific working memory task (forward and backward digit span), forward digit span resulted in greater activation in the mid-vlPFC, while for backward digit span there was greater activation in the mid-vlPFC and mid-dlPFC (Owen et al., 2000). Performance in the planning task ToL resulted in greater activation bilaterally in the dlPFC, in the right ventrolateral PFC and in the left frontal pole (Wagner et al., 2006). A further study by Kaller, Rahm, Spreer, Weiller, and Unterrainer (2010) for the planning task ToL showed that activation of the left or right dlPFC depended on which of the two independent parameters of planning were being utilised—goal hierarchy or search depth. Goal hierarchy (the degree to which the configuration of the goal state renders the order of single steps clearly) results in greater activation in the left dlPFC, whereas search depth (the degree of interdependence between consecutive steps) results in greater activation of the right dlPFC. These studies have shown that the EF domains of inhibition, updating, planning,

working memory, and the shifting set aspect of set-shifting tasks, activate different areas of the PFC, including the dlPFC, vlPFC, ACC and the frontal pole, while only the perseveration aspect of set-shifting tasks correspond to the OFC.

What is unknown is whether biological abnormalities in the PFC associated with EF, are due to the course of depression, or developmental/environmental factors which may predate depression onset. Firstly, Rajkowska, Miguel-Hidalgo et al. (1999) suggested that differences in neuronal density could be caused by a developmental deficiency as the decrease in densities of large neurons was accompanied by parallel increases in the density of small neurons. Secondly, studies with rats and mice demonstrate a causal link between developmental deficiencies, in the form of early adverse life events, and biological and cognitive deficits. Impairments in set-shifting were demonstrated in multiple rat isolation studies using reverse learning tasks (Jones, Marsden, & Robbins, 1991; Li, Wu, & Li, 2007), the attentional set-shifting task (Schrijver & Würbel, 2001; Schrijver, Pallier, Brown, & Würbel, 2004) and the rat 5-choice serial reaction time task (Dalley, Cardinal, & Robbins, 2004). Acquiring the rule in a set-shifting task, which depends on the hippocampal neocortical pathways was not affected by isolation. However, impairments in reverse learning, which depend primarily on PFC cortico-striatal pathways were (Fone & Porkess, 2008). Other animal studies have shown similar deficits where isolation occurs only at a critical time period. Makinodan, Rosen, Ito, and Corfas (2012) isolated mice for two weeks directly after weaning and then reintroduced them to a social environment. The isolated mice showed reduced working memory capacity and alterations in oligodendrocytes (glial cells) and myelination in the medial PFC. Similarly, Baarendse, Counotte, O'Donnell, and Vanderschuren (2013) isolated rats from days 21 to 42 before reintegrating them until adulthood. The isolated rats displayed impairments in a decision making task and also

resulted in changes to adult medial PFC pyramidal neurons. Stamatakis, Manatos, Kalpachidou, and Stylianopoulou (2016) used a different early adverse life experience, where rats would find their mother but would be unable to make contact. These rats displayed impaired EF, committing a significantly greater number of perseverative errors in the attentional set-shifting task. They also showed lower activation of the medial OFC and a decrease in neuronal density but increased micro- and astroglia-density in the medial OFC and infralimbic cortex. As above, previous studies using monkeys and rats have also linked perseveration to the OFC (Bistricky, Ingram, & Atchley, 2011; Brown & Bowman, 2002).

Biological abnormalities due to development deficiencies in animal studies can be compared in terms of brain location to cellular abnormalities found in human depression patients. Firstly, the OFC is implicated in both animal developmental studies (Stamatakis et al., 2016) and in human depression patients (Rajkowska, Miguel-Hidalgo et al., 1999). But whether the deficits found in the medial PFC in rodents in the isolation studies of Makinodan et al. (2012) and Baarendse et al. (2013) can be generalised to the biological abnormalities in dlPFC in humans is unclear. While there is some evidence that the medial PFC in rodents is functionally homologous to the dlPFC in humans, this remains debatable (Uylings, Groenewegen, & Kolb, 2003). What these animal developmental studies do demonstrate is that developmental deficiencies play a causal role in EF deficits and abnormalities in brain areas that are key to EF.

1.6 Summary

Studies of the biological structure and function of the brain have highlighted abnormalities in the dlPFC, OFC and the ACC for people with depression (Cotter et al., 2001; Öngür et al., 1998; Rajkowska, Miguel-Hidalgo et al., 1999). Brain activation studies have shown that the dlPFC and ACC are important for EF domains such as

inhibition, updating, planning, working memory, and the shifting set aspect of set-shifting tasks (Buckley et al., 2009; Killgore et al., 2007; Owen et al., 2000; Wagner et al., 2006), while OFC is central to the perseveration aspect of the set-shifting task (Birrell & Brown, 2000). This biological relationship seemingly mirrors the results from depression cognition studies. While all of the above forms of EF have been shown to be in deficit in various cognitive studies, multiple studies have identified set-shifting tasks as the main cognitive area of interest (see Section 1.2). Studies such as Grant et al. (2001), which examined young to middle-aged depression outpatients, showed modest impairments in set-shifting while showing no significant differences in other forms of cognition. However, non-set-shifting forms of EF should not be discounted, as non-significant trials could have been due to factors such as small sample sizes (see Section1.2.2). Regarding young adults with an anxiety disorder with no comorbid depression (i.e., anxiety disorder only), significant differences have been found in the literature in only one domain of EF: verbal learning and memory (Asmundson et al., 1995).

Chapter 2: Comorbid Depression: Primary and Secondary

2.1 Comorbid Depression

In the majority of cases, a young adult with depression will have an additional comorbid disorder and the depressive disorder usually occurs after the non-depressive disorder (Aalto-Setälä et al., 2002; Kessler & Walters, 1998). Among youths with depression, anxiety is the most common comorbid disorder, with previous studies demonstrating a wide range of rates of comorbid anxiety (approximately 15–75%) (Angold, Costello, & Erkanli, 1999; Brady & Kendall, 1992; Cummings et al., 2014). This chapter reviews the literature regarding the relationship between anxiety and depression. It also examines and creates a working definition for the depression subtypes, primary depression and secondary depression.

To examine the relationship between depression and anxiety disorders, longitudinal studies are employed. Utilising data from the Oregon Adolescent Depression Project, Olino et al. (2010) analysed 1,653 participants over four periods, from adolescence to adulthood. First, five disorder subgroups were identified, represented by a starting point (or disorder), and then the probability of a comorbid disorder at each period was calculated. The five disorder subgroups were (1) early-onset depression with low probability of anxiety; (2) early-onset anxiety with modest probability of depression; (3) later-onset anxiety (21 to 26 years of age) with modest but gradually increasing probability of depression; (4) later-onset depression with low probability of anxiety; and (5) high probability of anxiety before adolescence, with anxiety decreasing over time, with modest probability of depression decreasing over time but at a slower rate than that for the anxiety disorder. In Groups 1 and 4, with depression as the initial disorder, there was a small probability of anxiety. This contrasts with Groups 2, 3 and 5, in which anxiety was the initial disorder and there was a

moderate probability that the person would also have a depressive disorder. This agreed with the findings of Fichter, Quadflieg, Fischer and Kohlboeck's (2010) 20–25-year longitudinal study, which found a stronger path from early-onset anxiety to later depression than from early-onset depression to later anxiety. In summary, both of these longitudinal studies showed that if anxiety was the initial disorder, there was a higher likelihood that there would be an additional depressive disorder than an additional anxiety disorder if depression was the initial disorder.

Depression and anxiety are often comorbid because of a variety of factors. Both disorders have similar symptoms used in diagnosis and both share common risk or aetiological factors (Garber & Weersing, 2010; Siegman & Boyle, 1993). In addition, both disorders may share an underlying construct, such as rumination (Nolen-Hoeksema, 2000), which could be split between the two disorders (Siegman & Boyle, 1993). Finally, there is a relationship between depression and anxiety where the existence of one disorder may lead to the onset of the other (Cummings et al., 2014; Garber & Weersing, 2010). To better define the relationship or interaction between two disorders, the terms primary depression and secondary depression are often used.

2.2 Primary and Secondary Depression

Due to high rate of comorbid depression an alternative way of examining depression and comorbidity is categorising in terms of depression causation. For example, when referring to the interaction between depression and anxiety disorders, groups can be categorised as depression onset not due to an anxiety disorder and depression onset due to an anxiety disorder. In medical literature these categorisations are referred to as primary depression and secondary depression respectively (Angold et al., 1999). However when examining previous studies caution needs to apply in non-medical literature as the terms primary and secondary can refer to the timing of disorder

onset with a primary disorder occurring before a secondary disorder (Angold et al., 1999; Feighner et al., 1972). In these instances, causation of the secondary disorder by the primary disorder is not implied, whereas in medical terminology, the secondary condition is caused by the primary condition (Angold et al., 1999).

Several studies have highlighted possible mechanisms involved in secondary depression onset due to a non-depressive disorder. Kessler and Walters (1998) found for young adults, the number of preceding non-depressive disorders or the persistence of those disorders was significant factors in predicating secondary depression onset. Kessler and Walters stated that the type of preceding disorder was not a significant factor. They suggested that comorbid depression was an indicator of resignation or exhaustion in dealing with the preceding non-depressive disorder and that when depression occurs as a secondary disorder, it indicates the severity of the preceding disorders. However, a study by de Graaf, Bijl, ten Have, Beekman and Vollebergh (2004) found that when the initial disorder was anxiety, then non-clinical rather than clinical factors predicted future comorbid disorders. De Graaf et al.'s three-year longitudinal study, which involved mostly women aged 18–65 years, found non-clinical measures such as stressful life circumstances and physical functional disability predicted future comorbid disorders. Clinical factors such as anxiety disorder severity or disorder duration were not significant. However, it should be noted that de Graaf et al. did not state the proportion of future disorders that were depressive.

In a 15-year longitudinal study, Espejo et al. (2007) found that both clinical and non-clinical measures predicted future depression severity. They demonstrated that children with an anxiety disorder or high-level exposure to adversity in childhood showed an increased level of depression severity following low levels of episodic stress compared to children with no history of an anxiety disorder or adversity. They

suggested that children with a history of anxiety or adverse events might have a dysregulated stress response, which may contribute to comorbid depression. The above studies have shown that both clinical factors directly related to the non-depressive disorder and non-clinical factors play a role in comorbid depression onset. Whether or not the non-clinical factors, such as stress, are related to the initial non-depressive disorder demonstrates the difficulty of judging whether an initial non-depressive disorder is playing a direct role in causation of the secondary depressive disorder. For example, if a non-clinical factor such as stress plays a causal role in secondary depression onset, was the primary non-depressive disorder (e.g., anxiety disorder) independent of secondary depression onset and merely preceded the depressive disorder?

Comparisons between primary and secondary depression in terms of medical outcomes and biological factors have been limited. Coryell, Zimmerman and Pfohl (1985) found that patients with primary depression had a significantly greater decrease in depression severity with electroconvulsive therapy (ECT) than patients with secondary depression and that among patients with chronic depression, those with primary depression showed a greater recovery rate than those with secondary depression. In another ECT study comparing patients with primary depression to those with secondary depression due to anxiety, it was found that ECT was more effective for patients with primary depression than for patients with secondary depression (Davidson, Turnbull, & Miller, 1980). Further, in some cases, ECT made patients with secondary depression worse (Davidson et al., 1980). The same study found that patients with primary depression had a better response to tricyclic antidepressants than did patients with depression secondary to anxiety (Davidson et al., 1980). In a rapid-eye-movement (REM) sleep study, patients with primary depression experienced a shorter period of

time before the onset of REM sleep (REM latency), which was absent for people with secondary depression (Kupfer, 1976). Because of the dependability of this result, it was suggested that short REM latency was a biomarker for primary depression (Kupfer, 1976).

Finally, patients with primary depression had significantly lower plasma GABA levels than patients with secondary depression, while secondary depression levels were not significantly different from healthy controls (Petty, Kramer, & Feldman, 1987). While these studies are not recent (no recent comparisons have been made) and are limited in scope, they suggest some form of biological difference between primary and secondary depression. However, it should be noted that in terms of the actual depressive episodes themselves, no qualitative differences have been found between primary and secondary depression (Costello & Scott, 1991).

Given that secondary depression occurs after and possibly because of a primary non-depressive disorder or illness, positive outcomes for the primary non-depressive disorder may translate to positive outcomes for the secondary depressive disorder. Norton, Hayes and Hope (2004) found that when clients with secondary depression preceded by anxiety were treated with a transdiagnostic anxiety treatment, depression severity decreased in the treatment group while no difference was found in the wait-listed group. In a similar study featuring the anxiety medication Alprazolam, Lesser et al. (1989) found an overall significant decrease in depression severity after three weeks compared to the placebo group. Similar improvment was found in secondary depression when it was preceded by a medical condition. Hurst (2010) found that effective treatment of hyperparathyroidism resulted in successful outcomes for secondary depression.

Despite these positive outcomes through treatment of the perceived secondary depression onset trigger, Rubin and Lesser (1990) argued that positive outcomes in depression severity may not translate into meaningful improvements in depression. Their argument was based on the notion that improvements in depression severity are due to improvements in overall score of the Hamilton Depression Severity Scale (HAM-D) resulting from improvements in individual items such as agitation/anxiety, sleep disturbance or somatisation factors, which are also related to improvement in both anxiety and depression. Rubin and Lesser argued that there were no improvements in depression itself due to an unchanged mood depression item in the HAM-D. Rubin and Lesser suggested that treatments focusing on the primary non-depressive disorder may only appear to contribute to improvements in secondary depression through positive outcomes in aspects of depression that are also relevant to the primary causal disorder (such as agitation/anxiety or sleep disturbance, as stated above). However, there are two points on which Rubin and Lesser's conclusions can be questioned. First, the HAM-D is validated as a measure of depression severity through the sum of all the items. To state that there is no real improvement in secondary depression because there is no difference in one item that asks directly whether the participant is depressed may not be a valid measure. Second, in the Lesser et al. (1989) study, while the patients were treated with the antidepressant Alprazolam for eight weeks, dropouts from the placebo group meant the group comparison was done only at week three. A longer period may be required to allow improvements in the primary disorder (anxiety) to translate into improvements in the secondary disorder (depression), or more specifically, the mood depression item on the HAM-D. Overall these results, although fairly limited in number and despite Rubin and Lesser's comments, have provided a positive outlook for focusing treatment for secondary depression on the preceding causal disorder.

2.3 Defining Primary and Secondary Depression

The rationale for comparing cognitive deficits between young adults with primary or secondary depression and a healthy control group is to investigate the possible causal role of cognition in primary depression. Simply stated, if secondary depression onset is due to the preceding non-depressive disorder, then cognitive deficits would be independent of any role in depression onset. If primary depression onset is not due to a preceding non-depressive disorder or medical illness, then do cognitive deficits play a role in depression onset? Therefore, analysing the primary depression subgroup versus a healthy control group may better identify the role of trait cognitive deficits in depression.

The secondary depression group is also a valuable pseudo-control group. One of the difficulties in measuring trait cognitive deficits in a healthy control group made up of younger-aged groups is that trait cognitive deficits can exist before disorder onset. The healthy control group may contain members who display the hypothesised trait cognitive deficit and may be susceptible to depression onset in the future, thereby confounding the comparison. Using a comparison group such as young adults with secondary depression eliminates this possible confounding variable. Considering the ambiguous definitions of primary and secondary disorder in medical and non-medical literature (Angold et al., 1999; Feighner et al., 1972), the comparison groups in the current study are defined by the likelihood that the depression onset was due to a non-depressive disorder. Primary depression is defined as young adults with a classification of major depressive episode (MDE) whose onset was not, to the best of the participant's judgement, caused by a non-depressive disorder or medical condition. Secondary depression is defined as young adults with a classification of MDE whose onset was

most probably, to the best of the participant's judgement, caused by a non-depressive disorder.

2.4 Summary

In summary, a high proportion of people with depression also have at least one other clinical disorder, the most common being an anxiety disorder (Cummings et al., 2014). There are similarities between depression and anxiety in terms of symptoms and aetiology factors and each disorder may play a role in the onset of the other (Garber & Weersing, 2010). Longitudinal studies show that if anxiety is the first disorder then there is a higher probability of a comorbid disorder than if depression was the first disorder (Fichter et al., 2010; Olino et al., 2010). This implies that anxiety plays a greater role in the onset of depression than depression does for anxiety. Because of the high proportion of people with comorbid depression, the literature recommends restating comorbid depression in terms of primary and secondary depression (Winokur, 1990). This form of classification provides information regarding the causation of depression onset, as secondary depression can be defined as depression onset due to a non-depressive disorder such as anxiety (Angold et al., 1999). However, determining whether the non-depressive disorder played a causal role in depression onset (secondary depression) is difficult, as both clinical and non-clinical factors have been implicated in comorbid depression onset (de Graaf et al., 2004; Kessler & Walters, 1998). The limited comparisons involving primary depression and secondary depression suggest they should be treated differently and some positive outcomes from treating the non-depressive primary disorder have been reported (Davidson et al., 1980; Hurst, 2010; Norton et al., 2004). Finally, a rationale for the comparison and a working definition for the depression subtypes primary depression and secondary depression, has been proposed.

Chapter 3: Recurrent versus Non-Recurrent Depression

While previous research that examined correlations between cognitive deficits and number of depressive episodes are noted in this chapter, the main research question is whether there are cognitive differences between young adults who have non-recurrent depression (one or two depressive episodes only) compared to young adults with recurrent depression (three or more episodes). Essentially, what this chapter asks is what differentiates someone in terms of cognition, who has depression and then recovers from someone who continues to experience depressive episodes. While the focus for Chapters 1 and 2 was on EFs such as set-shifting, the previous studies involving number of depressive episodes have found that social cognition is of interest.

This chapter examines the statistics regarding the occurrence of recurrent depression, Beck's Cognitive Theory of Depression (CT), which involves the role of cognitive factors in depression maintenance, and previous literature examining the relationship between cognition and number of depressive episodes.

3.1 Introduction to Recurrent Depression

Between 50 and 75% of people who fit the classification for a MDE experience more than one episode (McClintock, Husain, Greer, & Cullum, 2010; Post, 1992). Whether there are differences in terms of depression severity between a single episode of depression compared to a person who has experienced ongoing depressive episodes is debatable (Kruijshaar, Hoeymans, Bijl, Spijker, & Essink-Bot, 2003). One form of recurrent depression that has been noted as being particularly severe is early-onset recurrent depression. When the initial depressive episode occurs in someone who is 15 years old or less, early-onset depression represents a high-risk subtype of depression (Hammen et al., 2008; Rohde et al., 1994). People with early-onset recurrent depression display a higher level of severity, chronic prognosis, suicidality and comorbid anxiety,

along with worse social functioning, than an early-onset youth with non-recurrent depression (Hammen et al., 2008). Of course, the argument can be made that it is the severe nature of early-onset recurrent depression, or another factor such as the resultant level of disability (Kruijshaar et al., 2003), which contributes to future depressive episodes. This chapter focuses on factors that differentiate non-recurrent depression from recurrent depression.

3.2 Beck's Cognitive Theory of Depression (CT)

Beck's Cognitive Theory of Depression (CT) suggested a role for cognition in not only the maintenance of depressive symptoms but also in depression onset. CT was formed during free association exercises, when Beck noticed that patients expressed thought patterns that they were seemingly not consciously aware of (Beck, 1991). Beck noted that these thought patterns arose quickly, were reflexive in nature and were followed by an unpleasant affect. In addition, Beck stated that depressed people display a cognitive triad, where thoughts reflect themes of loss and negative views of the self, the world and the future (Haaga, Dyck, & Ernst, 1991). Beck believed that this negativity was manifested in low self-esteem, self-blame and self-criticism, negative predictions, negative interpretations of experiences and unpleasant recollections (Beck, 1991). Beck also stated that in ambiguous situations, depressed patients were likely to show negative bias and make a negative interpretation when a positive one would be better suited, thus magnifying the negative and diminishing the positive (Beck, 1991). CT maintains that a person's negative and distorted thinking is responsible for the development and maintenance of depression (Moilanen, 1993). Whether there is any validity behind CT claims that cognition plays a part in depression onset or maintenance is examined next.

There is conflicting information in Beck's (1991) CT regarding whether cognitive factors play a causal role in depression onset or depression maintenance. In a 30-year review of the theory, Beck (1991) stated that negative bias does not have a causal role in depression onset but that the cognitive processes may maintain or increase symptoms of depression. However, Beck did acknowledge that CT does state that a combination of factors, including personality characteristics and an applicable stressor, may play a causal role in depression onset (Beck, 1991). Some of the confusion regarding whether CT has a causal aspect stems from two factors. First, Beck defined dysfunctional beliefs as a form of cognition that are purported to have a causal role in depression onset (Haaga et al., 1991). Second, Beck used the term 'primacy' in the form of the 'primacy hypothesis', which did not intend to mean causation but simply to note components associated with depression at its development (Haaga et al., 1991).

While there is a lack of evidence to support a causal role of negative cognitions in depression onset (Haaga et al., 1991), cognitive factors have been shown to play a causal role in depression maintenance and future depression severity. Studies involving depression reoccurrence have shown that maladaptive thoughts, paranoid beliefs (Kuyken, Kurzer, DeRubeis, Beck, & Brown, 2001), dysfunctional attitudes (Beevers, Keitner, Ryan, & Miller, 2003; Rush, Weissenburger, & Eaves, 1986) and negative self-description (Park, Goodyer, & Teasdale, 2005) show causal attributes that could contribute to depression maintenance. Studies have also shown that future levels of depression severity have been predicted by two cognitive factors: the level of negative thinking (Dent & Teasdale, 1988) and unmet emotional needs in people's relationships with significant others (Halvorsen, Wang, Eisemann, & Waterloo, 2010). However, the role of cognition in onset of the original depressive episode has not been discounted but simply acknowledged that before the initial depression onset, there is little focus on the

person's cognitions (Haaga et al., 1991). To test whether cognition plays a role in depression onset, wide-ranging longitudinal studies, beginning before depression onset, would have to be employed.

3.3 Cognitive differences between recurrent and non-recurrent depression

3.3.1 Executive function (EF)

Cognition studies focusing on attention, EF and working memory have found no significant differences between recurrent and non-recurrent depression groups. Grant et al. (2001) investigated the cognitive domains of attention, memory and learning and EF and found no differences between outpatients with recurrent depression (three or more episodes) and those with non-recurrent depression (one or two episodes). Similarly, Wang et al. (2006) found no significant differences between people with recurrent depression (two or more episodes) and a single episode of depression in tasks involving verbal memory. Other studies, while not directly comparing non-recurrent and recurrent depression, have found non-significant relationships between the number of depressive episodes and cognitive deficits (Harvey et al., 2004; Neu et al., 2005). The studies by Grant et al. (2001) (mean age 39 years) and Wang et al. (2006) (mean age 31 years) both used young to middle-aged adults as their participants. However, research by Kessing (1998), who focused on older adults (mean age 69.3 years), found that the number of depressive episodes were significantly associated with cognitive decline in the Cambridge Cognitive Examination and the Mattis Dementia Rating Scale. Therefore, while there does not appear to be any significant differences in EFs between recurrent and non-recurrent depression in young to middle-aged adults, there is evidence that recurrent depressive episodes may contribute to cognitive decline later in life.

3.3.2 Social cognition

A form of cognition that has been found to differentiate between recurrent and non-recurrent depression is social cognition. Social cognition refers to 'the processes and functions that allow a person to understand, act on, and benefit from the interpersonal world' (Corrigan & Penn, 2001, p. 3). Not only have significant differences in social cognition been found between young adults with MDD and healthy control groups but social cognitions have been shown to play a role in depression maintenance and outcomes (Bouhuys, Geerts, & Gordijn, 1999; Geerts & Bouhuys, 1998; Hale, 1998; Inoue, Yamada, & Kanba, 2006). Social cognition tasks may have greater validity in investigating depression, compared to experimental memory tasks, because social cognition tasks more closely represent real-world situations (Moilanen, 1993). Three forms of social cognition are examined next: facial affect, emotional prosody and theory of mind (ToM).

3.3.2.1 Facial affect

People with MDD have demonstrated deficits in facial affect, or misreading the facial emotion expression of others, in both tests of discrimination accuracy and in negative response bias. People with MDD, when compared to matched healthy controls, have difficulty in identifying sad faces but not in identifying happy or angry faces (Gur et al., 1992; Wright et al., 2009). Leppänen, Milders, Bell, Terriere and Hietanen (2004) found slightly different results, noting that people with MDD and healthy control participants both correctly identified happy and sad faces, but made more mistakes with neutral faces. This particular deficit was still evident when a person was in remission, which suggests a possible trait deficit. Studies have also demonstrated a negative response bias in people with MDD, who are more likely to identify happy faces as being neutral (Surguladze et al., 2004) or neutral faces as being sad (Gollan, Pane,

McCloskey, & Coccaro, 2008; Gur et al., 1992; Hale, 1998). However, deficits in facial affect may be mediated by slowed processing, impaired concentration and memory, all of which correlate with facial affect perception difficulties (Csukly et al., 2011). Some studies have shown that these deficits disappeared with a longer viewing period (Csukly et al., 2011; Surguladze et al., 2004) but that depression groups showed an increased reaction time when looking at sad faces (Gollan et al., 2008). The level of depression severity may also play a role in this effect, as participants with a severe level of depression severity reported an increased difficulty in differentiating between neutral and sad faces (Hale, 1998; van Marle, Hermans, Qin, & Fernández, 2009) and also rated faces as less aroused (Weniger, Lange, Rüther, & Irle, 2004). The role of depression severity in facial affect deficits suggest that facial affect may be a state deficit. The one exception as mentioned above was Leppänen et al. (2004), who found that deficits in facial affect were still present in remission, which suggested the presence of a trait deficit.

Deficits in facial affect recognition are also a predictor of future depressive episodes. In a study featuring male and female middle-aged psychiatric outpatients with depression, Hale (1998) found that judging ambiguous faces as negative (negative bias) was a predictor of future depressive episodes. Geerts and Bouhuys (1998) studied depression inpatients who otherwise had similar characteristics to Hale's participants and found that perceiving a greater amount of negative affect, such as fear, disgust, rejection and sadness, predicted longer depressive episodes. Bouhuys et al. (1999) found that in participants in remission (age ranging from 18 to 77), perceiving greater levels of negative facial affect predicted a greater risk of relapse. In each of these studies, whether they involved outpatients, inpatients or participants in remission, increased negative bias predicted either future or longer depressive episodes. The

involvement of negative bias in predicting and maintaining depression is consistent with Beck's CT (Beck, 1991).

3.3.2.2 Prosody

Deficits in prosody (the rhythm, stress and intonation of speech) have been found in people with MDD. Uekermann, Abdel-Hamid, Lehmkämper, Vollmoeller and Daum (2008) showed that an MDD group had deficits in both matching affective prosody to facial expressions and matching facial expressions to affective prosody, when compared to a matched healthy control group. Interestingly, the significant affect categories were happiness, anger, neutrality and fear, while sadness was the only non-significant category. Uekermann, Abdel-Hamid et al. suggested that sadness was not significant, owing to a negative bias towards sadness resulting in selective or focused attention on sad stimuli. In addition, deficits in affective prosody were significantly correlated to other areas of cognition, including inhibition, set-shifting and working memory, which suggested that EF deficits might contribute to impairments in affective prosody. In a study measuring the judgement of emotions in both verbal (semantic) and non-verbal (prosody) conditions, Schlipf et al. (2013) found that the MDD group performed significantly worse than a healthy control group in judging positive emotional word content (semantic) and positive emotional prosody statements, but not negative emotional word content or prosody. Deficits in the word meaning (semantic) correlated with depression severity, while deficits in prosody did not, which suggested that deficits in prosody might be a trait deficit. Non-significant results in negative content in both of these studies suggested that deficits in prosody were characterised by impairments of positive or neutral emotional processing, rather than by negative emotional processing, suggesting that negative bias may not be a factor in deficits of prosody.

One study that did find prosodic deficits in negative content was Emerson, Harrison and Everhart (1999), who compared boys aged 9 to 11 years with MDD to a healthy control group. Emerson et al. found that the depression group's ability to identify prosody was significantly lower in each prosodic category: happy, angry, sad and neutral. Little research has been conducted to determine whether deficits in prosody have an effect on depression maintenance. However, it has been suggested that negative auditory perception may hamper social interaction and thereby account for an increased risk of depression reoccurrence (Bos et al., 2005).

Prosodic studies that involve speaking in sarcastic or ironic tones have not been examined specifically in depression studies. In the above studies, statements were read out in happy, neutral, angry, fearful, surprised and sad tones. The use of irony or sarcasm examines whether the participant understands the meaning of a statement, rather than whether the participant demonstrates negative bias. Prosodic studies utilising sarcasm and irony have been undertaken with non-depressive medical conditions such as Parkinson's disorder (Anderson, Simpson, Channon, Samuel, & Brown, 2013; Pell et al., 2014), amnesic mild cognitive impairment (Gaudreau et al., 2013), Huntington's disease (Larsen, Vinther-Jensen, Gade, Nielsen, & Vogel, 2016) and temporal lobe epilepsy (Hennion et al., 2015). In general, prosodic deficits associated with sarcasm or irony have, for the most part, been associated with other cognitive deficits in the other non-depressive medical conditions. Anderson et al. (2013) found that only Parkinson's disorder patients who had general cognitive deficits also demonstrated difficulties in interpreting sarcastic remarks. This finding was similar to a study of patients with amnesic mild cognitive impairment, whose deficits in identifying ironic statements correlated with deficits in EF tasks (Gaudreau et al., 2013). These results suggest that difficulties in prosody involving sarcasm or irony may occur in the context of more

general cognitive deficits. The exception is Huntington's disease, in which difficulties in prosody have been found to increase as the disorder progressed (Larsen et al., 2016). For non-depression studies that use statements spoken in sarcastic or ironic tones, deficits in prosody appear, in general, to be associated with other cognitive deficits. However, the lack of research in this area of depression studies makes it an area of interest, given the results of the ToM studies described in the next section.

3.3.2.3 Theory of mind (ToM)

Deficits in social cognition have been evident in situations not related to negative bias, when the inability to understand the meaning of a statement or situation has been demonstrated through humour comprehension and ToM tasks. Uekermann, Channon et al. (2008) found that in a humour task, people with depression selected fewer correct funny punchlines, more slapstick endings and more logical endings than the control group. Misinterpretation of the meaning behind the humour could have been due to other cognitive deficits, as the depression group also performed worse in attention, inhibition, verbal fluency and working memory tasks. The Uekermann, Channon et al. study also included a ToM task. ToM, which includes first- and second-order tasks, refers to the ability to infer others' mental states and predict their behaviour (Bruine 2003, as cited in Inoue, Tonooka, Yamada, & Kanba, 2004). A first-order ToM task involves attempting to infer the mental state of another person, while a second-order ToM task involves inferring one person's mental state about another person's mental state (Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008). In the ToM task, the depression group performed significantly worse than the control group, while there was no significant difference in general comprehension tasks.

In another ToM study, Inoue, Tonooka et al. (2004) found that depression patients performed significantly worse on the second-order false belief question,

although no differences were found in the first-order false belief question, reality question or the tactile question. In a later study, Inoue, Yamada and Kanba (2006) found that patients in remission from depression not only performed poorly in ToM tasks but that the poor ToM performance was linked to a high risk of depression reoccurrence. This last study suggested the possible link between deficits in ToM and depression reoccurrence, and since the participants were in remission, that these ToM deficits could represent a trait deficit.

These studies have demonstrated the existence of cognitive deficits in depression groups, which are based on an inability to understand the meaning of a statement or situation, rather than in conjunction with negative bias. As these deficits may also be related to depression relapse, as tasks involving understanding a statement or situation correctly are relevant to recurrent depression studies.

3.4 Summary

This chapter has examined whether deficits in cognition may play a role in depression reoccurrence. Deficits in the social cognition domain of facial affect have been identified when comparing depression to healthy control groups (Leppänen et al., 2004; Wright et al., 2009). Further, facial affect has been shown to be significant factor in depression reoccurrence, possibly owing to negative bias (Geerts & Bouhuys, 1998; Hale, 1998). Similarly, deficits in prosody have been shown in depression groups compared to healthy control groups (Schlipf et al., 2013; Uekermann, Abdel-Hamid et al., 2008). Notably though, prosody has not been implicated as a significant factor in depression reoccurrence (Bos et al., 2005). However, prosody statements in situations when the meaning is ambiguous, such as when sarcasm or irony is employed, are of particular interest, owing to significant findings in non-depressive disorders. Deficits in other forms of social cognition, such as ToM, where the goal is to understand the

meaning of a statement or situation, have also significantly predicated depression reoccurrence (Inoue, Tonooka et al., 2004; Uekermann, Channon et al., 2008).

Chapter 4: Intelligence and Executive Function

Chapters 1 to 3 have provided a theoretical and empirical review for this thesis, spanning cognitive deficits of young adults with depression/anxiety, effects of comorbid depression and number of depression episodes. This chapter reviews the literature regarding intelligence and EF, to provide a basis for investigating the cognitive differences between high school students who studied advanced mathematics or physics compared to those who studied ordinary mathematics. The aim of gathering this information is to begin a discussion regarding an 'education pathway' for cognitive skills that relate to depression. This chapter examines the intelligence measures used in previous cognition studies and the relationship between cognition and intelligence.

4.1 A Measure of Intelligence

Research has suggested that studies of cognition should include a measure of intelligence, to ensure that level of intelligence is not a confounding variable (Castaneda, Tuulio-Henriksson et al., 2008; Snyder, 2013). Table 4.1 provides details of the intelligence measures used in the cognition studies referenced in Chapter 1. The majority of these intelligence measures involve vocabulary or word recognition tests. Tests such as the National Adult Reading Test (NART) and Wechsler Test of Adult Reading (WTAR) (Whitney, Shepard, Mariner, Mossbarger, & Herman, 2010) are not time consuming and correlate with comprehensive intelligence measures such as the Wechsler Adult Intelligence Scale (WAIS) (The Psychology Corporation 2001, as cited in Whitney et al., 2010). However, as EF is the main cognitive area of interest and there is a strong relationship between EF skills and mathematical achievement (Cragg & Gilmore, 2014), a form of numerical intelligence may also be required as a measure.

Table 4.1

Intelligence Measures Used in Depression/cognition Studies

Author	Intelligence measures	Other measures
Quinn et al. (this current study)	WTAR	School subject grades
Bearden et al. (2006)	WTAR, TONI-3	Education years, parental education
Castaneda, Suvisaari et al. (2008)	WAIS-R: Vocabulary, Digit Symbol; WAIS-III letter number sequencing	Education level
Channon (1996)	Nil	Vocabulary pre-test
Channon & Green (1999)	Nil	Nil
Fitzgerald et al. (2008)	Nil	Education years
Fossati et al. (1999)	Binois-Pichot Vocabulary Subtest	Nil
Grant et al. (2001)	Ammons Verbal IQ score	Education
Harvey et al. (2004)	Verbal IQ	Education years
Hill et al. (2004)	WRAT-R	Education years
Horan et al. (1997)	WRAT-R	Nil
Mannie, Barnes et al. (2009)	NART	Nil
Mannie, Harmer et al. (2009)	NART	Nil
Merriam et al. (1999)	IQ	Education years
Neu et al. (2005)	Nil	Education years
Paradiso et al. (1997)	Nil	Education level
Porter et al. (2003)	NART	Education years
Preiss et al. (2009)	Nil	12-point education scale
Purcell et al. (1997)	NART	Education years
Rose & Ebmeier (2006)	NART	Nil
Smith et al. (2006)	NART, WAIS-R	Nil
Stordal et al. (2004)	WAIS-R	Education years
Uekermann, Channon et al. (2008)	WAIS: similarities, picture completion	Education years
Wang et al. (2006)	Nil	Nil

NART = National Adult Reading Test; TONI-3 = Test of Non-verbal Intelligence-3; WAIS-R = Wechsler Adult Intelligence Scale – Revised; WRAT-R = Wide-Range Achievement Test – Revised word recognition subtest; WTAR = Wechsler Test of Adult Reading.

4.2 How Cognition Affects Intelligence

EF is pivotal to the formation of both mathematical and literacy skills in preschool to adolescent-aged children. Both Steele, Karmiloff-Smith, Cornish and Scerif (2012) and Welsh, Nix, Blair, Bierman and Nelson (2010) demonstrated that skills in EF in preschool-aged children predicted mathematical and literacy skills, while Thorell (2007) demonstrated that for children with attention deficit/hyperactivity disorder, deficits in both mathematics and literacy are mediated by deficits in EF. Willoughby, Blair, Wirth and Greenberg (2012) found with 5-year-old children that although EF correlated significantly with standardised tests of academic performance in both numeracy and literacy (mathematics r=.62, applied problems r=.63, quantitative concepts r=.62, letter-word r=.39 and phonological r=.56). For school Grades 1 to 5, Geary (2011) found that working memory was more important to mathematical ability than it was to reading achievement. Geary found that increased performance in the working memory component visuo-spatial sketchpad resulted in an increase in mathematical achievement across Grades 1 to 5. In addition, for the central executive aspect of working memory, increased ability resulted in increased mathematical scores at Grade 5, although not initially at Grade 1. In contrast, higher scores on the working memory system's phonological loop and central executive contributed to high reading achievement in Grade 1, but the importance of the central executive then declined linearly as the grades increased. For older students (11 to 14 years), both Nunes, Bryant, Barros and Sylva (2012) and St Clair-Thompson and Gathercole (2006) found that working memory predicted ability in literacy and numeracy skills equally. In summary, high performance in EF results in improved scores in both mathematics and literacy, although several studies assert that EF is more important for mathematics than for literacy.

4.3 How Intelligence Affects Cognition

Studies investigating whether the intelligence of children and adolescents affects their cognition scores have found that years of education and intelligence measures both correlate with improved cognition performance. In a meta-analysis of studies featuring level of education, adults with more than 12 years of education performed better in perseverative errors and categories completed in the WCST than those with less than 12 years of education (Rhodes, 2004). In addition, a study of children aged 9 to 14 years who were deemed gifted (IQ > 130) or above-average intelligence (114–129) and completed the WCST found that intelligence accounted for 17–18% of the variance in perseverative errors, non-perseverative errors and total errors (Arffa, Lovell, Podell, & Goldberg, 1998). The performance for both gifted and above-average students was significantly above the averages reported in the WCST manuals (Arffa et al., 1998). In a separate study comparing the performance in the WCST of children with normal (90–114), above-average (115–129) and gifted IQ (>130), it was found that gifted children performed significantly better than the average children in the perseverative and non-perseverative errors (Arffa, 2007). In an inhibition task (the Stroop Test), the gifted children performed significantly better than both the above-average and normal group, while for verbal learning and memory (Rey Auditory Verbal Learning Test), the above-average group was superior to the normal group (Arffa, 2007). When comparing the performance of children aged 13 to 16 years in the WCST and the Wechsler Intelligence Scale for Children – Revised, there were significant negative correlations between perseverative errors on the WCST and verbal IQ ($p<.01$) and full-scale IQ (FSIQ: $p<.05$), as well as on the subtests Arithmetic ($p<.01$), Block Design ($p<.01$), Information, and Similarities ($p<.05$) (Ardila, Pineda, & Rosselli, 2000).

However, not all studies showed a relationship between IQ and performance on the WCST. Welsh, Pennington and Groisser (1991) found that for participants aged 7 through to adult, perseverative errors did not correlate with verbal, quantitative, non-verbal, or mean IQ. The majority of these studies demonstrated that intelligence is a significant factor in EF performance.

4.4 Intelligence and Cognitive Performance

For the studies shown in Table 4.1, there was little analysis by the researchers regarding intelligence measures and performance on cognitive tests, as most intelligence measures were used to ensure that the comparison groups were matched. In one study, Purcell et al. (1997) found that education and NART-estimated IQ scores were not associated with cognitive performance in middle-aged adult depression patients. However, Merriam et al. (1999) found in a study involving middle-aged adults with depression, schizophrenia and healthy control participants that intelligence was significantly related to performance on the WCST. Merriam et al. listed only IQ, without noting what type of IQ test was undertaken. It is also unknown whether the relationship existed for individual groups or only for the reported total sample.

The following two studies were not included in Table 4.1 because aspects of the studies were not relevant to this current study. However, they do provide analysis with intelligence measures that have numerical components. Ilonen et al. (2000) tested people with psychotic depression, non-psychotic depression and healthy control participants and found that FSIQ and subtest digit symbol of the WAIS-R were significantly correlated with perseverative errors in the WCST, while only FSIQ correlated significantly with non-perseverative errors. Koren et al. (1998) conducted a study involving schizophrenia patients and control participants and found that for the control participants, the WAIS-R subtests of vocabulary, block design and academic

achievement correlated with perseverative errors in the WCST. These two studies suggest that when an intelligence test includes mathematical or problem-solving measures such as block design (part of the WAIS subtest on perceptual reasoning) or the entire WAIS (which includes working memory and perceptual reasoning subtests), intelligence measures correlate with cognitive performance. Too few studies have included analysis regarding cognitive ability and intelligence to be able to conclude whether intelligence has significantly affected cognition scores. However, there are limited studies with significant correlations, which would at least encourage future researchers to include this form of comparison to ensure that level of intelligence is not a confounding variable in cognition studies.

4.5 Summary

This chapter has identified that most existing cognition studies have employed literary-based intelligence tests, mostly to ensure that comparison groups were matched. These intelligences tests could also have been used to identify outliers, although this has not been noted in the studies. Previous studies have demonstrated a significant link between EF ability and literary skills (Nunes et al., 2012; Steele et al., 2012; Welsh et al., 2010). However, there may be some debate regarding whether this relationship exists beyond the earliest years of formal education (Geary, 2011; Willoughby et al., 2012). There is a more robust relationship between EF and numeracy (Geary, 2011; Nunes et al., 2012; St Clair-Thompson & Gathercole, 2006; Willoughby et al., 2012). Therefore, some form of mathematical intelligence measure may be required to ensure that a study is not confounded by smaller cohorts with poor numeracy skills within the study. While this chapter has reviewed previous literature investigating EF and intelligence, Chapter 5 takes a biological approach, investigating the relationship between cognition and GABA a probable biological marker of depression.

Chapter 5: Plasma GABA and Cognition

This chapter examines the neurotransmitter GABA and its relationship with depression, as well as the common links between EF and GABA concentration and the notion of GABA concentration as an indicator of glial abnormality in the PFC.

5.1 Gamma-aminobutyric Acid (GABA)

Low levels of GABA have been identified as a probable biological marker or indicator of vulnerability to depression (Petty, Kramer, Fulton, Davis, & Rush, 1995; Sanacora, Gueorguieva et al., 2004). GABA is the most abundant neurotransmitter in the brain and is a primary mediator of inhibitory transmission in the mammalian central nervous system (Brambilla, Perez, Barale, Schettini, & Soares, 2003). GABA binds to two classes of receptors, GABA receptor A ($GABA_A$) and GABA receptor B ($GABA_B$) (Pehrson & Sanchez, 2015). $GABA_A$ receptors inhibit the neuron firing rate through ligand-activated ion channels, which impacts brain excitability, while $GABA_B$ receptors inhibit postsynaptic neurotransmission through long-term protein-coupled reduction in potentiation (Kalueff & Nutt, 2007). Positive modulators of $GABA_A$ can have antidepressant effects, while negative modulators of $GABA_A$ often produce depressive effects (Kalueff & Nutt, 2007). While the exact mechanisms involved in the relationship between GABA concentration and MDD are beyond the scope of this thesis, the research by Pehrson and Sanchez (2015) provides further information.

5.2 Depression and GABA Concentration

Several studies have demonstrated a relationship between depression and GABA concentration levels in both the blood and the brain. Petty, Kramer, Gullion and Rush (1992) found that male adult MDD patients had plasma GABA concentration levels lower than the healthy controls: 40% of depression patients had levels lower than 100 pmol/ml, compared to only 6% for healthy controls. (Note that Petty et al. chose

100 pmol/ml as a suitable comparison level because approximately 5% of healthy control participants were below this level.) Petty and Sherman (1984) compared plasma GABA levels between healthy control participants and participants with alcoholism, bipolar affective disorder, schizophrenia, or MDD and found that participants with MDD or alcoholism had significantly lower plasma GABA levels compared to healthy controls. Additionally, Kucukibrahimoglu et al. (2009) found that young to middle-aged female MDD inpatients had lower plasma GABA levels than matched healthy control participants. Studies have also found that brain GABA concentration, specifically in the OFC (Kosel et al., 2004; Kugaya et al., 2003; Sanacora, Mason, Rothman, Behar et al., 1999) and the occipital cortex (Sanacora, Gueorguieva et al., 2004), is lower in depressed patients than in healthy control participants. While previous literature has demonstrated a relationship between depression and GABA concentration in both the blood and the brain, the mechanisms involved in the correlation between blood and brain GABA concentrations are unknown.

Plasma GABA is often used in studies as an indicator of GABA concentration of the brain because of ease of access to blood; however, the relationship between the two is unknown. Although most of the body's GABA (95–98%) resides in the central nervous system, it is suggested that plasma GABA is relevant to brain function (Petty et al., 1999). GABA is synthesised in the brain and animal studies have shown that when manipulations of cerebral spinal fluid GABA levels occur, they are followed by similar changes in plasma GABA levels (Ferkany et al. 1978, as cited in Petty et al., 1995). Kuriyama and Sze (1971) attempted to explore the relationship between plasma and brain GABA through animal studies using a radioactive tracer. They found that GABA injected into the blood could not be detected in the brain, whereas when GABA was injected in the brain, radioactivity was detected in the liver and the blood; however, it

was in the form of other metabolites, not GABA. This led to the conclusion that the blood–brain barrier was impermeable to plasma and cerebral GABA (Kuriyama & Sze, 1971). While there appears to be a relationship between plasma and cerebral GABA concentration levels, either in corresponding changes or in the relationship to depression, the actual mechanism of the relationship between plasma GABA and brain GABA concentration is unknown.

Observed differences in plasma (or brain) GABA levels may exist in subtypes of depression such as primary depression or melancholic depression. Petty et al. (1987) showed that participants with primary depression had significantly lower plasma GABA levels than participants with secondary depression, while secondary depression levels were not significantly different from those of healthy controls. Using magnetic resonance spectroscopy to measure GABA levels in the brain, Sanacora, Gueorguieva et al. (2004) found that people with the subtype melancholic depression had lower GABA levels than people with depression without the subtype. This difference was most profound when including melancholic participants who also had psychotic features. These results concurred with a study by Petty et al. (2002, as cited in Sanacora, Gueorguieva et al., 2004), who found the lowest levels of plasma GABA in participants with melancholic depression. Identifying why these differences in GABA concentration exist in depression subtypes may offer an explanation to the role of GABA in depression.

Low plasma GABA concentration may be indicative of a biological trait deficit, owing to its independent relationship with depression severity. Concentrations of plasma GABA have been found to be independent of disorder severity and to be stable over a four-year period, including in those participants who had recovered from depression (Petty et al., 1995; Petty, Steinberg, Kramer, Fulton, & Moeller, 1993).

Additionally, differences in disorder severity have been found to be non-significant when comparing high and low plasma GABA concentrations groups (Petty et al., 1992). Measures of GABA concentration in the brain have been found to not correlate with disorder severity (Sanacora, Gueorguieva et al., 2004). However, not all studies have shown a non-significant relationship between GABA concentration and depression severity. Kucukibrahimoglu et al. (2009) found that when they classified female inpatients as mild (n = 13) and moderate (n = 17), the moderate-severity group had significantly lower plasma GABA concentration than the mild-severity group. The above studies (with the exception of Kucukibrahimoglu et al.) demonstrated an independent relationship between plasma GABA and disorder severity, suggesting that GABA concentration could be a trait deficit.

Changes in GABA concentration due to medical treatment may be dependent on the type of treatment. GABA concentration was found to increase in the occipital cortex after treatment with ECT (Sanacora, Mason, Rothman, Hyder et al., 2003), while no change was detected after cognitive behavioural therapy (Sanacora, Fenton et al., 2006). Type of antidepressant medication may also be a factor, with increases in GABA concentration after the administration of selective serotonin reuptake inhibitors (SSRIs) (Kucukibrahimoglu et al., 2009; Sanacora, Mason, Rothman, & Krystal, 2002), yet no significant differences after the administration of desipramine, a tricyclic antidepressant (Petty, Steinberg et al., 1993). In studies with schizophrenia patients treated with antipsychotics such as risperidone (Cai et al., 2010; Goto et al., 2010) and bipolar patients treated with an anticonvulsant lamotrigine (Shiah, Yatham, Gau, & Baker, 2003), no significant changes in GABA concentration were recorded from pre to post treatment. Thus, changes in GABA concentration due to medical treatments seem to be dependent on the type of treatment, with both ECT and SSRIs resulting in increases in

GABA concentration, while no significant differences were seen following a range of other treatments.

5.3 Executive Function (EF) and GABA Concentration

No depression studies have investigated whether there is a relationship between EF and GABA concentration. A relationship may exist, as the dlPFC and the OFC play a role in both deficits in EF and low GABA concentration in depression studies. As reported in Section 1.5, Rajkowska, Miguel-Hidalgo et al. (1999) showed abnormalities in the brain tissue (in the dlPFC and OFC) of people with depression compared to matched healthy control tissue, including a decrease in neuronal size and glial density. Rajkowska, Miguel-Hidalgo et al. (1999) suggested that a decrease in glial density results in altered cell metabolism, which may explain deficits in EF, owing to their locality around the dlPFC and OFC. Brain activation studies have shown increased activation for the dlPFC for the EF domains of inhibition, updating, planning, working memory, and the shifting set aspect of set-shifting (Buckley et al., 2009; Kaller et al., 2010; Killgore et al., 2007; Owen et al., 2005). Similarly, the OFC has been shown to be central to the perseveration aspect of set-shifting (Dias et al., 1996a).

Reduction in glial density in the dlPFC and OFC may also be responsible for decreases in GABA concentration. Glial cells affect several processes, including the uptake of synapticly released glutamate (a precursor to GABA) (Öngür et al., 1998). Depression studies have shown significantly lower concentrations of the GABA interneuron, calbindin-IR, in the dlPFC and trending lower in the OFC (Rajkowska, O'Dwyer, Teleki, Stockmeier, & Miguel-Hidalgo, 2007), and a reduction of glutamic acid decarboxylase in the dlPFC (Gos et al., 2009; Karolewicz et al., 2010). However, the links between GABA and the PFC should be treated with caution. Only a single interneuron study has linked GABA to the dlPFC and OFC, and other glutamic acid

decarboxylase /dlPFC studies have shown non-significant results (Pehrson & Sanchez, 2015). While both EF and GABA concentration are associated with the dlPFC and OFC, there is no definitive evidence of a link between the two. However, deficits in both may have the same biological basis, with decrease in glial density in the dlPFC and OFC. Low GABA concentration could simply be an indicator of decrease in glial density in the dlPFC and OFC, without directly affecting EF.

5.4 Summary

GABA is a common neurotransmitter and probable biological marker for depression (Brambilla et al., 2003). Several studies have shown a relationship between low GABA concentration in both plasma and the brain for people with depression compared to control participants (Kosel et al., 2004; Kucukibrahimoglu et al., 2009; Petty et al., 1992; Sanacora, Gueorguieva et al., 2004). While low GABA concentration is evident in both the plasma and brain GABA of people with depression, the mechanism of this relationship is unknown (Petty et al., 1999). The levels of GABA concentration appear to be stable, except for treatments involving ECT and the antidepressant SSRI (Sanacora, Mason, Rothman & Krystal, 2002). Currently, no studies have investigated the relationship between EF and GABA concentration, although it is possible that deficits in EF and low GABA concentration share a common biological basis; namely, decrease in glial density in the PFC. This current study suggests that GABA's role as a possible biomarker for depression could be an indicator of decrease in glial density in the PFC, rather than GABA having any mechanical role in EF deficits.

Chapters 6 to 10 report and discuss specific studies that correspond to and extend the literature reviewed in Chapters 1 to 5.

Chapter 6: Cognitive Deficits in Young Adults with Depression or Anxiety Disorder Only (Study 1)

6.1 Study Context

The current study had three aims. The first was to explore cognitive deficits in young adults with depression. Specifically, it was hypothesised that young adults with depression would show significant deficits in EF, including set-shifting, inhibition, updating, planning and verbal learning and memory, compared to healthy matched control participants. While set-shifting has been shown to be the most prominent of the potential cognitive deficits (Grant et al., 2001), other forms of EF are also anticipated to show significant deficits, as factors such as sample sizes may have played a role in the non-significant results in other studies (Fossati et al., 1999; Hill et al., 2004). The second aim was to test the hypothesis that young adults with anxiety disorder only would show significant deficits in verbal learning and memory compared to healthy matched control participants. No other forms of EF were expected to show significant differences. The third aim was to explore cognitive differences between early-onset and non-early-onset depression. As this element of this study was exploratory in nature and it was the first study to examine early-onset and non-early-onset depression and cognition, no data-driven hypotheses were specified.

6.2 Method

6.2.1 Participants

The study sample consisted primarily of undergraduate university students from first- and second-year psychology classes at James Cook University, Townsville, Australia. As the sample was composed of undergraduate students and not hospital inpatients or outpatients, it was classified as subclinical. The participants consisted

mostly of psychology, social work and exercise science students. The remaining participants were recruited through advertisements at undergraduate lectures, posters on noticeboards, or via snowball recruitment. Prospective participants were informed that the study required people who were experiencing or who had experienced a form of anxiety disorder or depressive symptoms. Participants were told they did not need to have been diagnosed by a medical professional to take part in the study. A healthy control group was also recruited, consisting of young adults who had not experienced depressive or anxiety symptoms. The only other eligibility requirement was that the participants had to be between 17 and 35 years of age. Participants were omitted from the study if they received a classification for post-traumatic stress disorder according to the classification from the Mini International Neuropsychiatric Interview English version 5.0.0 Plus (MINI PLUS).

The demographic information of the participants is shown in Table 6.1. The healthy control participants were required not to meet any of criteria for disorders outlined by the MINI PLUS. In addition, they had to have severity scores of less than 8 on the Structured Interview Guide for the Hamilton Depression and Anxiety Scales (SIGH-AD) and less than 15 for the Centre for Epidemiologic Studies Depression Scale (CES-D). The anxiety disorder only group had to receive no classification from the MINI PLUS for MDE or dysthymia but at least one classification for PD, social phobia, specific phobia, OCD, anorexia nervosa, bulimia nervosa, GAD, body dysmorphic disorder, pain disorder or premenstrual dysphoric disorder. To be classified in the MDE group, the participant had to have a classification in the MINI PLUS of an MDE.

Table 6.1

Demographic Characteristics of Participants

Sociodemographic & clinical variables	Healthy control n = 34		Anxiety disorder only n = 26		MDE group n = 119	
	M	*SD*	*M*	*SD*	*M*	*SD*
Gender % female	58.8		76.9		77.3	
Age years	18.7	1.82	19.7	2.54	20.1	3.98
WTAR	39.0	5.66	39.3	5.58	39.19	5.55
Severity measures						
Depression severity	0.26	.79	3.46	4.14	7.97	7.17
Anxiety severity	0.74	1.21	6.12	5.65	10.73	8.91
CES-D	6.35	4.06	14.6	8.95	19.21	12.3
Age of depression onset	n/a	n/a	n/a	n/a	15.4	3.84
Number of depressive episodes	n/a	n/a	n/a	n/a	5.36	4.70

Table 6.2 presents the demographic characteristics for the young adults with early-onset and non-early-onset depression. The sample consisted of 118 young adults, including an early-onset depression group (n=67) and a non-early-onset depression group (n=51). (Note that one participant from the 119 in the MDE group in Table 6.1 was omitted, as age of disorder onset data were missing.) If a young adult's first depressive episode occurred at age 15 or earlier, they were classified as early onset. Young adults whose first MDE occurred at age 16 years or over were classified as non-early-onset.

Table 6.2

Demographic Characteristics for Early-onset and Non-early-onset Depression

Sociodemographic and clinical variables	Early-onset depression n = 67		Non-early-onset depression n = 51	
	M	*SD*	*M*	*SD*
Gender % female	77.6		76.5	
Age	20.3	3.43	22.3	4.39
WTAR	39.7	5.67	38.6	5.44
Severity measure				
Depression severity	7.45	6.85	8.75	7.62
Anxiety severity	10.1	9.04	11.7	8.79
CES-D	18.7	12.8	19.9	11.9
Number of depressive episodes	6.41	5.08	4.06	3.74
Age of depression onset	12.9	2.08	18.7	3.06

6.2.2 Materials.

6.2.2.1 Neuropsychological assessment.

6.2.2.1.1 Card Sort

The Card Sort test was based on the Wisconsin Card Sorting Test (Berg, 1948) and part of the Colorado Assessment Tests (CATS) test battery. The Card Sort test measured set-shifting, cognitive flexibility and problem-solving abilities (Baune, Czira, Smith, Mitchell, & Sinnamon, 2012). Four stimulus cards, similar to playing cards, appeared at the top of the screen, distinguished by colour, type of shape and number of shapes. For example, Card 1 had one red diamond; Card 2 had two green spades, Card 3 had three yellow clubs and Card 4 had four blue hearts. Below the four stimulus cards there was a single card called the key card, which participants had to match to one of the stimulus cards. Participants were informed whether their match was correct. A correct match was determined by the matching pattern: colour, shape or number. After 10 correct selections, the pattern changed, for example, from colour to shape. A total of six categories (two each of colour, shape and number) were needed to complete the task, or

the task would stop after 120 matching attempts. Participants were not warned of the pattern change and had to discover the new pattern themselves, using the feedback provided.

The items being measured were perseverative errors, non-perseverative errors and sorting categories completed (a total of six). Perseverative errors occurred when the matching pattern changed but the participant continued to use the previous matching pattern. For example, if the matching pattern changed from colour to shape, but the participant continued to match using colour, then a perseverative error occurred. Non-perseverative errors included both 'failure to maintain set' and 'efficient errors'. Failure to maintain set refers to errors made through lack of concentration or interference; for example, a participant is matching correctly using colour and then makes an error by not matching by colour when the pattern has not changed. Efficient errors occurred when errors were made when the matching pattern changed and the participant tried to discover the new pattern (shifting set). The successful completion of a card-sorting test requires the ability to think abstractly, selectively attend to a particular perceptual dimension, and shift cognitive set (Merriam et al., 1999).

6.2.2.1.2 Tower of London (ToL)

The computerised CATS version of the ToL is a variation of the Tower of Hanoi (Shallice, 1982). The ToL tests spatial problem solving, spatial memory, and planning ability (Carder, Handley, & Perfect, 2004) and is used to study frontal lobe dysfunctions (Berg & Byrd, 2002). Coloured balls are placed on three, four or five vertical pegs. Participants are required to rearrange the balls from their original position into a different specific configuration, which is shown on the screen, with each vertical peg able to hold only a limited number of coloured balls. The number of times a coloured ball is moved to achieve the new configuration that is greater than the optimum amount

is measured; in essence, excess moves. In total, the participant undergoes 21 trials, seven for each of three, four or five pegs.

6.2.2.1.3 N-back

The computerised CATS version of N-back was used to test updating. It consisted of three levels: 1-back, 2-back and 3-back. N-back requires monitoring, updating and manipulating remembered information (Owen et al., 2005). In this version, seven uppercase letters (A, E, I, J, N, O and T) were used, with one letter flashed on the screen every four seconds in a randomised order. In the 1-back trial, the participants had to determine whether the current letter was the same as the letter that had appeared 'one back' or previously and then press the corresponding 'yes' or 'no' key. Following the same idea for the 2-back and 3-back trials, the participants had to determine whether the current letter was the same as the letter two letters back and three back, respectively. The percentages of correct answers for 1-back, 2-back and 3-back were recorded.

6.2.2.1.4 Stroop Test

The Victoria Stroop Test (VST) (Troyer, Leach, & Strauss, 2006) was used to measure response inhibition. The VST is a brief, easily administered, psychometrically sound version of the Stroop Test (Troyer et al., 2006). The VST consisted of three levels, each containing a 5x10 matrix of coloured dots (Level 1), non-coloured words, words coloured as per the coloured dots in Level 1 (Level 2), or words coloured in an incongruous font colour (Level 3). The participant was required to name the colour of the dots or text as quickly as possible, reading from left to right. The time to complete each level can be calculated singularly but in addition, a Stroop total time is calculated using the Golden Method (Golden, 1978), in which Stroop total = Stroop Level 3 - (Stroop Level 1 + Stroop Level 2).

6.2.2.1.5 Verbal Recall

Verbal learning and memory was assessed using the CATs test of Verbal Recall, which is based on the Rey Auditory Verbal Learning Test (Rey, 1964). In the task, the instructor read a list of 15 words as they were flashed on a computer screen. The screen was visible to the instructor but not to the participant. The participants were then required to recall the 15 words verbally. There was no delay. After a 20-second pause, the process was repeated with the same words read out, but in a different order, for a total of five trials. The number of correctly recalled words for each trial and the total number of words recalled were recorded.

6.2.2.1.6 Social Cognition Tests

Social perception was assessed using three tasks: affect naming, prosody face matching and prosody pair matching, which were sourced from the *Advanced Clinical Solutions for WAIS-IV and WMS-IV* Social Cognition Stimulus Book. In affect naming, a series of photos of faces were examined by the participant and the expression on the face was matched to a list of feelings. In the prosody face-matching task, a photo of a face was selected to match the emotional content of a verbal statement that was played on the computer. In prosody pair matching, the emotional content of a verbal statement was first matched with a selection of photos of interacting pairs and then the meaning of the statement was determined.

6.2.2.2 Classification tests

6.2.2.2.1 Structured Interview Guide for the Hamilton Depression and Anxiety Scales (SIGH-AD)

The SIGH-AD is a combination of the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Hamilton, 1960) and the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) (Hamilton, 1959). SIGH-

AD measures depression and anxiety severity and consists of 31 questions: 17 measure depression severity and 14 measure anxiety severity. The output has two scores, one for depression severity and the other for anxiety severity. The experimenter read each question and sub-question to the participant. For example, Question 1 was, 'What's your mood been like this week?' Below the question were a series of sub-questions such as. 'Have you been feeling down or depressed?' and 'How are you feeling about the future?' Adjacent to the question and sub-questions was an indicator of what the question was measuring and a number scale with a worded description corresponding to each number. For the above question, the item to be measured was 'depressed mood (sadness, hopeless, helpless, worthless)'. Under the statement, the numbers 0–4 contained the following worded descriptions: (0) absent; (1) indicated only on questioning (occasional, mild depression); (2) spontaneously reported verbally (persistent, mild to moderate depression); (3) communicated non-verbally; i.e., facial expression, posture, voice, tendency to weep (persistent, moderate to severe depression); (4) virtually only those feeling states reported in spontaneous verbal and non-verbal communication (persistent, very severe depression, with extreme hopelessness or tearfulness). With the aid of the worded descriptions, the investigator chose a numbered answer to match the participant's answer (see Appendix A). These descriptions were taken from the Early Clinical Drug Evaluation Program Assessment Manual (Guy, 1976). SIGH-D was developed to improve the reliability of the Hamilton Depression Rating Scale. Reliability information for the SIGH-D can be found in Williams (1988). The Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) has been shown to have high test–retest reliability and interrater reliability and good validity when compared to the Beck Anxiety Inventory (Shear et al., 2001). In the current study, overall the SIGH-AD had good internal consistency with a Cronbach

alpha coefficient of .95. With the scale split into the two individual scales, SIGH-D and SIGH-A, the Cronbach alpha coefficient was .88 and .91 respectively.

6.2.2.2.2 Centre for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a depression severity self-report scale designed to measure depressive symptomology in the general population (Radloff, 1977). The CES-D consists of 20 questions that aim to elicit how the individual felt or behaved in the last week. For each question, the participant chooses between four periods such as (a) none of the time, (b) some of the time, (c) a moderate amount of time and (d) most of the time. Selection (a) scores 1, (b) scores 2, (c) scores 3 and (d) scores 4, except for questions 4, 8, 12 and 16, which are reversed scored. The total is then added. Scores below 15 indicate that the person is not suffering from depression. Scores 15 to 21 indicate the person may be suffering from mild to moderate depression and for scores 22 or higher, the person may be suffering from major depression (see Appendix B) (Radloff, 1977). CES-D has very high internal consistency and adequate test–retest repeatability, with a coefficient alpha of approximately 0.85 for the general population sample and 0.90 for a psychiatric (depression) patient sample (Radloff, 1977). The CES-D also correlates moderately with the Hamilton Clinician's Rating Scale at patient admission (.44 to .54) and higher after four weeks of treatment (.69 to .75) (Radloff, 1977). In the current study, the Cronbach alpha coefficient was .94.

6.2.2.2.3 Mini International Neuropsychiatric Interview English version 5.0.0 (MINI PLUS)

The MINI PLUS was used to obtain medical diagnostic material to categorise participants by medical disorder (Sheehan et al., 1998). The MINI PLUS is a short, structured diagnostic interview that takes approximately 15 to 20 minutes to administer (Pinninti, Madison, Musser, & Rissmiller, 2003) (see Appendix C). Structured

diagnostic paper tests are more advantageous than a clinical diagnosis, as clinical diagnoses have been found to be unreliable, owing to diagnostic disagreements between clinicians (Pinninti et al., 2003). Substantial inconsistencies between clinicians have been found to be due to the context surrounding the diagnosis and the type of professional (Kirk & Hsieh, 2004). An advantage of the MINI PLUS is that it is structured to allow interviewing by non-specialised interviewers (Lecrubier et al., 1997).

The MINI PLUS was chosen over the standard Mini International Neuropsychiatric Interview (MINI), as it included additional items including pain disorder and premenstrual dysmorphic disorder. To compare the validity and reliability of the MINI PLUS, the MINI was instead used. This was because first, there is limited validation data for the MINI PLUS specifically and second, the additional items in the MINI PLUS were not essential to this study. The MINI was validated through comparisons with known diagnostic tests, such as the Structured Clinical Interview for the DSM-III-R (SCID-P) and the Composite International Diagnostic Interview, and it scored highly in interrater and test–retest reliability studies. The MINI compared favourably to the SCID-P (Sheehan et al., 1997), the Composite International Diagnostic Interview (Lecrubier et al., 1997) and to diagnosis in a clinical setting (Pinninti et al., 2003). The MINI demonstrated excellent interrater reliability with all kappa values greater than .7 (Lecrubier et al., 1997; Sheehan et al., 1997). It showed very good test–retest reliability, with one study showing that 14 of 23 items had kappa values greater than .7 (Sheehan et al., 1997) and a second study showing kappa values ranging from .76 to .93 (Lecrubier et al., 1997).

6.2.2.2.4 Psychiatric and medical questionnaires

Psychiatric and medical questionnaires (Appendices D & E) were utilised to obtain further relevant information such as family history and past and present medical conditions. The questionnaires examined whether the participant had received any medical diagnosis, number of depressive episodes in the past year and information regarding hospitalisation and suicidality. It also recorded the participant's past medical diagnosis and whether family members had received a medical diagnosis of MDD, bipolar disorder or schizophrenia.

6.2.2.3 Intelligence measures

6.2.2.3.1 Wechsler Test of Adult Reading (WTAR)

The WTAR is a neuropsychological tool used to provide an estimate of premorbid intelligence. The WTAR contained a list of 50 short, irregular words that the participant was asked to read aloud. The instructor was given a pronunciation guide to aid in determining whether the participant pronounced the words correctly. The WTAR was developed with the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) and correlates significantly with the WAIS-III general intelligence measures: verbal IQ (r=.75); performance IQ (r=.59); and full-scale IQ (r=.73) (The Psychology Corporation 2001, as cited in Whitney et al., 2010). The WTAR performance results from The Psychology Corporation were in part agreed upon by Whitney et al. (2010), who demonstrated significant correlations between the WTAR and WAIS-III verbal IQ (r=.67), but only marginally significant correlations in other WAIS-III measures: logical memory (r=.31) and visual reproduction (r=.28). The WTAR correlated highly with the NART (r=.89) and demonstrated very good stability over a three-year period (test–retest reliability: $r > .9$) and high interrater reliability (Dykiert & Deary, 2013). There was also an interesting relationship between WTAR and the Test of Memory Malingering, which

indicates suboptimal effort. While participants who failed the Test of Memory Malingering did poorly on cognitive tests, scores on the WTAR by the same participants were unaffected. This suggests that the WTAR may be a robust measure of intelligence even if participants are using suboptimal effort (Whitney et al., 2010).

6.2.2.3.2 High school subject information

Individual high school subject grades for the final year of high school were collected. School subject results were scored from 5 to 1, with 5 being equivalent to an 'A' or a very high achievement. See Table 6.3 for all corresponding scores.

Table 6.3

Corresponding High School Subject Grade Scores

Grading score	Alphabetised system	Queensland High School system
5	A	Very high achievement
4	B	High achievement
3	C	Sound achievement
2	D	Low achievement
1	F	Very low achievement

The collection of subject selection grades began only half way through testing phase of this study; therefore, some information was gathered retrospectively through email, while other data points are missing. These data were added to the experimental design when the experimenter noticed a subgroup of participants who performed very poorly on cognition tests and subsequently the experimenter used high school grades as an additional measure of intelligence.

6.2.3 Procedure

Participants initially undertook the six cognitive tasks: Card Sort, ToL, Verbal Recall, N-back, Social Cognition and the Stroop Test in a counterbalanced order. The experimenter then interviewed the participants in a series of structured interviews. The

SIGH-AD (Williams, 2005), which measured depression and anxiety severity, was administered first, followed by the MINI PLUS (Sheehan et al., 1998), a clinical interview that determined disorder classification. Participants were then given the psychiatric and medical questionnaires to determine medical and psychological history, and the CES-D (Radloff, 1977), a second depression severity scale. Finally, education information in the form of high school exit scores and high school subject grades were gathered and the WTAR (Whitney et al., 2010) was administered.

6.3 Statistical Analysis

6.3.1 Exclusion including outliers

Thirteen participants who were classified according to the MINI PLUS with post-traumatic stress disorder were excluded from the study. Non-perseverative errors were examined for outliers. If a participant did not understand the change in rule for the Card Sort test, they would simply guess the answers for the 120 trials, resulting in a large number of non-perseverative errors as well as increased perseverative errors that were due to guessing, not perseveration. A box plot was used to identify outliers in non-perseverative errors, with the lowest outlier of 40 used as a cut-off point. Thirteen participants with 40 or greater non-perseverative errors were excluded from the study.

6.3.2 Statistical tests

6.3.2.1 Means, standard deviations and frequency (percentages)

Means and standard deviations of descriptive variables and cognition scores were calculated and reported. The exception was gender, which was presented as a percentage of female participants in that group. Other data were also entered in percentage form, such as the number of participants who had been hospitalised.

6.3.2.2 Chi-square test for independence

To calculate whether there were significant differences between percentages in groups, a chi-square test for independence was carried out. For each chi-square test for independence, a minimum expected cell frequency was observed. If the value for any cell was less than 5, then Fisher's exact probability test was used.

6.3.2.3 Chi-square test for independence 2 by 2

For any 2 by 2 tables, such as 'gender' (male and female) and 'non-recurrent/recurrent' (non-recurrent depression and recurrent depression), then Yates continuity correction was used, as it compensates for the overestimation of chi-squared value with a 2 by 2 table. The corresponding significance level (*p*-value) was recorded, along with the phi coefficient, a measure of effect size. To measure the magnitude of the phi coefficient, Cohen's criteria (Pallant, 2013) was used, which equated to .10 for a small effect, .30 for a medium effect and .50 for a large effect.

6.3.2.4 Chi-square test for independence 2 by 3

For a 2 by 3 table, such as 'gender' (male and female) and 'disorder type' (healthy control group, anxiety only and MDE group), the Pearson chi-square value was recorded, along with the corresponding significance level (*p*-value). For effect size for a 2 by 3 table, Cramer's V was reported, as it takes into account degrees of freedom (Pallant, 2013). The magnitude of Cramer's V effect sizes were .07 for a small effect, .21 for a medium effect and .35 for a large effect.

6.3.2.5 Independent-sample t-test

To compare a categorical variable with two levels, such as 'depression group' (e.g., non-recurrent depression, recurrent depression) with a continuous variable (e.g., cognition score), independent-sample t-tests were employed. A parametric test with no transformations were used for two reasons: first, group sizes were above 30, with only

one exception—'non-early-onset recurrent depression' (n=29)—and second, the statistical test used is robust. If Levene's test was significant ($p<.05$), indicating unequal variances, then a Welch-Satterwaithe adjustment to degrees of freedom was used. *T*-values, degrees of freedom and significance level (*p*-value) were reported. The effect size for independent-sample t-test was calculated using eta squared = $t^2/ (t^2 + (N1 + N2 - 2))$, where t equals the *t*-statistic (or *t*-value) and N1 is the number of participants in Group 1 and N2 is the number of participants in Group 2. The corresponding values for interpreting eta squared are: .01 = small effect, .06 = moderate effect and .14 = large effect (Cohen 1988, as cited in Pallant, 2013).

6.3.2.6 One-way analysis of variance (ANOVA)

To compare a categorical variable with three levels such as 'disorder type' (healthy control, anxiety disorder only and MDE group) and a continuous variable (e.g., cognition value), a one-way analysis of variance (ANOVA) was employed. A parametric test with no transformations was used for two reasons: first, group sizes were above 30, with only a few exceptions such as 'anxiety disorder only' (n=26) and second, the statistical test used to compare the groups was robust. When Levene's test for homogeneity of variances was violated, that is the significance value was under .05, then Welch's *F* was used. Welch's *F* was used rather than Brown-Forsythe's F, as according to Field (2013), Welch's *F* has better power. The effect size eta squared was calculated by dividing the 'sum of squares between groups' by the 'total sum of squares'. As above, the corresponding values for interpreting eta squared were: .01 = small effect, .06 = moderate effect and .14 = large effect (Cohen 1988, as cited in Pallant, 2013). For a measure of effect size when using Welch's *F*, an estimate of omega squared was calculated using: est. omega squared = df_{bet} (*F*-1)/ (df_{bet} (*F*-1) +*N*t).

6.3.2.7 Post hoc

To determine whether there were significant differences among the different groups, *post hoc* comparisons (rather than planned comparisons) were undertaken to test all pairwise comparisons in the dependent variable. While planned comparisons can be more suitable for testing specific comparisons, a *post hoc* analysis was better suited for this study. In order for planned comparisons to be used, comparisons must be supported by literature (Field, 2013). In this study, several comparisons, such as the cognitive differences between primary and secondary depression, had never been attempted before. While in the literature, comparisons of primary versus secondary depression have been made in other areas such as medication success and ECT treatment, this study was the first study to identify differences in cognition. Tukey's test was used for *post hoc* pairwise comparisons. However, if homogeneity of variance was violated and Welch's *F* was used, then the Games–Howell test was employed. Tukey's test is a conservative test that controls Type I errors well. For large sample sizes it has better power than Bonferroni's test (Field, 2013).

6.3.2.8 Mixed between-within subjects analysis of variance (MANOVA)

If the cognitive test had more than one level, such as the three N-back tests or the five Word Recall tests, then a mixed between-within subjects analysis of variance (MANOVA) was used. Usually, tests such as Word Recall are measured as individual trials, although they can also be measured as a whole (Bearden et al., 2006; Smith et al., 2006). In a repeated measures design, sphericity was measured using Mauchly's test. If $p < .05$, then sphericity was not met and the Greenhouse-Geisser estimate was used. If the Greenhouse-Geisser estimate was greater than .75, then Huynh-Feldt's estimate was reported (Field, 2013). With the N-back task, the difficulty level increased as the three trials progressed; the opposite occurred with the Word Recall task, in which the

difficulty decreased through Trials 1 to 5. Therefore, significant main effects 'within group' were expected but were not of interest to this study. The output of interest in the MANOVA was the comparison between groups, where the *F* value, degrees of freedom, significance level (*p*-value) and the effect size (partial eta squared) were recorded. Values for interpreting partial eta squared were: .01 = small effect, .06 = moderate effect and .14 = large effect (Cohen 1988, as cited in Pallant, 2013).

6.3.2.9 Correlation

To compare two continuous variables (e.g., disorder severity and cognition scores), the Pearson correlation coefficient (r) was used. For Pearson point correlation (r) value, the strength of the relationship was determined using the following guideline: small r=.10 to .29; medium r=.30 to .49; and large r=.50 to 1.0 (Pallant, 2013). Note that *r* not significance level (*p*) determined the strength of the relationship.

6.3.2.10 Family-wise or experimental error rate

Study 1 utilised *post hoc* comparisons that took into account family-wise error calculations. Studies 2 to 4 involved further comparisons in which family-wise error needed to be considered. In the discussion, *p* values approximate to .01 and their corresponding effect sizes are noted and discussed. Relationships with significance values between .02 and .05, if they are referred to, are noted as marginally significant.

6.3.2.11 Controlling for covariates

Due to the nature of purposeful sampling in this study, there were significant differences between descriptive variables (e.g., age) in groups that were compared. If a descriptive variable was deemed a possible covariate, then a hierarchical multiple regression was run. The groups being compared (e.g., non-recurrent versus recurrent depression) were coded as a dummy variable. In the hierarchical regression, the covariate was entered in the first block and the dummy variable entered in the second

block, thereby statistically controlling for the covariate. *R* square change, *F* change and significance level (*p*-value) were reported, to demonstrate whether the dummy variable significantly contributed to the dependent variable once the covariate had been controlled for. In addition, beta values and corresponding significance values from the final model were reported.

6.3.2.12 One sample T-test

From Baune et al. (2012), for an approximation of the difference between the proportion of parents with psychotic illness to the healthy control group in Study 1, a one sample t-test was used. The *t* and *p* values were reported.

6.4 Results

6.4.1 Depression, anxiety disorder only, versus healthy control

The sample with consisted of 179 young adults with 34 healthy control participants, 26 classified with an anxiety disorder but not a depressive disorder and 119 classified as having at least one MDE. The final number of participants above, were after participants classified with PTSD and statistical outliers were removed (See Section 6.3.1). Table 6.4 presents further information on the demographics of the sample. An ANOVA was conducted to explore the differences in descriptive variables among the healthy control, anxiety disorder only and MDE groups. Means, standard deviations and *F* statistics are reported.

Table 6.4

Demographic Characteristic of Participants Comparing Healthy Control, Anxiety Disorder Only and MDE Groups

Sociodemographic & clinical variables	Healthy control n = 34		Anxiety disorder only n = 26		MDE group n = 119		$F_{(2,177)}$	p-value	Effect size eta^2	*Post hoc*
	M	*SD*	*M*	*SD*	*M*	*SD*				
Gender % female	58.8		76.9		77.3		4.83[b]	.09		
Age	18.7	1.82	19.7	2.54	20.1	3.98	12.3[a]	.000	.113[c]	1,3
WTAR	39.0	5.66	39.3	5.58	39.2	5.55	0.3	.970		
Severity measures										
Depression severity	0.26	.790	3.46	4.14	7.97	7.17	71.2[a]	.000	.440[c]	1,2; 1,3; 2,3
Anxiety severity	0.74	1.21	6.12	5.65	10.73	8.91	78.3[a]	.000	.465[c]	1,2; 1,3; 2,3
CES-D	6.35	4.06	14.6	8.95	19.21	12.3	49.8[a]	.000	.356[c]	1,2; 1,3
Age of depression onset	n/a		n/a		15.4	3.84				
Number of depressive episodes	n/a		n/a		5.36	4.70				

a) Welch's adjusted *F*; b) Pearson chi-square value df=2; c) Estimated Omega squared effect size for Welch's *F*; Cramer's V: .07 = small effect; .21 = medium effect; .35 = large effect; *Post hoc*: 1 = healthy control; 2 = anxiety disorder only; 3 = MDE.

Table 6.5 shows chi-square values for independence between the disorder groups and the relevant depression variables. There was a significant association with a medium effect size between family psychiatric history and disorder group ($p<.05$) and a large effect size for suicide attempt and disorder group ($p<.001$).

Table 6.5

Group Percentages for Relevant Depression Variables

Sociodemographic and clinical variables	Healthy control n=34	Anxiety disorder only n=26	MDE group n=119	Pearson chi-square df=2	p-value	Effect size Cramer's V
Family psychiatric history%						
MDD only	24.2	40.0	53.4	9.25	.01	.229
MDD, BPD, or schizophrenia	33.3	56.0	65.3	10.8	.004	.248
Suicide attempt %	0	0	26.9	19.4	.000	.328
Antidepressant medication %						
Current	n/a	n/a	14.1			
Past only	n/a	n/a	24.2			
MDD medical diagnosis %	n/a	n/a	53.8			
Hospitalisation for depression %	n/a	n/a	11			
Disorders and phobias (past or current) %						
Dysthymia	n/a	n/a	23.5			
Manic episode	n/a	3.8	3.4	.082[a]	.774	
PD	n/a	0	21.0	5.21 [a]	.022	.213[b]
Social phobia	n/a	15.4	21.8	.221 [a]	.638	
Specific phobia	n/a	7.7	7.6	.000 [a]	1.000	
OCD	n/a	23.1	18.5	.069 [a]	.793	
Anorexia nervosa	n/a	3.8	1.7		.450[c]	
Bulimia nervosa	n/a	11.5	5.9		.386[c]	
GAD	n/a	23.1	52.1	6.01 [a]	.014	.223[b]
Body dysmorphic disorder	n/a	11.5	9.2		.717[c]	
Pain disorder	n/a	0	2.5		1.00[c]	
Premenstrual dysphoric disorder	n/a	26.9	15.1		.159[c]	

a) Yate's Community Correction; b) Phi coefficient; c) Fisher's exact test; Cramer's V: .07 = small effect; .21 = medium effect; .35 = large effect. Phi coefficient: .10 = small effect, .30 = medium effect; .50 = large effect.

An ANOVA was conducted to explore the effect of the three disorder groups on cognition. There was very little difference between the three groups: Table 6.6 shows a main effect for the ToL task with three rings ($p< .05$) and *post hoc* comparisons revealing the MDE group committing significantly more errors than the healthy control group ($p<.05$). However, this is only a small difference, with an estimated omega square value of .034 indicting the disorder group was responsible for 3.4% of variance in cognition. In Trial 1 of the Word Recall task there was not a main effect between the groups; however, it approached significance ($p>.05$) and *post hoc* analysis showed that participants with anxiety disorder only recalled fewer words than the healthy control group ($p<.05$). The magnitude of differences in the means was small. There were no other significant differences between the three groups.

Table 6.6

Cognitive Scores for Young Adults Comparing Healthy Control, Anxiety Disorder Only and MDE Group

	No depression n=34		Anxiety disorder only n=26		MDE group n=119		*F* value	*p*-value	Effect size eta[2]	*Post hoc*
Neuropsychological domains	*M*	*SD*	*M*	*SD*	*M*	*SD*				
Social cognition										
Affect naming	18.7	2.57	19.1	2.12	19.1	2.16	.586	.557		
Prosody face matching[a]	9.44	1.31	8.85	2.38	9.43	1.68	.728	.488		
Prosody pair matching	9.62	1.21	9.65	1.32	9.9	1.39	.784	.458		
Social perception pairs	33.8	3.68	34.5	3.54	34.6	3.77	.651	.523		
Social perception	37.7	3.46	37.8	3.67	38.5	3.53	.793	.454		
Social perception prosody	19.1	2.03	18.5	2.98	19.3	2.45	1.24	.292		
Stroop Test										
Stroop (Golden)	−5.95	4.62	−6.22	2.83	−5.39	3.86	.646	.525		
Stroop A	11.9	3.01	11.7	1.61	11.6	2.22	.300	.741		
Stroop B	13.2	2.97	12.6	2.14	12.7	2.55	.508	.603		
Stroop C	19.1	6.22	18.0	3.52	18.9	5.13	.418	.659		
N-back										
N-back: 1-back % accuracy	85.5	18.3	82.1	23.5	87.2	17.8	.799	.452		
N-back: 2-back % accuracy	82.0	20.9	80.1	21.9	81.1	21.9	.030	.971		
N-back: 3-back % accuracy	70.6	23.2	67.2	24.5	69.7	21.6	.180	.836		
N-back[c]							.211	.810		
Card Sort										
Perseverative errors	9.09	8.39	7.46	5.81	7.10	6.20	1.20	.305		
Non-perseverative errors	9.15	9.43	8.69	9.83	9.43	8.80	.074	.929		
Total errors	18.1	15.7	15.4	12.4	16.5	13.7	.287	.751		
Categories	5.74	.751	5.54	.99	5.82	.536	1.05[a]	.360		
ToL										
ToL3 ring	1.85	4.10	2.27	3.29	4.37	6.60	4.49[a]	.015	.034[b]	1,3

ToL4 ring	2.62	3.54	2.38	3.65	2.34	3.28	.092	.912		
ToL5 ring	1.35	1.76	2.27	2.97	1.69	2.49	1.05	.353		
ToL total	5.82	7.19	6.92	6.99	8.29	8.49	1.35	.263		
Word Recall										
Trial 1	8.00	2.24	6.73	1.51	7.56	2.03	3.01	.052	.022	1,2
Trial 2	9.97	2.65	9.12	1.90	9.70	2.27	1.06	.350		
Trial 3	11.4	2.45	10.1	2.03	10.9	2.63	1.82	.165		
Trial 4	11.6	2.52	11.2	3.00	11.8	2.45	.674	.511		
Trial 5	12.1	2.66	12.1	2.64	12.9	2.40	.747	.475		
Total	53.1	10.9	49.3	8.71	52.8	9.62	1.47	.234		
Word Recall[d]							1.44	.240		

a) Welch's adjusted *F*; b) Estimated Omega squared: effect size for Welch's *F*; c) 2 by 3 MANOVA; d) 2 by 5 MANOVA; Eta^2: .01 = small effect; .06 = moderate effect; .14 = large effect; *Post hoc*: 1 = healthy control; 2 = anxiety disorder only; 3 = MDE group.

6.4.2 Correlations of clinical status with cognitive performance

Relationships between relevant demographic variables, such as disorder severity, were investigated using Pearson correlation coefficients. Only participants who had been classified as experiencing an MDE were included in this analysis (n=119). Table 6.7 shows Pearson correlation coefficients (r) for descriptive variables. There was a small but significant correlation between number of depressive episodes and each of the three disorder severity measures; for example, depression severity $r= .257$, $n= 119$, $p< .01$. There was a significant negative correlation between number of depressive episodes and the age of first symptoms. However, if years active (current age minus first symptoms) was controlled for, there was no longer a significant correlation between 'number of episodes' and 'first symptoms', $r=-.08$, $n=112$, $p>.05$.

Table 6.7

Pearson Product-Moment Correlations Between Descriptive Variables

	1	2	3	4	5	6	7
1. Age	-						
2. WTAR	.081	-					
3. Depression severity	.147	-.099	-				
4. Anxiety severity	.159	-.122	.901**	-			
5. CES-D	.045	-.092	.803**	.776**	-		
6. Age of depression onset	.401**	-.100	.110	.092	.032	-	
7. Number of depressive episodes	.174	-.049	.257**	.272**	.214*	-.261**	-

* $p<.05$, ** $p<.01$ (two tailed); Strength of relationship: small r=.10 to .29; medium r=.30 to r=.49; large r=.50 to 1.0.

The relationships between relevant demographic variables, such as disorder severity and cognitive scores, were investigated using Pearson correlations. There were two correlations where $p<.01$: a small significant correlation between 'age of depression onset' and 'Card Sort categories' $r=.251$, $n=118$, $p<.01$; and a medium significant correlation between 'age' and 'ToL 5' $r=-.3$, $n=119$, $p<.01$. Table 6.8 shows all significant correlations between descriptive variables and cognition data.

Table 6.8

Pearson Product-Moment Correlations between Descriptive Variables and Cognition Scores

	Age	WTAR	Depression severity	Anxiety severity	CES-D	Age of depression onset	Number of depressive episodes
Affect naming	−.134	−.063	−.071	−.008	.077	−.129	.063
Prosody face	−.040	.051	−.140	−.120	−.088	−.082	−.029
Prosody pair	−.058	.169	−.019	−.042	.026	−.015	−.223*
SP pairs	.008	.194*	−.066	−.036	−.079	−.098	−.075
SP	−.124	.051	−.117	−.078	.016	−.123	−.062
SP prosody	−.061	.132	−.107	−.106	−.045	−.065	−.147
Stroop Golden	.007	−.180	.059	.018	.045	.183*	.056
Stroop A	.034	.018	−.029	−.041	.048	−.139	−.022
Stroop B	.086	−.101	.104	.098	.174	−.060	.056
Stroop C	.063	−.177	.084	.044	.141	.047	.060
N-back 1	.045	.160	−.064	−.028	.001	−.037	.060
N-back 2	.040	.208*	−.091	−.069	−.041	.036	.106
N-back 3	−.062	.149	.029	.041	.061	−.025	.008
Pers. errors	−.063	−.035	.160	.082	.106	−.081	.138
N-pers. errors	−.079	−.032	.131	.105	.124	−.145	.014
Total errors	−.073	−.040	.148	.096	.118	−.135	.068
Categories	−.048	−.008	−.116	−.092	−.094	.251**	−1.26
ToL3 ring	−.046	.038	.048	.041	.061	−.042	−.086
ToL4 ring	−.196*	−.176	.040	.065	.062	−.094	−.070
ToL5 ring	−.304**	−.169	.054	.082	.001	−.084	−.029
ToL total	−.196*	−.079	.058	.071	.055	−.096	.099
WR Trial 1	.139	.139	−.006	−.026	−.095	−.054	−.065
WR Trial 2	.096	−.009	−.048	.002	−.024	.006	−.044
WR Trial 3	.064	.048	−.075	−.040	.052	.061	−.070
WR Trial 4	.130	−.001	−.188*	−.108	−.097	.038	−.081
WR Trial 5	.064	−.141	−.042	−.005	.015	−.081	−.035
WR total	.119	.009	−.091	−.039	−.051	.020	−.079

* $p<.05$, ** $p<.01$ (two tailed); Strength of relationship: small r=.10 to .29; medium r=.30 to r=.49; large r=.50 to 1.0.

6.4.3 Early onset versus non-early-onset depression

An independent-sample t-test was conducted to compare both group in terms of descriptive variables (see Table 6.9).

Table 6.9

Descriptive Statistics Comparing Young Adults with Early-onset Depression and Non-early-onset Depression

Sociodemographic and clinical variables	Early-onset depression n= 67		Non-early-onset depression n= 51		$t_{(116)}$ value	p-value	Effect size eta^2
	M	*SD*	*M*	*SD*			
Gender % female	77.6		76.5		.000[a]	1.00	
Age years	20.3	3.43	22.3	4.39	−2.67	.009	.058
WTAR	39.7	5.67	38.6	5.44	.994	.322	
Severity measures							
Depression severity	7.45	6.85	8.75	7.62	−.971	.333	
Anxiety severity	10.1	9.04	11.7	8.79	−.974	.332	
CES-D	18.7	12.8	19.9	11.9	−.512	.609	
Number of depressive episodes	6.41	5.08	4.06	3.74	2.85	.005	.108
Age of depression onset	12.9	2.08	18.7	3.06	−12.2	.000	.562
Number of suicide attempts[b]	2.52	1.99	2.40	2.07	.122	.904	

a) Yates continuity correction; b) Of those who attempted suicide; Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

Table 6.10 shows the chi-square tests for independence between relevant sociodemographic and clinical variables for early-onset depression compared to non-early-onset depression. Young adults with early-onset depression showed a higher proportion of suicide attempts (p<.001) and incidence of dysthymia (p<.01). The magnitude of differences in the means were both medium effects. There was no significant difference in familial history (p>.05).

Table 6.10

Group Percentages for Relevant Depression Variables for Early-onset and Non-early-onset Depression

Sociodemographic and clinical variables	Early-onset depression n= 67	Non-early-onset depression n= 51	Yates continuity correction	p-value	Effect size Phi coefficient
Family psychiatric history					
MDD only	52.2	56.0	.047	.829	
MDD, BPD, or schizophrenia	67.2	64.0	.026	.873	
Suicide attempt	40.3	9.8	12.1	.000	−.340
Antidepressant medication					
Current	12.3	17.1	.142	.707	
Past only	22.8	26.8	.048	.827	
MDD medical diagnosis	54.5	58.3	.045	.833	
Hospitalisation for depression	16.7	3.9	3.53	.060	
Comorbid					
MDD only	20.9	25.5	.135	.713	
MDD & dysthymia	34.3	7.8	10.1	.002	−.312
MDD & anxiety1	77.6	66.7	1.25	.264	
MDD & eating disorder	10.4	2.0		.135[a]	
MDD & mania	6.0	0		.132[a]	

a) Fisher's exact test; Phi coefficient: .10 = small effect, .30 = medium effect; .50 = large effect.

Independent-sample t-tests were conducted to compare cognition scores for young adults with early-onset depression and non-early-onset depression. The non-early-onset group completed significantly more categories of the Card Sort task than the early-onset group ($p<.01$), although there were no other significant differences in the Card Sort task ($p>.05$). The magnitude of the differences in the means for categories completed was moderate. There were no significant differences in cognition scores in any other of the cognitive tasks ($p>.05$) (see Table 6.11).

Table 6.11

Cognitive Scores for Young Adults Comparing Early-onset Depression and Non-early-onset Depression

	Early-onset depression n = 67		Non-early-onset depression n= 51		*t* value	*p*-value	Effect size eta^2
Neuropsychological domains	*M*	*SD*	*M*	*SD*			
Social cognition							
Affect naming	19.1	2.10	19.1	2.22	−.033	.974	
Prosody face matching	9.43	1.63	9.41	1.78	.067	.947	
Prosody pair matching	9.84	1.43	10.0	1.34	−.634	.527	
Social perception pairs	34.9	3.49	34.3	4.11	.865	.389	
Social perception	38.4	3.46	38.5	3.33	−.237	.813	
Social perception prosody	19.3	2.45	19.4	2.49	−.312	.756	
Stroop Test							
Stroop (Golden)	−5.90	3.34	−4.63	4.37	−1.79	.076	
Stroop A	11.7	2.46	11.3	1.90	.997	.321	
Stroop B	13.0	3.00	12.4	1.80	1.31	.194	
Stroop C	18.8	5.10	19.1	5.25	−.287	.775	
N-back							
N-back: 1-back % accuracy	86.9	18.8	87.4	16.7	−.17	.865	
N-back: 2-back % accuracy	81.0	21.8	81.1	22.3	−.015	.988	
N-back: 3-back % accuracy	70.8	20.4	68.1	23.3	.681	.497	
N-back[a]					.042	.838	
Card sort							
Perseverative errors	7.55	6.58	6.65	5.65	.786	.434	
Non-perseverative errors	10.4	9.83	8.02	7.16	1.54	.126	
Total errors	18.1	15.2	14.5	11.3	1.47	.143	
Categories	5.70	.675	5.96	.196	−2.99	.004	.072
ToL							
ToL3 ring	4.61	6.34	3.86	6.90	.612	.542	
ToL4 ring	2.39	3.67	2.29	2.75	.153	.879	
ToL5 ring	1.82	2.55	1.55	2.44	.585	.559	
ToL total	8.82	8.65	7.45	8.33	.866	.388	
Word Recall							
Trial 1	7.45	2.20	7.73	1.80	−.733	.465	
Trial 2	9.51	2.40	9.92	2.10	−.979	.329	
Trial 3	10.7	2.60	11.3	2.67	−1.35	.179	

Trial 4	11.6	2.46	12.2	2.39	−1.44	.154
Trial 5	12.5	2.15	12.65	2.73	−.278	.782
Total	51.9	9.63	54.0	9.66	−1.19	.236
Word Recall[b]					1.41	.238

a) 2 by 3 MANOVA; b) 2 by 5 MANOVA; Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

6.5 Discussion

6.5.1 Depression versus healthy control

This current study investigated whether young adults with depression or young adults with anxiety disorder only had deficits in EF compared to a healthy control group. The results of this study did not support the hypothesis that young adults with depression would demonstrate deficits in the domains of EF (set-shifting, inhibition, updating, planning or verbal learning and memory) compared to the healthy control group. In addition, the results did not support the hypothesis that young adults with anxiety disorder would perform significantly worse only on the verbal learning and memory task. In the five trials, the anxiety disorder only group performed worse than both the healthy control group and the MDE group, with the exception of Trial 5, which tied with the healthy control group; however, the differences were not significant.

Because of the mixed nature of previous studies, these results were consistent with some previous studies of young adults with depression, which also demonstrated no significant difference in EFs between young adults with depression and healthy control groups. Previous studies have shown either no impairments (Castaneda, Suvisaari et al., 2008; Wang et al., 2006) or minor impairments (Grant et al., 2001) in cognitive functioning. There is a large body of work that has also found non-significant results in the individual EF domains of set-shifting (Fossati et al., 1999; Hill et al., 2004; Stordal et al., 2004), inhibition (Hill et al.; Smith et al., 2006), updating

(Fitzgerald et al., 2008; Walsh et al., 2007), planning (Porter et al., 2003; Stordal et al., 2004) and verbal learning and memory (Fossati et al., 1999).

The use of a subclinical sample may have contributed to finding non-significant differences between the depression and healthy control groups. The current study included participants who were not hospital inpatients or outpatients currently (although participants may have been recently hospitalised coincidently) but who had experienced depressive symptoms. This resulted in a mild to moderate depression sample. A subclinical sample was used for several reasons. First, there are few depression studies using the present type of sample. Second, recruiting almost entirely from first- and second-year university students allowed the level of education to be kept constant. Finally, it allowed larger group sizes, which has been a limiting factor in previous studies (Castaneda, Tuulio-Henriksson et al., 2008).

Both Grant et al. (2001) (outpatients) and Channon (1996) (undergraduate students) used mild to moderate depression samples and showed deficits in set-shifting. Grant et al. suggested that using a relatively young, mild to moderate depression sample might have been responsible for the lack of EF impairments associated with memory and learning tasks. However, Bearden et al. (2006), featuring outpatients and Smith et al. (2006), with young adults in remission, both showed significant deficits in verbal learning and memory using non-severe depression samples. A subclinical sample may affect state deficits; however, forms of cognition defined as trait deficits, such as set-shifting, should not be affected, owing to their independent relationship with depression severity. However, defining an EF deficit as singularly a state or trait deficit may be problematic. Verbal learning and memory shows the properties of a state deficit, correlating with depression severity (Porter et al., 2003), as well as with a trait deficit, by being present in remission (Neu et al., 2005; Preiss et al., 2009; Smith et al., 2006).

6.5.2 Anxiety disorder only

The finding that the anxiety disorder only group did not perform worse in the verbal learning and memory task was not consistent with Airaksinen et al. (2005), who found that their anxiety disorder group performed significantly worse in a memory task. In Airaksinen et al., further analysis showed that PD, OCD and social phobia were the contributing disorders to the memory deficits. In other studies, samples that include patients with PD have been associated with cognitive deficits in verbal learning and memory (Asmundson et al., 1995) and spatial learning (Boldrini et al., 2005). However, in this current study, the anxiety group did not contain any participants with PD (see Table 6.5 for a complete group breakdown), as all of the young adults with a classification for PD also had comorbid depression. The lack of young adults with PD could be a factor behind the lack of significant differences, although the anxiety group scores were consistently lower than those for the healthy control group.

The lack of significant differences in other forms of EF between the anxiety only group and the healthy control group was supported by previous studies (Airaksinen et al., 2005; Boldrini et al., 2005; Kaplan et al., 2006). In general, the deficits exhibited by young adults with a classification of anxiety disorder only did not support the findings regarding deficits in the verbal learning and memory task of previous literature, which has been based mostly on middle-aged adults. However, it should be noted that there is a limited number of previous studies, owing to the high rate of comorbidity between anxiety and depression.

6.5.3 Correlations of clinical status with cognitive performance

The current study also investigated whether disorder severity significantly correlated with cognition scores. From Table 6.8 it can be noted that disorder severity did not correlate with any cognitive tests except for a small correlation with one of the

trials of verbal learning and memory task. These non-significant results are most likely indicative of the subclinical sample. Several earlier studies with subclinical samples or mild to moderate depressive samples have found either no relationship or only a modest relationship between disorder severity and cognitive performance. Grant et al. (2001), using outpatients, found no significant relationship between disorder severity, EFs and memory measures, with the exception being modest relationships between measures of the CANTAB, a computerised cognitive testing package. Bearden et al. (2006), also using outpatients, found no relationship between cognitive performance and clinical measures such as disorder severity, hospital visits, medication usage, or familial history. Both Smith et al. (2006), using young adults in remission and Channon (1996), using undergraduate students, did not analyse clinical status and cognitive performance. Therefore, non-significant correlations between clinical status and cognitive measures are not uncommon with a subclinical or mild or moderate depressive sample.

6.5.4 Early onset depression

The results of this study showed that the early-onset group was not more severe in term of disorder severity than the non-early-onset group, with non-significant differences in the three measures of disorder severity (see Table 6.9). However, the early onset group had a significantly higher proportion of young adults with dsythymia and suicide attempts. This agreed with Hammen et al. (2008), who found that early-onset depression was a more chronic form, with higher suicidality. Dysthymia represents a more chronic form of depression, with epsiodes measured in years rather than in weeks. However, there was no significant difference in familial history or comorbid anxiety in this current study, which differed from previous studies (Hammen et al., 2008; Rohde et al., 1994).

There were no significant differences in cognition between early-onset and non-early-onset depression, with the exception of categories completed in the set-shifting task Card Sort. The early-onset group completed significant fewer categories, which usually is associated with a higher number of perseverative and non-perseverative errors. Although the early-onset group committed more perseverative and non-perseverative errors, there were no significant differences. In future studies, a better comparision for early-onset depression rather than non-early-onset depression would be to define the age limit for later-onset depression as approximately greater than 20 years. According to Klein et al. (2013), early-onset depression is a result of comorbid depression associated with early-onset anxiety and comorbid depression is also associated with later-onset anxiety, which occurs around ages 21 to 26. Therefore, depression onset between the ages of 16 and 19 years, which was classified as non-early-onset, may be measuring similar constructs to depression onset at 15 years and younger, such as depression associated with changes in puberty, stressors due to high school, and early romantic relationships. In the current study, this comparison could not be made, as 90% of the sample had experienced depression onset before the age of 21.

6.5.5 Healthy control group

Non-significant differences between the depression and the control group in EF may have resulted because of members of the healthy control group being susceptible to future depressive episodes. Predictors of future depressive episodes include family members diagnosed with a mood disorder and subclinical symptoms, as discussed below (Klein et al., 2013). In the current study, 21.4% of the control group had a relative with a MDD diagnosis and that number increased to 28.6% if diagnoses of bipolar disorder (BPD) or schizophrenia were included. This percentage of familial diagnosis is significantly higher than those found in a similar depression study by Baune

et al. (2012), who found that 18.5% of their healthy control group had a family history of psychiatric illness ($t_{(32)}$=2.28, p<.05). According to a 20-year longitudinal study by Weissman et al. (2006), the probability of a non-depressed offspring with a parent who has a MDD diagnosis being diagnosed in the future with MDD is 3.3 times greater than a non-depressed offspring with no parents with an MDD diagnosis. In addition, there is evidence that people classified as healthy but with a parent with a psychiatric diagnosis show decreased performance on cognitive tests. Non-depressed females with a family history of depression have been found to perform significantly worse in verbal learning and memory tasks (Mannie, Barnes et al., 2009). In addition, young to middle-aged healthy adults with a family history of schizophrenia performed significantly worse on a set-shifting task (Szöke et al., 2006). Therefore, a parent with a disorder diagnosis is a predictor of not only increased risk of future depression onset but also poor performance in cognitive testing. However, in this study and other depression cognition studies, there was no mechanism to exclude non-depressed offspring who had a familial psychotic history.

Subclinical depressive symptoms are also a predictor of future depressive episodes (Klein et al., 2013) and may have affected this study. To qualify for the healthy control group, scores lower than 8 on the SIGH-AD and lower than 18 for the CES-D were required, thus ensuring the exclusion of individuals with subclinical depressive symptoms from the healthy control group. However, three participants demonstrated other measures that could have required them to be excluded. One participant for the MDE checklist in the MINI PLUS answered affirmatively to both A1 and A2 sections but only answered ‘yes’ to two of the questions in Section A3 regarding a past episode, not the three affirmative answers, which would have then considered them for MDE classification. A second participant expressed concern regarding

schizophrenic symptoms (which were not tested) and a third believed she had experienced a depressive episode post testing. With the second and third participants, there were no official data to back up the self-reported claims. Under the methodology for this study, there was no official procedure to exclude these participants and therefore they were included. It is recommended for future studies that potential healthy control participants with subclinical symptoms should be classified as participants with subclinical symptoms.

Gender and age were also possible issues with the young adult healthy control group, due to future depression susceptibility. The majority of depression studies cited in this thesis have noted the higher percentage of depressed females, which reflects the higher incidence of both depression and anxiety for females than for males (NHS, 2014). Corresponding control groups would need to have non-significant gender differences, which means a large number of healthy female control participants would be required. The difficulty is that as well as the above-mentioned familial loading and subclinical symptoms, gender, notably the participant being female, is a significant predictor of future depressive episode (Airaksinen, Wahlin, Forsell, & Larsson, 2007; Klein et al., 2013; Lewinsohn et al., 1994). In addition, the young age of the participants may represent a confounding factor. In the current study, the mean age of the healthy control group was approximately 18 years and therefore, there is less certainty around whether they may experience a future depressive episode compared to a middle-aged adult. Two possible reasons for this are that a young adult of approximately 18 years of age would be less likely to have experienced stressful life events that may trigger a depressive episode, such as financial strain or breakdown in pivotal relationships (Airaksinen et al., 2007); and an older participant, when compared to a young participant, has no history of depression for a longer period. This is particularly relevant

when attempting to identify cognitive deficits that may be present before depression onset. For example, a participant may exhibit the cognitive deficit but may 'not yet' have manifested a depressive episode. Gender and young age provide difficulties in identifying a comparable healthy control group when studying young adults, owing to their susceptibility to future depressive episodes.

A final issue with the healthy control group was mathematical ability, which is explored in more detail in Chapter 9. During the administration of the tests, the experimenter noticed a cohort of young male athletic participants who had not experienced depressive or anxiety symptoms and they were hence classified as being in the healthy control group, but committed a large number of errors during cognitive testing. As the sample was made up of primarily psychology, social work and sports science students, the experimenter surmised that what differentiated the sports science students from the humanities students was mathematical ability. The experimenter introduced a mathematical measure into the data-collecting process.

In summary, methodological strategies are needed to increase the validity of healthy control groups in future studies of this nature. Participants who are susceptible to future depressive episodes, such as those with a familial history of mental illness or subclinical symptoms, may need to be reclassified. Increasing the size of the healthy control group may enable reclassification of susceptible participants. However, due to the lengthy time commitment and perhaps a lack of intrinsic motivation on behalf of eligible participants without depressive symptoms, it is difficult to recruit healthy control participants compared to those in disorder groups. Even studies such as Grant et al. (2001), who had a large depression group (n=123), still only managed to recruit 36 healthy control participants, which may reflect a difficulty in recruiting control groups. In future studies, a streamlined (validated and reliable) computer-based experimentation

process could be adopted to decrease testing time, as well as the use of extrinsic rewards such as monetary compensation.

6.5.6 Biological basis of EF

Whether depression samples differ in terms of cognition from healthy control samples may be due to biological differences in the PFC. As detailed in Section 1.5, cellular abnormalities found in depression patients, such as differences in neuronal size and density, cortical thickness and glial density in the dlPFC and OFC have been suggested to lead to altered metabolism (performance) (Rajkowska, Miguel-Hidalgo et al., 1999). As the dlPFC and OFC are pivotal to EF (see Section 1.5), the abnormalities in their cellular structure could be the mechanism that leads to reduced performance in EF. Interestingly, these cellular abnormalities may not be due to the course of the depression, but due to developmental or environmental factors. Animal studies have shown that developmental deficiencies in the form of early adverse life experiences, result in deficits in EF and cellular abnormalities in associated brain areas (Baarendse et al., 2013; Fone & Porkess, 2008; Makinodan et al., 2012; Stamatakis et al., 2016). Therefore, further investigation could examine whether developmental or environmental factors lead to cellular abnormalities in the PFC, playing a causal role in EF deficits in humans (see Figure 6.1).

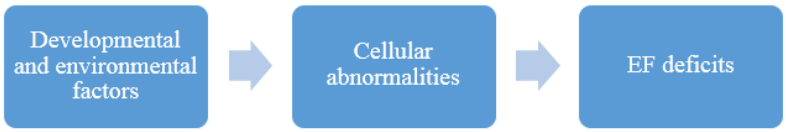

Figure 6.1. Proposed biological basis for EF deficits.

The concept of EF deficits having a biological basis is especially relevant for studies using a subclinical sample. Due to the mild to moderate depression severity of the sample in this current study, the likelihood of detecting clinical state deficits that

correlated with depression severity was low. Therefore, according to the proposed theory in Figure 6.1, identification of EF deficits may depend on the proportion of the sample who had experienced suboptimal developmental or environmental conditions.

6.5.7 Conclusion

In conclusion, in this study, young adults with depression or young adults with anxiety disorder only did not show deficits in EF. Use of a subclinical sample may have affected the results, because the mild to moderate depression sample could have affected possible state deficits that correlate with depression severity. Analysis of the healthy control group identified factors such as familial psychiatric history and subclinical symptoms, indicators of future depressive episodes, which may have confounded the results. These, among other factors such as age and gender, highlighted the difficulty of recruiting a healthy control group owing to the participants' susceptibility to future depressive episodes. It is recommended that a wider search for healthy control participants should be conducted with financial incentives to boost participation numbers, enabling the classification of familial and subclinical subgroups.

A biological basis for EF deficits has been proposed, emanating from developmental or environmental factors contributing to cellular abnormalities in the PFC. It is suggested that especially for a subclinical sample, the proportion of young adults with cellular abnormalities in a depression group may be a determinant for identification of group differences in EF. A future direction would be to investigate subgroups of depression, based on their likelihood that EF deficits played a role in depression onset.

Chapter 7: Primary and Secondary Depression versus Healthy Control Group (Study 2)

7.1 Study Context

This study had two concurrent aims. The first aim was to explore the concept of comorbid depression, where young adults with depression also have an additional disorder. This was done by comparing the depression subtypes primary depression and secondary depression with the healthy control group from Study 1. In primary depression, a non-depressive disorder or medical condition did not play a role in depression onset, whereas for secondary depression, the most probable cause of depression onset was a non-depressive disorder. The genesis of these definitions was discussed in Section 2.3. The advantage of this comparison was that it included the way the depressive and non-depressive disorders interacted. This concept led into the second aim, which was the identification of subgroups of depression where EF deficits may play a role in depression onset. Essentially, the question being asked was whether in primary depression, if the non-depressive disorder was not responsible for depression onset, does EF played a part in depression onset?

It was hypothesised that young adults with primary depression would have significantly greater cognitive deficits in EF, including set-shifting, inhibition, updating, planning and verbal learning and memory, than the young adults in the healthy control group. It was also hypothesised that young adults with primary depression would have significantly greater cognitive deficits in EF, including set-shifting, inhibition, updating, planning and verbal learning and memory, than young adults with secondary depression.

7.2 Method

7.2.1 Participants

The sample consisted of 114 young adults from the sample in Study 1 who met the classification for primary depression, secondary depression or healthy control group. The primary depression group was defined as young adults with a classification of MDE whose onset was not caused by a non-depressive disorder or medical condition. The secondary depression group was defined as young adults with a classification of MDE whose onset was most probably caused by a non-depressive disorder. Demographic information for the participants is provided in Table 7.1. Participants were excluded from the study if they did not match the exact definitions for primary depression or secondary depression. For example, if a participant experienced concurrent comorbidity, with both a depressive and a non-depressive disorder present simultaneously, they were excluded. Participants were also excluded if they were classified with multiple depressive episodes but not all of their depressive episodes fitted into the same group. For example, if the first MDE was due to a non-depressive disorder (secondary depression) but the second depressive episode was not (primary depression), then the participant was excluded. Three other participants who were excluded were classified initially as probable secondary depression due to a medical disorder. Of the three medical conditions—a virus, cancer and arrhythmia—two matched Feighner et al.'s (1972) definition of secondary depression, while none matched Bech's (2010); hence, they were excluded.

7.2.2 Materials

Neuropsychological assessment consisted of cognition tests: Card Sort, ToL, N-back, the Stroop Test, Verbal Recall and Social Cognition. Classification tests included SIGH-AD, CES-D. MINI PLUS, psychiatric and medical questionnaires, and

intelligence measure WTAR. High school subject information was also collected. For further information see Section 6.2.2.

7.2.3 Procedure

Participants initially undertook the six cognitive tasks: Card Sort, ToL, Verbal Recall, N-back, Social Cognition and the Stroop Test in a counterbalanced order. Participants then completed a series of structured or self-assessed classification tests: SIGH-AD, MINI PLUS, psychiatric and medical questionnaires, CES-D, education information and the WTAR. For further information see 6.2.3. At the end of the classification process the experimenter asked the participant regarding factors leading up to the onset of each MDE, in order to determine whether the episode could be classified as primary or secondary.

7.3 Statistical Analysis

7.3.1 Exclusion including outliers

As per Study 1 thirteen participants who were classified according to the MINI PLUS with post-traumatic stress disorder were previously excluded from the study. Thirteen other participants were classified as outliers who committed 40 or greater non-perseverative errors. For further information see Section 6.3.1. A further thirty four participants were excluded from the study as they did not match the exact definitions for primary depression or secondary depression. This included participants who experienced concurrent comorbidity, secondary depression due to a medical disorder, or if they experienced multiple depressive episodes which did not classify into solely primary or secondary depression.

7.3.2 Statistical tests

Means and standard deviations of descriptive variables and cognition scores were calculated and reported. Other data including gender and number of participants

hospitalised was presented as percentages. Chi-square test for independence was used to calculate whether there were significant differences between percentages in groups. An ANOVA was employed to compare a categorical variable with three levels such as 'disorder type' (healthy control, primary depression and secondary depression) and a continuous variable (e.g., cognition value). MANOVA's were employed if the cognitive test had more than one level, such as the three N-back tests or the five Word Recall tests. Post hoc comparisons were used to determine whether there were significant differences among the different groups. To control for covariate a hierarchical multiple regression was run. The groups being compared (e.g., primary depression versus secondary depression) were coded as a dummy variable. In the hierarchical regression, the covariate was entered in the first block and the dummy variable entered in the second block, thereby statistically controlling for the covariate. For more in-depth information on statistical tests see Section 6.3.2.

7.4 Results

Table 7.1 shows an ANOVA to compare the descriptive variables of the healthy control, primary depression and secondary depression groups. Means, standard deviations and *F* statistics are reported. As there was a violation in homogeneity of variance in age and disorder severity, Welch's *F* was used and estimated omega squared for a measure of effect size. There were significant age differences between the three groups ($p<.001$). Significant differences in depression severity between the healthy control group and depression groups were expected ($p<.05$), but note there were no differences in disorder severity between the primary depression and secondary depression ($p>.05$).

Table 7.1

Descriptive Statistics Comparing Healthy Control, Primary and Secondary Depression

Sociodemographic and clinical variables	Healthy control n=34		Primary depression n=59		Secondary depression (S) n=21		$F_{(113)}$ / $t_{(78)}$ value	p-value	Effect size eta^2	*Post hoc* p<.05)
	M	*SD*	*M*	*SD*	*M*	*SD*				
Gender % female	58.8		78.0		61.9		4.38[a]	.112		
Age	18.7	1.82	20.3	3.64	23.3	3.88	14.8[b]	.000	.196[c]	1,2; 1,3; 2,3
WTAR	39.0	5.66	39.1	5.13	40.2	5.99	.375	.688		
Severity measures										
Depression severity	0.26	.79	8.29	7.18	5.33	6.21	41.9[b]	.000	.420[c]	1,2; 1,3
Anxiety severity	0.74	1.21	10.5	9.39	8.43	7.88	39.4[b]	.000	.405[c]	1,2; 1,3
CES-D	6.35	4.06	19.0	12.4	16.0	11.5	29.6[b]	.000	.336[c]	1,2; 1,3
Number of depressive episodes	n/a		5.32	4.94	5.63	4.41	−.243[d]	.808		
Age of depression onset	n/a		14.7	3.67	17.1	5.23	−1.98[d]	.058		

a) Pearson chi-square value df=2; b) Welch's adjusted *F*; c) Estimated Omega squared effect size for Welch's *F*; d) t-test for analysis with two groups only; Eta^2: .01=small effect; .06=moderate effect; .14= large effect; *Post hoc*: 1= Healthy control; 2= Primary depression; 3= Secondary depression.

Table 7.2 shows the chi-square test for independence between disorder groups and relevant depression variables. There was a significant association with suicide (p<.001), with 42.4% of the young adults with primary depression having attempted suicide. Other significant associations were expected due to disorder group type, such as a significant higher proportion of comorbid anxiety (p< .01) in the secondary depression group.

Table 7.2

Group Percentages for Relevant Depression Variables

Percentage of variable in each group	Healthy control n=34	Primary depression n=59	Secondary depression N=21	Pearson chi-square value df=2	p-value	Effect size Cramer's V
Family psychiatric history						
MDD only	24.2	49.2	61.9	8.58	.014	.276
MDD, BPD, or schizophrenia	33.3	64.4	66.7	9.53	.009	.290
Suicide attempt	0	42.4	14.3	21.5	.000	.438
Antidepressant medication						
Current	n/a	13.0	10.5		1.00[b]	
Past only	n/a	18.5	31.6		.333[b]	
MDD medical diagnosis		42.1	66.7	2.79[a]	.095	
Hospitalisation for depression %	n/a	17.2	4.8		.271[b]	
Comorbid						
MDD only	n/a	33.9	0	7.77[a]	.005	−.344[c]
MDD & dysthymia	n/a	27.1	19.0	.194[a]	.660	
MDD & anxiety	n/a	61.0	100	9.67[a]	.002	.379[c]
MDD & eating disorder	n/a	5.1	14.3		.182[b]	
MDD & mania	n/a	6.8	0		.568[b]	

a) Yates continuity correction U; b) Fisher's exact probability test; c) Phi coefficient; Cramer's V: .07 = small effect; .21 = medium effect; .35 = large effect; Phi coefficient: .10 small, .30 medium, .50 large,

An ANOVA was conducted to explore the impact of depression type (healthy control, primary depression and secondary depression) on cognition. Means, standard deviations and *F* statistics are reported. Where violation of homogeneity of variance occurred, Welch's *F* was utilised. Significant main effects were found for perseverative, non-perseverative and total errors in the Card Sort task, as well as ToL3 ring and ToL total ($p<.05$) (see Table 7.3).

Table 7.3

Cognitive Scores for Young Adults Comparing Healthy Control, Primary Depression and Secondary Depression Groups

Neuropsychological domains	Healthy control n=34		Primary n=59		Secondary n=21		$F_{(2,113)}$ value	p-value	Effect size eta^2
			M	*SD*	*M*	*SD*			
Social cognition									
Affect naming	18.7	2.56	18.7	1.95	18.9	2.52	.042	.959	
Prosody face matching	9.44	1.31	9.34	1.94	9.52	1.60	.102	.904	
Prosody pair matching	9.62	1.21	9.92	1.33	9.95	1.47	.652	.523	
Social perception pairs	33.8	3.67	34.9	3.87	34.1	5.01	.956	.388	
Social perception	37.7	3.46	38.0	3.61	38.3	4.24	.171	.843	
Social perception prosody	19.1	2.03	19.3	2.71	19.5	2.77	.179	.837	
Stroop									
Golden Stroop	−5.95	4.62	−5.72	3.41	−4.80	4.38	.588	.557	
Stroop A	11.9	3.01	11.8	2.10	11.3	2.00	.380	.685	
Stroop B	13.2	2.97	12.9	2.32	12.4	2.17	.639	.530	
Stroop C	19.1	6.22	18.9	4.88	18.9	5.05	.016	.984	
N-back									
N-back: 1-back % accuracy	85.5	18.3	87.0	17.5	84.8	17.2	.136	.873	
N-back: 2-back % accuracy	82.0	20.9	79.4	20.9	83.0	26.1	.271	.763	
N-back: 3-back % accuracy	70.6	23.2	69.6	21.7	66.2	25.1	.255	.776	
N-back 3 by 3 MANOVA							.039	.962	
Card Sort									
Perseverative errors	9.09	8.39	8.44	6.94	4.24	2.90	9.74[a]	.000	.134[b]
Non-perseverative errors	9.15	9.43	11.4	9.94	6.14	6.56	3.66[a]	.032	.045[b]
Total errors	18.1	15.7	19.8	15.3	10.4	7.79	7.17[a]	.002	.098[b]
Categories	5.74	.751	5.68	.71	6.00	.000	1.90	.155	
ToL									
ToL3 ring	1.85	4.10	4.42	6.08	1.43	1.91	5.60[a]	.006	.075[b]
ToL4 ring	2.62	3.54	2.63	3.67	2.14	3.24	.157	.855	

ToL5 ring	1.35	1.76	2.03	2.54	1.10	2.26	1.74	.180	
ToL total	5.82	7.19	9.12	8.90	4.62	4.22	3.51	.033	.059
Word Recall									
Trial 1	8.00	2.24	7.56	1.95	7.76	2.36	.470	.626	
Trial 2	9.97	2.65	9.53	2.25	9.62	2.33	.382	.683	
Trial 3	11.4	2.45	10.6	2.81	11.2	2.56	.954	.388	
Trial 4	11.6	2.52	11.3	2.52	12.4	2.04	1.61	.205	
Trial 5	12.1	2.66	12.1	2.32	12.8	3.06	.684	.507	
Total	53.1	10.9	51.1	9.99	54.2	9.33	.874	.420	
Word Recall 3 by 5 MANOVA							.755	.472	

a) Welch's *F*; b) Estimated Omega squared: effect size for Welch's *F;* Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

From *post hoc* analyses there were significant differences between the depression groups in perseverative errors, non-perseverative errors and total errors (see Table 7.4). The secondary depression group committed significantly less preservative errors and total errors than the healthy control group ($p<.05$) and the primary depression group ($p<.01$). The secondary depression group also committed significantly less non-preservative errors than the primary depression group ($p<.05$). The largest estimated total variance accounted for by depression type was for perseverative errors, which was 13.4% (see Table 7.3). For ToL only one of the three individual trials had a significant main effect ($p<.01$) and for ToL total score had no significant *post hoc* analysis.

Table 7.4

Post Hoc Analysis for Healthy Control, Primary Depression and Secondary Depression Groups

Neuropsychological domains	*Welch's F*	df1	df2	p-value	*Post hoc* Games–Howell	p-value
Card Sort test						
Perseverative errors	9.74	2	65.6	.000	1,3; 2,3	.01, .001
Non-perseverative errors	3.66	2	59.4	.032	2,3	.024
Total errors	7.17	2	64.2	.002	1,3; 2,3	.05, .002
Categories[a]						
ToL						
ToL3 ring	5.59	2	70.3	.006	1,2; 2,3	.045, .004
ToL total	3.51[b]	2	113	.033	ns	

a) Welch's *F* cannot be calculated as one group has 0 variance; b) F ratio; *Post hoc*: 1= Healthy control; 2 = Primary depression; 3= Secondary depression.

To further investigate the influence of age on the dependant variables perseverative errors, non-perseverative errors and total errors, separate hierarchical multiple regressions were run with primary/secondary used as a dummy variable. For perseverative errors as the dependant variable, after controlling for age, primary/secondary significantly added to the model, *R* squared change=.071, *F* change $_{(1, 77)} = 5.99$, $p<.05$. In the final model, only primary/secondary was statistically significant (*beta* =−.284, $p<.05$). Similar results were shown for non-perseverative errors as the dependant variable, *R* squared change=.057, *F* change $_{(1, 77)} = 4.70$, $p<.05$; *beta* =−.254, $p<.05$, and for total errors as the dependant variable, *R* squared change= .078, *F* change $_{(1, 77)} = 6.60$, $p<.05$; *beta* =−.298, $p<.05$.

7.5 Discussion

This study investigated the cognitive differences between groups with primary or secondary depression and a healthy control group. The results of this study did not support the first hypothesis that young adults with primary depression would have

significant cognitive deficits in comparison to the healthy control group, as there were no significant differences between the two groups. The results did support the second hypothesis that the primary depression group would have significantly greater EF deficits compared to the secondary depression group. The primary depression group committed significantly more perseverative, non-perseverative and total errors than the secondary depression group, with no significant difference in Card Sort categories in the Card Sort task. The healthy control group committed significantly more perseverative and total errors than the secondary depression group did. In all other cognitive tasks, there were no overall significant differences between the groups.

Greater errors in set-shifting by the primary depression group highlighted primary depression as a subgroup of interest. However, in the current study the primary depression group did not differ from the healthy control group. Therefore, questions can be asked whether the secondary depression group was made up of young adults who were particularly good at cognitive tests and/or the healthy control group contained young adults who were particularly bad at cognitive tests. This is discussed in the next section.

EF deficits in the primary depression group compared to the secondary depression group suggested that EF deficits may play a role in primary depression that is absent in secondary depression. This suggestion is proposed, as depression onset for secondary depression is due to a non-depressive disorder, indicating a possible independent relationship with EF deficits.

7.5.1 Healthy control group

Factors such as familial history and subclinical symptoms in the healthy control group may have contributed to the relatively high perseverative and non-perseverative error count in the healthy control group. Section 6.5.5 outlined potential issues with the

healthy control group, which are briefly reviewed here. First, approximately one-third of the members of the healthy control group showed a high susceptibility to future depressive episodes, because of relatives with a diagnosis of MDD, bipolar disorder, or schizophrenia (Weissman et al., 2006), or sub-threshold symptoms (Klein et al., 2013). Familial psychotic history has also been directly linked to cognitive deficits. While no studies have been conducted to determine whether familial history of MDD leads to cognitive deficits, studies of people with a familial history of bipolar or schizophrenia have shown significantly more errors in the set-shifting task than for non-familial individuals (Liu et al., 2003; Szöke et al., 2006). Second, the issue of potential future depressive episodes in a healthy control sample is especially relevant when studying young adults, as young adults may not have yet experienced potential stressors that could trigger an initial depressive episode, such as financial hardships or relationship breakdowns (Airaksinen et al., 2007). This highlights the advantage of using alternative control groups for young adults with depression such as secondary depression. With young adults with secondary depression, there is no concern whether the participants are susceptible to future depression and the factors surrounding disorder onset have been identified.

7.5.2 Comparison to similar studies

EF deficits in primary depression compared to secondary depression may provide an explanation for mixed results in previous studies, where the proportion in the sample of primary depression may be the determining factor in the identification of significant deficits. However, as this is the first study to compare cognitive differences between young adults with primary or secondary depression and a healthy control group, there are no previous studies to compare. Comparisons to similar studies in terms of the severity of the depression group (mild to moderate) and in which comorbid

information has been recorded can be made. Grant et al. (2001) compared middle-aged depression outpatients with mild to moderate depression severity and found significant differences in perseverative and non-perseverative errors. In Grant et al., 17.1% in the depression group had a comorbid disorder (anxiety n = 20, eating disorder n = 1). Therefore, the study by Grant et al. appears to have a depression sample consisting mostly of outpatients with primary depression.

Castaneda, Suvisaari et al.'s (2008) study was similar to Grant et al. (2001) in terms of depression severity, except no significant differences were found between the depression and healthy control group. In Castaneda, Suvisaari et al. (2008), the 68 participants with depression were categorised as having MDD (n = 46), depression not otherwise specified (n = 11) and anxiety and depressive mood (n = 11). The 11 anxiety and depressive mood participants in Castaneda, Suvisaari et al. made up 16% of the total depression sample, which similar to the percentage of participants with comorbid anxiety in Grant et al.'s (2001) study. Castaneda, Suvisaari et al. (2008) specified that for the MDD group, participants did not have a lifetime diagnosis for any other DSM Axis I disorders. Therefore, the suggestion that depression groups with a high level of primary depression would be more likely to result in significant differences in EF is questioned by their research, which had a similar portion of comorbid anxiety in the depression sample to the work by Grant et al. (2001), but non-significant cognitive differences. However, although it can be assumed that with the absence of a comorbid anxiety disorder that the depressive disorder could be characterised as primary, in these studies there was no mechanism in place to determine the probable aetiology of the depressive disorder.

7.6 Conclusion

In conclusion, young adults with primary depression and the healthy control group committed significantly more errors in set-shifting than those with secondary depression did. A limitation of this study was that there were questions surrounding the suitability of the healthy control group, owing to familial psychiatric disorders and sub-threshold symptoms that may have affected cognition scores. This study has identified primary depression as a depression subgroup of interest in cognition studies and suggested that depression onset for secondary depression is independent of cognition. It is recommended that future depression cognition studies contain a mechanism to determine circumstances surrounding depression onset, to further explore whether significant cognitive differences are due to samples predominantly featuring a subtype of depression, such as primary depression. As suggested in Study 1, future research could investigate whether primary depression is linked to the proposed biological basis of EF deficits (see Figure 6.1).

Chapter 8: Recurrent versus Non-recurrent Depression (Study 3)

8.1 Study Context

The aim of this study was to investigate cognitive differences between young adults who experienced one or two MDEs only (non-recurrent depression) and those who experienced three or more MDEs (recurrent depression). Essentially, the research question was whether there is a difference in cognition between young adults who experience only one or two MDEs, compared to those who continue to experience MDEs. It was hypothesised that young adults with recurrent depression commit significantly more errors on measures of social cognition—facial affect and prosody matching—than do young adults with non-recurrent depression.

8.2 Method

8.2.1 Participants

For Study 3, the data on 114 young adults was taken from the larger population sample used in Study 1. The non-recurrent group (n=33) consisted of young adults who, according to classification from the MINI PLUS, had experienced one or two MDEs only, while the recurrent group (n=81) consisted of young adults who had experienced three or more MDEs. Non-recurrent depression was classified as one or two episodes rather than only one episode, as the experimenter noticed that often the second depressive epsiode was linked to the same trigger as the first depressive episode. Thus, one trigger could result in two depressive episodes but no more. Therefore, it was determined that a person who experienced only two depressive episodes would be better classifed as non-recurrent. Table 8.1 shows further information regarding the demographics of the sample.

8.2.2 Materials

Neuropsychological assessment consisted of cognition tests: Card Sort, ToL, N-back, the Stroop Test, Verbal Recall and Social Cognition. Classification tests included SIGH-AD, CES-D. MINI PLUS, psychiatric and medical questionnaires, and intelligence measure WTAR. High school subject information was also collected. For further information see Section 6.2.2.

8.2.3 Procedure

Participants initially undertook the six cognitive tasks: Card Sort, ToL, Verbal Recall, N-back, Social Cognition and the Stroop Test in a counterbalanced order. Participants then completed a series of structured or self-assessed classification tests: SIGH-AD, MINI PLUS, psychiatric and medical questionnaires, CES-D, education information and the WTAR. For further information see 6.2.3.

8.3 Statistical analysis

8.3.1 Exclusion including outliers

In forming the original sample for Study 1 thirteen participants who were classified according to the MINI PLUS with post-traumatic stress disorder were excluded from the study. Thirteen other participants were classified as outliers who committed 40 or greater non-perseverative errors. For further information see Section 6.3.1. A healthy control group was not part of this study.

8.3.2 Statistical tests

Means and standard deviations of descriptive variables and cognition scores were calculated and reported. Other data including gender and number of participants hospitalised was presented in percentages of the sample. Chi-square test for independence was used to calculate whether there were significant differences between percentages in groups. Independent-sample t-tests were used to compare a categorical

variable with two levels, such as ‘depression group’ (e.g., non-recurrent depression, recurrent depression) with a continuous variable (e.g., cognition score). MANOVA’s were employed if the cognitive test had more than one level, such as the three N-back tests or the five Word Recall tests. To control for covariate a hierarchical multiple regression was run. The groups being compared (e.g., non-recurrent versus recurrent depression) were coded as a dummy variable. In the hierarchical regression, the covariate was entered in the first block and the dummy variable entered in the second block, thereby statistically controlling for the covariate. For more in-depth information on statistical tests see Section 6.3.2.

8.4 Results

Independent-sample t-tests were conducted to compare young adults with non-recurrent and recurrent depression on demographic and clinical variables. The recurrent depression group had significantly higher disorder severity ($p<.01$) than the non-recurrent group. The recurrent group was also significantly older ($p<.05$), although there was no significant difference in age of depression onset ($p>.05$).

Table 8.1

Descriptive Statistics Comparing Non-Recurrent and Recurrent Depression

Sociodemographic and clinical variables	Non-recurrent depression n=33		Recurrent depression n=81		$t_{(112)}$ value	p-value	Effect size eta^2
	M	*SD*	*M*	*SD*			
Gender[a] % female	74.3		75.3		.024[b]	.878	
Age	19.8	3.21	21.7	4.21	−2.64	.010	.0586
WTAR	39.4	4.55	39.1	6.09	.294	.769	
Severity measures							
Depression severity	4.79	5.19	9.51	7.46	−3.85	.000	.117
Anxiety severity	6.67	7.33	12.7	9.04	−3.37	.001	.0921
CES-D	13.9	7.78	21.6	13.3	−3.81	.000	.115
Number of depressive episodes	1.42	.502	7.10	4.63	−10.9	.000	.515
Age of depression onset	16.1	2.57	15.2	4.18	1.47	.145	
Number of suicide attempts[c]	1.33	.866	2.96	2.10	−3.10	.004	.0790

a) 2 by 2 chi-square test used; b) Yates continuity correction; c) Of those who attempted suicide; Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

Table 8.2 shows the chi-square tests for independence between the disorder groups and the relevant depression variables. The non-recurrent group had a significantly higher proportion of MDD only (p<.05) and the recurrent group had a significantly higher proportion of comorbid anxiety (p<.01). The magnitude of both of these differences was small.

Table 8.2

Group Percentages for Relevant Depression Variables

Sociodemographic and clinical variables	Non-recurrent depression n=33	Recurrent depression n=81	Yates continuity correction	p-value	Phi coefficient
Family psychiatric history %					
MDD only	39.4	58.8	2.78	.095	
MDD, BPD, or schizophrenia	51.5	71.3	3.20	.074	
Suicide attempt %	27.3	28.4	.000	1.00	
Antidepressant medication %					
Current	3.7	19.1	2.53	.112	
Past only	22.2	25	.000	.984	
MDD medical diagnosis %	43.3	61.3	2.17	.141	
Hospitalisation for depression %	12.1	11.3	.000	1.00	
Comorbid %					
MDD only	39.4	17.3	5.177	.023	.236
MDD & dysthymia	18.2	25.9	.409	.523	
MDD & anxiety[a]	51.5	80.2	8.22	.004	.290
MDD & eating disorder	0	8.6	1.72	.189	
MDD & mania	0	4.9	.545	.460	

a) anxiety = PD, agoraphobia, specific disorder, OCD, GAD; Phi coefficient: .10 small, .30 medium, .50 large.

Independent-sample t-tests were conducted to compare the cognition scores for young adults with non-recurrent depression and those with recurrent depression. There was no significant difference in the social cognition task affect naming (p>.05). However, the recurrent group made significantly more errors than the non-recurrent group in prosody pair matching (p <.05) and social perception prosody (p <.05). Social perception prosody was a combination of prosody face matching and prosody pair matching. The magnitude of the differences in the means for prosody pair matching and social perception prosody was small (see Table 8.3).

Table 8.3

Cognitive Scores for Young Adults with Non-Recurrent Versus Recurrent Depression

Neuropsychological domains	Non-recurrent MDD n=33		Recurrent MDD n=81		$t_{(112)}$ value	p-value	Effect size eta^2
	M	*SD*	*M*	*SD*			
Social cognition							
Affect naming	19.0	2.24	19.1	2.12	−.373	.710	
Prosody face matching	9.79	1.62	9.23	1.71	1.59	.115	
Prosody pair matching	10.3	1.10	9.72	1.47	2.07	.041	.037
Social perception pairs	34.7	4.20	34.5	3.61	.189	.850	
Social perception	39.1	3.34	38.1	3.64	1.33	.188	
Social perception prosody	20.1	2.17	19.0	2.50	2.29	.024	.044
Stroop Test							
Stroop (Golden)	−6.11	4.64	−5.01	3.54	−1.37	.175	
Stroop A	12.0	2.53	11.4	2.09	1.35	.179	
Stroop B	12.5	2.22	12.9	2.71	−.590	.556	
Stroop C	18.4	5.79	19.2	4.98	−.731	.466	
N-back							
N-back: 1-back % accuracy	88.9	12.9	86.7	19.5	.597	.552	
N-back: 2-back % accuracy	83.7	17.7	80.5	23.3	.711	.478	
N-back: 3-back % accuracy	71.2	22.9	69.6	21.2	.348	.728	
N-back[a]				.375	.541		
Card sort							
Perseverative errors	7.03	6.09	7.21	6.33	−.139	.890	
Non-perseverative errors	9.18	9.64	9.44	8.65	−.142	.887	
Total errors	16.4	15.3	16.6	13.3	−.065	.948	
Categories	5.82	.584	5.80	.534	.139	.890	
ToL							
ToL3 ring	3.82	5.42	4.62	7.12	−.579	.564	
ToL4 ring	3.36	3.42	1.88	3.15	2.23	.028	.043
ToL5 ring	2.27	2.71	1.54	2.42	1.41	.162	
ToL total	9.42	7.50	7.89	9.04	.861	.391	
Word Recall							
Trial 1	7.42	1.73	7.69	2.15	−.633	.528	
Trial 2	10.0	1.98	9.60	2.35	.916	.362	
Trial 3	11.2	2.53	10.9	2.67	.549	.584	
Trial 4	12.1	2.25	11.8	2.43	.500	.618	
Trial 5	12.5	2.15	12.7	2.47	−.406	.686	

Total	53.3	8.58	52.8	9.84	.243	.809
Word Recall[b]				.066	.798	

a) 2 by 3 MANOVA; b) 2 by 5 MANOVA; Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

Each of the 24 prosody trials were individually analysed and the non-recurrent and recurrent groups compared using independent-sample t-tests. Table 8.4 lists the seven individual trials, with $p<.05$. The magnitude of the differences of the means, as determined by eta squared, varied from small to moderate.

Table 8.4

Individual Prosody Items Where the Recurrent Group Made Significantly More Errors than the Non-recurrent Group

Prosody matching item	Type of statement	Non-recurrent MDD n=33		Recurrent MDD n=81		$t_{(107)}$ value	p-value	Effect size eta^2
		M	*SD*	*M*	*SD*			
4	Sad	.935	.250	.795	.406	2.19	.031	.043
9	Neutral	1.00	.000	.897	.305	2.97	.004	.076
11	Sarcastic	.807	.402	.564	.499	2.65	.010	.062
12[a]	Sarcastic	.903	.301	.731	.446	2.33	.022	.048
14	Sarcastic	.968	.180	.756	.432	3.61	.000	.109
18	Sad	1.00	.000	.846	.363	3.74	.000	.116
19	Sarcastic	.968	.180	.859	.350	2.13	.036	.041

a) Item 12 is a sarcastic statement said in an angry tone; Eta^2: .01=small effect; .06=moderate effect; .14= large effect.

Prosody trials were grouped in terms of the type of statement (happy, surprised, afraid, sad, angry, neutral and sarcastic) and were compared using independent-sample t-tests. Table 8.5 shows that the recurrent group made significantly more errors than the non-recurrent group in the prosody statement types ‘sad’ ($p<.01$) and ‘sarcasm’ ($p<.01$), with both displaying moderate effect sizes.

Table 8.5

Comparison of Prosody Items Categories for Non-recurrent and Recurrent Depression

Type of statement	Items	Non-recurrent MDD n=33		Recurrent MDD n=81		$t_{(107)}$ value	p-value	Effect size eta^2
		M	*SD*	*M*	*SD*			
Happy	1, 7	1.68	.475	1.68	.546	−.018	.985	
Surprised	2, 15, 20	2.58	.620	2.65	.621	−.556	.580	
Afraid	3, 6	1.68	.475	1.65	.505	.223	.824	
Sad	4, 18, 23	2.81	.402	2.44	.731	3.37	.001	.0962
Angry	10, 12[a], 22	2.65	.661	2.47	.575	1.34	.183	
Neutral	9, 13, 16	2.81	.401	2.60	.651	1.98	.051	
Sarcastic	5, 8, 11, 12[a], 14, 17, 19, 21, 24	6.94	1.21	6.10	1.36	2.97	.004	.0760

a) Item 12 is a sarcastic statement said in an angry tone; Eta^2: .01=small effect; .06=moderate effect; .14 = large effect.

To determine whether there was a relationship between prosody statements ‘sad’ and ‘sarcastic’ and the descriptive variables ‘age’ and ‘disorder severity’, separate hierarchical multiple regressions were run, with non-recurrent/recurrent used as a dummy variable. For the dependant variable ‘sad’, after controlling for age and disorder severity, non-recurrent/recurrent significantly added to the model, *R* squared change= .038, *F* change $_{(1,103)}$ = 4.37, $p<.05$. In the final model only, non-recurrent/recurrent was statistically significant (*beta* =-.210, $p<.05$). For the dependant variable ‘sarcasm’, after controlling for age and disorder severity, non-recurrent/recurrent significantly added to the model, *R* squared change = .068, *F* change $_{(1,103)}$ = 7.67, $p<.01$. In the final model, only non-recurrent/recurrent was statistically significant (*beta* =−.280, $p<.01$).

8.5 Discussion

The current study investigated cognitive differences between young adults with non-recurrent and recurrent depression. The results of this study partially supported the hypothesis that young adults with recurrent depression would commit significantly

more errors in social cognition tests than young adults with non-recurrent depression would. There were no significant differences in the two groups in the facial affect task, but the recurrent depression group committed significantly more errors in the prosody matching task. Significant differences were found in prosody categories ‘sarcastic’ and ‘sad’.

The finding that there were no significant differences between the non-recurrent and recurrent groups in the facial affect task did not support previous results, where deficits in facial affect increased vulnerability to depression relapse or resulted in unfavourable short-term outcomes (Bouhuys et al., 1999; Geerts & Bouhuys, 1998; Hale, 1998). However, methodological differences between this study and previous studies regarding disorder severity may account for the different results. In the current study, although the recurrent group had significantly higher scores in the three disorder severity measures, as the sample was subclinical, the actual level of severity of the recurrent group was low in both SIGH-AD disorder severity measures and rated as mild to moderate in the CES-D (Radloff, 1977). In the studies of Bouhuys et al. (1999) and Hale (1998), both of which found that deficits in facial affect predicted poor depression outcomes, the mean Beck Depression Inventory scores were 26.6 (7.9) and 27.8 (7.1) respectively, indicating moderate to severe depression (Beck et al., 1988). Both studies showed a positive relationship between depression severity and deficits in facial affect. Bouhuys et al. (1999) stated that the severity of depression amplified the negative bias in the facial affect task, which was a vulnerability to depression relapse. In Hale (1998), deficits in facial affect significantly correlated with depression severity. Given that deficits in facial affect appear to be state deficits, the mild to moderate disorder severity of the depression sample in this study may account for the non-significant results.

The finding that the recurrent depression group committed significantly more errors in prosody matching tasks than the non-recurrent group has not been reported previously in the depression literature, although the concept of misunderstanding the meaning of a statement resulting in poorer depression outcomes has. The finding that the recurrent group committed significantly more errors in understanding statements where the meaning was ambiguous, due to the statements being read in a sarcastic tone, is supported by a related ToM study. Although not directly a comparison of recurrent and non-recurrent depression, Inoue, Yamada et al. (2006) found that misunderstanding the meaning in a situation (a second-order ToM task) was a risk factor in the relapse of depression for patients in remission. While Inoue, Yamada et al.'s study is the only one that links deficits in ToM to depression relapse or maintenance, other studies have found significant differences between depression and healthy control groups in the ability to understand the meaning of statements or situations (Inoue, Tonooka et al., 2004; Uekermann, Channon et al., 2008).

Deficits in prosody in the current study were most likely trait deficits due to the non-significant relationship between prosodic deficits and disorder severity. This is consistent with past studies, where participants with deficits in ToM were in remission, another indicator of a trait deficit (Inoue, Tonooka et al., 2004; Inoue, Yamada et al., 2006). The result of this current study and the results of past studies have shown that not all deficits in social cognition are due to negative bias (Bouhuys et al., 1999; Hale, 1998) but also that deficits in understanding the meaning of a statement or situation could have detrimental effects on depression outcomes.

The second finding that the recurrent group performed significantly worse than the non-recurrent group regarding 'sad' statements, partially conflicts with the findings in previous literature. While no previous studies have looked specifically at recurrent

and non-recurrent group differences in positive and negative prosodic statements, studies comparing depression and healthy control groups have found that the depression groups perform significantly worse in positive prosody but not in negative prosody (Schlipf et al., 2013; Uekermann, Abdel-Hamid et al., 2008). Uekermann, Abdel-Hamid et al. (2008) found the depression group performed significantly worse than the healthy control group regarding happy, angry, neutral and fearful prosodic statements but not in sad ones. Similarly, Schlipf et al. (2013) found the depression group performed worse regarding positive prosodic statements but there was no significant difference regarding negative statements. The only study to find significant differences between a depression group and healthy control group was Emerson et al. (1999), who in a study of males aged 9 to 11 years found the depression group was significantly worse at recognising prosodic statements in not only sad categories but also in happy, angry and neutral ones. The role of prosodic deficits in depression relapse is recommended for further study.

The effect of anxiety on egocentrism may account for why young adults with recurrent depression experience deficits in the prosodic category sarcasm. Todd, Forstmann, Burgmer, Brooks and Galinsky (2015) studied the way specific emotions influence perspective taking and found that participants with enhanced anxiety compared to enhanced anger, disgust or neutrality, showed an increased reliance on egocentric self-knowledge when trying to understand a person's mental state. Todd et al. found that the effect was mediated by uncertainty. The relationship between anxiety and poor performance on mental state tasks are backed by Hezel and McNally (2014) and Hünefeldt, Laghi, Ortu and Belardinelli (2013), who found a significant relationship between anxiety and poor performance in ToM tasks. Relating this result to this study, if the participant analysed the ambiguous statement with an increased focus on the self, that could negate perceiving the altered meaning of the statement provided by the

sarcastic tone. The recurrent group had significantly higher scores on two anxiety measures than the non-recurrent group: anxiety comorbidity and anxiety severity. However, the actual value of the anxiety severity for the recurrent group (see Table 8.1: SIGH-A = 12.5 (8.97)) was not considered severe (Hamilton, 1959).

There was also a non-significant correlation between prosody (sarcasm) and anxiety severity (see Table 8.6), which differed from the above ToM studies. The relationship between anxiety and prosody in this current study did not conclusively support or deny the theory that the ability to detect prosody was altered by an increased reliance on egocentric self-knowledge due to the effects of anxiety. Future research is needed to determine whether there is a relationship between anxiety, uncertainty, egocentrism and prosodic deficits (sarcasm).

Beck's CT may provide an explanation for how deficits in understanding the meaning of a statement may contribute to depression reoccurrence (Haaga et al., 1991). Generally, CT is associated with negative bias due to a depressed mood; however, Beck also stated that when a person with depression is faced with an ambiguous situation, they perceive a negative interpretation even though a positive one would have been better suited (Beck, 1991). For example, if Person A said, 'You don't have any friends' in a sarcastic tone to imply that Person B really *does* have friends, then a Person B with prosodic deficits (sarcasm) would infer the negative interpretation that they don't have any friends. Focusing on the negative aspects of the scenario would lead to an increased negative affect for Person B, thus perpetuating the depression (McFarland & Miller, 1994).

A second explanation regarding the way deficits in prosody could contribute to depression reoccurrence is considering whether the negative effects from the prosodic deficits lead to non-severe life events. Non-severe life events are rated *none/little* to

some in terms of long term threat and long term positivity (Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008). Several studies, including some with adolescents, have shown that non-severe life events, which are personal in nature, affect the occurrence of future depressive episodes (Hankin, Mermelstein, & Roesch, 2007; Lenze et al., 2008; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). Stress caused by prosodic deficits fits the necessary 'personal in nature' description of non-severe life events due to the act of communication between two people. What is unknown is whether deficits in prosody play a causal role in the formation of non-severe life events. This topic is recommended for future research.

While studies have shown that negative interpretations and non-severe life events lead to an increase in depressive symptoms (Hankin, 2008; Stange, Alloy, Flynn, & Abramson, 2013), whether these factors play a causal role in the initial depressive episode has been explored in several studies. Brown (1993) found that severe life events predicted both initial onset of depression and anxiety disorders in women, although non-severe life events were not part of their study's methodology. Kendler, Kessler, Neale, Heath and Eaves (1993) found in a population of people both with and without a prior history of depression that recent stressful life events were the most powerful predictor of depression. When differences between those with and without a prior history of depression were examined, Kendler et al. stated that previous predictors were still significant, implying that stressful life events were a significant predictor of an initial depressive episode. Additionally, Phelan et al. (1991), who studied the relationship between depression and domestic and occupational stress, found that stressors associated with an initial depressive episode did not differ significantly from those associated with recurrent depression. However, Stegenga et al. (2012) disagreed with both of these studies. Investigating the effect of risk factors leading to depression,

Stegenga et al. found that negative life events were a significant predictor of depression reoccurrence, but not for the first onset. The current evidence regarding whether non-severe life events are significant predictors of an initial depressive episode is mixed.

8.6 The Prosodic Uncertainty Depression Pathway (Prosodic Pathway)

This study found that young adults with recurrent depression made significantly greater errors in prosodic statements involving sarcasm than young adults with non-recurrent depression. The above discussion has suggested that anxiety, mediated by uncertainty, results in egocentric behaviour (Todd et al., 2015) that nullifies prosodic cues. It has also been suggested that these prosodic deficits would lead to negative interpretations, resulting in increased negative affect and/or non-severe life events (Beck, 1991). The increased negative affect and/or non-severe life events would then lead to the onset of a depressive episode (Hankin et al., 2007; Lenze et al., 2008; Stroud et al., 2011). Figure 8.1 shows the proposed depression pathway titled the Prosodic Uncertainty Depression Pathway (Prosodic Pathway).

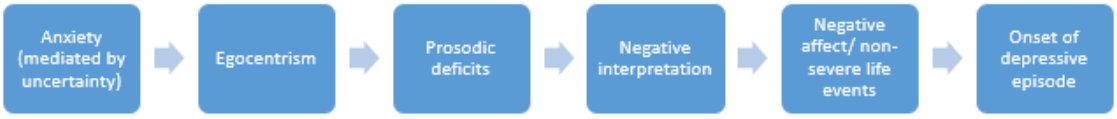

Figure 8.1. The Prosodic Uncertainty Depression Pathway

Previous literature has suggested that the pathway from a non-depressive disorder, such as anxiety, to depression is due to the persistence of the non-depressive disorder. Kessler and Walters (1998) described this persistence as a form of resignation or exhaustion, which results in depression onset. Bech (2010) agreed partially with Kessler and Walters (1998) but stated that the stress from the persistence of the non-depressive disorder was the mechanism behind depression onset. The Prosodic Pathway proposes a different mechanism between an anxiety disorder and depression onset, a progression from anxiety (mediated by uncertainty), increased egocentric behaviour,

prosodic deficits and negative interpretation, leading to increased negative affect and/or non-severe life events and onset of a depressive episode (see Figure 8.1). It is not known whether the proposed pathway is valid only for depression reoccurrence rather than onset of the initial depressive episode. The current evidence regarding the level of severity required for initial depression onset is mixed (Brown, 1993; Kendler et al., 1993; Phelan et al., 1991; Stegenga et al., 2012). The Prosodic Pathway would be a suitable model for future research.

8.7 Conclusion

This part of this study has examined whether young adults with recurrent depression committed significantly more errors in social cognitive tasks than did young adults with non-recurrent depression. The results showed no significant differences in terms of facial affect, possibly due to the low disorder severity associated with a subclinical sample. There was a significant difference in prosody deficits when the statements were spoken in a sarcastic or sad tone. Egocentric behaviour due to anxiety (mediated by uncertainty) was suggested as an explanation for the occurrence of deficits in understanding prosodic statements involving sarcasm. It was also suggested that deficits in prosody are associated with recurrent depression, as the negative interpretation of the statement results in increased negative affect or non-severe life events. The increased egocentrism and negative interpretation theories were combined to form a proposed model, entitled the Prosodic Pathway. The Prosodic Pathway explores an alternative mechanism from anxiety to comorbid depression and is recommended as a model for future research.

Chapter 9: Mathematical Ability (Study 4)

9.1 Study Context

The majority of participants for this study were students enrolled in the Introductory to Psychology I and II courses at James Cook University, Townsville and were mostly psychology, social work and exercise science students. It was noted midway through the data collection that there appeared to be a cohort of young athletic males who had not experienced depressive symptoms but did poorly on cognitive testing. While not definitive, these males were not enrolled in other psychology classes and therefore it was inferred that they might be exercise science students. It was suggested that level of mathematics might differentiate the exercise science students from others participants and this factor would be worth adding to the collected information.

Although some form of intelligence measure is recommended in cognition studies (Castaneda, Tuulio-Henriksson et al., 2008; Snyder, 2013), intelligence measures based on mathematical ability have rarely been used (see Table 4.1). As background information was part of the ethics application, questions to gather information regarding senior-year high school subject selection and grades were added to the study. For participants whose data had already been collected and had given consent to be contacted by the primary investigator, an email was sent requesting their high school subject information. While numerous studies have shown a significant positive correlation between EF and numeracy (see Cragg & Gilmore, 2014), this current study is the first to specifically examine differentiating groups by high school subjects.

The aim of this part of the study was to investigate whether the type of mathematics studied in the final year of high school was significantly related to

performance in cognitive tests. It was hypothesised that young adults in the advanced mathematics group (who had received a grade of at least B in Mathematics B, Mathematic C or Physics) would commit significantly fewer errors in EF tests (set-shifting, updating, inhibition, planning and verbal learning and memory) than young adults who were in the ordinary mathematics group (enrolled in Mathematics A).

9.2 Method

9.2.1 Participants

The sample for this part of the study consisted of 117 undergraduate students who attended James Cook University, Townsville. The participants' demographic information is provided in Table 9.1. The ordinary mathematics group (*n*=79) consisted of students who had studied Mathematics A in their senior year of secondary education. Mathematics A includes financial mathematics, applied geometry, and statistics and probability, and is suitable as a precursor for university courses with a moderate demand in mathematics (Queensland Studies Authority (QSA), 2014a). The advanced mathematics group (*n*=38) consisted of young adults who had achieved a score of at least a B (high achievement) in Mathematics B, Mathematics C, or Physics in their senior year of secondary education. Mathematics B includes units on rates of change, exponential and logarithmic functions, integration, applied statistical analysis and optimisation (QSA, 2014b), while Mathematics C includes units on real and complex number systems, matrices, vectors and calculus. Students study Mathematics B and/or Mathematics C as preparation for tertiary subjects with a high degree of mathematics, such as areas of finance, business, engineering, sciences, medicine, information technology and economics (QSA, 2014c).

9.2.2 Materials

Neuropsychological assessment consisted of cognition tests: Card Sort, ToL, N-back, the Stroop Test, Verbal Recall and Social Cognition. Classification tests included SIGH-AD, CES-D. MINI PLUS, psychiatric and medical questionnaires, and intelligence measure WTAR. High school subject information was also collected. For further information see Section 6.2.2.

9.2.3 Procedure

Participants initially undertook the six cognitive tasks: Card Sort, ToL, Verbal Recall, N-back, Social Cognition and the Stroop Test in a counterbalanced order. Participants then completed a series of structured or self-assessed classification tests: SIGH-AD, MINI PLUS, psychiatric and medical questionnaires, CES-D, education information and the WTAR. For further information see 6.2.3.

9.3 Statistical analysis

9.3.1 Exclusion including outliers.

In the original Study 1 thirteen participants who were classified according to the MINI PLUS with post-traumatic stress disorder were excluded from the study. Thirteen other participants were classified as outliers who committed 40 or greater non-perseverative errors. For further information see Section 6.3.1. For Study 4, only participants who were able to provide senior-year high school subject selection and grades were included from the Study 1 sample.

9.3.2 Statistical tests.

Means and standard deviations of descriptive variables and cognition scores were calculated and reported. Other data including gender was presented in percentages of the sample. Chi-square test for independence was used to calculate whether there were significant differences between percentages in groups. Independent-sample t-tests

were used to compare a categorical variable with two levels, such as ‘education group’ (e.g., ordinary mathematics, advanced mathematics) with a continuous variable (e.g., cognition score). MANOVA’s were employed if the cognitive test had more than one level, such as the three N-back tests or the five Word Recall tests. To control for covariate a hierarchical multiple regression was run. The groups being compared (e.g., ordinary mathematics, advanced mathematics) were coded as a dummy variable. In the hierarchical regression, the covariate was entered in the first block and the dummy variable entered in the second block, thereby statistically controlling for the covariate. For more in-depth information on statistical tests see Section 6.3.2.

9.4 Results

Independent-sample t-tests were conducted to compare the descriptive variables of the ordinary mathematics and advanced mathematics groups. Means, standard deviations, t values, significance values and effect sizes are shown in Table 9.1. When compared to the advanced mathematics group, the ordinary mathematics group had significantly greater depression severity, CES-D score and depressive episodes ($p<.05$). For these variables, the magnitude of the differences were small (eta squared <.06).

Table 9.1

Descriptive Statistics Comparing Young Adults Who Had Studied Ordinary Mathematics Compared to Those Who Had Studied Advanced Mathematics

Sociodemographic and clinical variables	Ordinary mathematics (*n*=79)		Advanced mathematics (*n*=38)		$t_{(117)}$ value	p-value	Effect size eta^2
	M	*SD*	*M*	*SD*			
Gender % female[a]	72.2		73.7		.000[b]	1.00	
Age	20.2	3.60	20.0	2.95	.264	.778	
WTAR	38.6	5.26	40.7	5.67	-1.94	.055	
Severity measures							
Depression severity	6.97	7.22	3.74	6.47	2.35	.021	.0457
Anxiety severity	9.20	9.19	5.74	8.50	1.96	.053	
CES-D	18.0	11.7	12.3	12.6	2.41	.017	.0483
Number of depressive episodes	4.18	5.10	2.37	3.15	2.01	.047	.0339

a) 2 by2 chi-square test used; b) Yates continuity correction; Eta^2: .01=small effect; .06=moderate effect; .14 = large effect.

Table 9.2 shows the chi-square tests for independence for the relevant sociodemographic and clinical variables, comparing young adults in the ordinary mathematics and advanced mathematics groups. A higher proportion of young adults who had studied ordinary mathematics met the classification for a MDE (p<.001). This means that the advanced mathematics group had a higher proportion of young adults who were in either the healthy control group or the anxiety only group.

Table 9.2

Group Percentages for Relevant Depression Variables for Ordinary Mathematics and Advanced Mathematics

Sociodemographic and clinical variables	Ordinary mathematics (*n*=79)	Advanced mathematics(*n*=38)	Yates continuity correction	p-value	Effect size phi coeff.
MDE %	81.3	47.4	12.3	.000	−.35
Family psychiatric history %					
MDD only	51.9	40.5	.887	.346	
MDD, BPD, or schizophrenia	63.3	51.4	1.04	.309	
Suicide attempt %	21.5	10.8	1.29	.255	

Phi: .1 = small effect; .30 = medium effect; .50 = large effect.

Independent-sample t-tests were conducted to compare cognition scores for the ordinary mathematics and advanced mathematics groups. The means and standard deviations, *t* statistic, significance levels and effect sizes are shown in Table 9.3. In the Card Sort test, the ordinary mathematics group had significantly more perseverative errors ($p<.05$), non-perseverative errors ($p<.01$) and total errors ($p<.01$) and completed significantly fewer categories ($p<.05$) than the advanced mathematics group. The magnitude of differences for non-perseverative errors and total errors was moderate, while differences for perseverative errors and categories were small. In the Word Recall test, the ordinary mathematics group remembered significantly fewer words than the advanced mathematics group in Trial 1 ($p<.001$), Trial 3 ($p<.05$) and overall ($p<.05$). A 2 by 5 MANOVA showed that the ordinary mathematics group performed significantly worse overall in the Word Recall task than the advanced mathematics group ($p<.05$). The magnitude of differences between the two groups in the Word Recall task was moderate for Trial 1 and small for Trial 3 and overall.

Table 9.3

Cognitive Difference between the Ordinary Mathematics Group and the Advanced Mathematics Group

Neuropsychological domains	Ordinary mathematics (*n* = 79)		Advanced mathematics (*n* = 38)		*t* (117) value	*p*-value	Effect size eta^2
	M	*SD*	*M*	*SD*			
Social cognition							
Affect naming	19.0	2.19	19.5	2.54	−.953	.343	
Prosody face matching	9.30	17.6	9.55	1.35	−.768	.444	
Prosody pair matching	9.82	1.30	10.1	1.17	−1.03	.305	
Social perception pairs	34.1	3.58	35.6	3.91	−2.15	.033	.0386
Social perception	38.1	3.52	3.9.1	3.32	−1.38	.171	
Social perception prosody	19.1	2.44	19.6	1.82	−1.13	.259	
The Stroop Test							
Stroop (Golden)	−5.52	3.76	−6.27	3.64	1.02	.309	
Stroop A	11.5	2.28	11.4	2.18	.313	.755	
Stroop B	12.4	2.17	12.9	3.15	−.883	.379	
Stroop C	18.5	4.82	18.0	5.92	.438	.663	
N-back							
N-back: 1-back % accuracy	84.6	20.3	89.2	18.2	−1.17	.247	
N-back: 2-back % accuracy	80.8	22.9	82.4	20.5	−.376	.708	
N-back: 3-back % accuracy	68.5	22.6	73.2	22.6	−1.06	.289	
N-back[a]					.878	.351	
Card sort							
Perseverative errors	8.54	7.53	5.32	5.14	2.39	.019	.0473
Non-perseverative errors	12.0	9.89	6.55	7.95	3.21	.002	.0822
Total errors	20.3	15.4	11.7	11.2	3.44	.001	.0933
Categories	5.66	.766	5.92	.487	−2.25	.027	.0422
ToL							
ToL3 ring	4.27	6.63	3.53	5.43	.597	.551	
ToL4 ring	2.78	3.90	2.11	3.39	.920	.359	
ToL5 ring	1.87	2.73	1.05	1.52	1.73	.040	.025
ToL total	8.92	9.59	6.68	7.25	1.28	.205	
Word Recall							
Trial 1	7.15	1.70	8.50	2.25	−3.61	.000	.10

Trial 2	9.51	2.07	10.4	2.72	−1.84	.072	
Trial 3	10.4	2.48	11.7	2.66	−2.50	.014	.052
Trial 4	11.5	2.71	12.2	2.70	−1.30	.197	
Trial 5	12.3	2.49	12.8	2.30	−1.18	.242	
Total	51.0	9.23	56.0	10.6	−2.64	.010	.057
Word Recall[b]					6.17	.014	.051[c]

a) 2 by 3 MANOVA; b) 2 by 5 MANOVA; c) Partial eta squared; Eta^2: .01=small effect; .06=moderate effect; .14 = large effect.

To determine whether there was a relationship between significant cognitive variables (perseverative errors, non-perseverative errors, total errors, categories, Word Recall Trial 1, 3 and Total) (see Table 9.3) and descriptive variables (depression severity, CES-D, number of depressive episodes and depression Y/N) (see Table 9.1), separate hierarchical multiple regressions were run, with ordinary mathematics/ advanced mathematics used as a dummy variable. Table 9.4 shows that the type of mathematical group was a significant predictor of each of the dependant variables when controlling for the influence of descriptive variables.

Table 9.4

Change in R Square and F after Controlling for Descriptive Variables

Dependant variable	*R* square change	$F_{(1, 107)}$ change	*p-value*	*Beta*	*p-value*
Perseverative errors	.069	8.20	.005	-.283	.005
Non-perseverative errors	.068	7.97	.006	-.280	.006
Total errors	.087	10.3	.002	-.316	.002
Categories	.046	5.20	.025	.230	.025
Word Recall Trial 1	.109	13.8	.000	.354	.000
Word Recall Trial 3	.055	6.30	.014	.252	.014
Word Recall Trial total	.070	8.18	.005	.284	.005

9.5 Discussion

The hypothesis that students who had achieved a grade of at least B in either advanced mathematics or physics (advanced mathematics group) in their senior year of high school would perform better on tests of EF was partially supported, with this group

making significantly fewer errors in the set-shifting task (Card Sort) and remembering more words in the verbal learning and memory task (Word Recall) than the ordinary mathematics group. There was no significant difference between the two groups in updating, inhibition and planning. There was also no significant difference in the two mathematical groups in the literary-based intelligence measure WTAR. Note that although the ordinary mathematics group had significantly higher depression descriptive measures, such as disorder severity and participants with a diagnosis of MDE, none of the descriptive measures had a significant influence on the EF measures (see Table 9.4).

As this was the first study in which participants have been divided according to whether they had studied advanced or ordinary mathematics in high school, there was no previous research with which to compare these results. However, studies that have investigated the relationship between mathematics and EF were reviewed. The finding in this study regarding set-shifting was found to be supported by previous research, which has shown that intelligence is a significant factor in set-shifting for children and adolescents. Improved set-shifting performance has been demonstrated in adolescents with a higher level of education (Rhodes, 2004), as well as in studies comparing the performance of gifted and high-IQ participants (Arffa et al., 1998) and gifted and normal-IQ participants (Arffa, 2007). Performance in set-shifting has also been positively correlated with intelligence measures in past cognition studies (Ilonen et al., 2000; Koren et al., 1998; Merriam et al., 1999).

In this current study, the advanced mathematics group remembered significantly more words in the verbal learning and memory task (Word Recall) than the ordinary mathematics group. This result was supported by similar past research that had found that high IQ predicted better performance on this task (Arffa, 2007). In the current study, the advanced mathematics group performed better than the ordinary mathematics

group in Trials 1 and 3 and Total Trials, with Trial 1 showing the greatest effect size (see Table 9.3). In depression studies in which the depression group has remembered fewer words than the healthy control group, the differences have occurred typically in Trials 4 and 5 (Bearden et al., 2006; Smith et al., 2006), which demonstrated that the healthy control group continued to improve as the trials progressed, while the depressed participants plateaued. However, this result was not found in this current study. Participant feedback from those in the advanced mathematics group suggested that visualisation and themes were used to aid the encoding and recall process. Therefore, given the lack of significant differences in Trials 2, 4 and 5 and only a small effect size in Trial 3, the improved performance in the Word Recall task was most likely due to the advanced mathematics group employing better memory strategies.

The interchangeable role of mathematical ability and EF should be further investigated in terms of whether it contributes to depressive symptoms or the onset of depression. While there is no evidence linking mathematical ability or EF as a causal factor in depression, the superior performance of the advanced mathematics group in the set-shifting and verbal learning and memory tasks highlights this as an area of interest. EF skills are not only associated with mathematical ability (Cragg & Gilmore, 2014) but also play a role in learning new mathematical material (Swanson, 2011; Van der Ven, Kroesbergen, Boom, & Leseman, 2012). Additionally, EF skills, especially problem solving and flexible thinking, aid in unexpected or novel situations, in which past experience may not serve as a guide (Cragg & Gilmore, 2014). Therefore, EF skills enabling a person to deal with new or novel situations could buffer an individual against future stressors that could contribute to depression onset. Adding measures of EF, such as set-shifting and verbal learning and memory, to a longitudinal study investigating initial depressive episode onset would be recommended for future research.

9.6 Conclusion

Studies of depression and cognition have measured intelligence to ensure that comparison groups are matched. Intelligence measures have tended to be literacy based rather than numeracy based. This study found that mathematical group and not a literacy-based intelligence measure (WTAR) predicted superior cognitive performance in set-shifting and verbal learning and memory. This study argued that owing to the nature of skills tested in depression studies, namely EF, that the inclusion of a numeracy-based intelligence measure could benefit the study, such as WAIS subtests Perceptual Reasoning (block design, matrix reasoning) and Working Memory (digit span, arithmetic). The inclusion of a mathematical intelligence test would allow those with very limited mathematical ability, which may be a confounding variable, to be omitted as outliers.

Chapter 10: GABA and Cognition (Study 5)

10.1 Study Context

Originally, there was a cognitive training aspect to this thesis, in which young adults who demonstrated deficits in EF would undergo either cognitive training based on cognitive flexibility (experimental group) or on attention (control/waitlist group). However, because of the high time demands of the training, this training was abandoned and replaced with a biological investigation. Plasma GABA concentration was chosen for investigation, as it is considered a biological marker for depression (Petty, Kramer, Fulton et al., 1995; Sanacora, Gueorguieva et al., 2004). The original idea was to explore whether there was a relationship between plasma GABA (probable biological marker) and EF (possible cognitive marker), especially for subgroups such as primary depression, which is linked with lower plasma GABA concentration (Petty, Kramer & Feldman, 1987).

The aim of this study was to identify any significant relationships between plasma GABA concentration and cognition. Subgroups such as primary depression and ordinary mathematics were also examined. Ordinary mathematics was chosen as a subgroup owing its demonstrated negative relationship with EF (see Section 9.4), which is similar to that for primary depression. As this element of the thesis was exploratory in nature and the first to examine plasma GABA concentration and cognition, no data-driven hypotheses were specified.

10.2 Method

10.2.1 Participants

The sample for this part of the study consisted of 53 participants (M = 21.49 years of age; SD = 3.95) who were part of a Study 1. Thirty-eight participants designated *current* gave a blood sample within two weeks of completing the cognitive

test battery. Fifteen participants designated *past* had completed the cognitive tests within two years previously. The demographics of the participants are presented in Tables 10.1 and 10.2.

Table 10.1

Demographic Characteristics of Young Adults Who Gave a Blood Sample

Sociodemographic and clinical variables	Current n=38		Past n=15	
	M	*SD*	*M*	*SD*
Gender % female	71		67	
Age	21.5	3.75	21.5	4.53
WTAR	38.7	6.67	41.73	4.17
Severity measures				
Depression severity	9.11	7.08	9.33	9.52
Anxiety severity	12.7	8.69	12.0	12.5
CES-D	21.9	13.1	21.1	15.7

Table 10.2 shows the proportion of comorbid depression and healthy control participants in each subsample.

Table 10.2

Percentage of Disorder Subgroups for Both Current and Past Groups

Sociodemographic and clinical variables	Current n=38	Past n=15
Comorbid %		
MDD only	23.7	13.3
MDD & dysthymia	21.1	26.7
MDD & anxiety	52.6	53.3
Healthy control participant	13.2	6.7

Note: Percentages do not add to 100% as a person can have dysthymia and anxiety.

10.2.2 Materials

10.2.2.1 Cognitive testing

Neuropsychological assessment consisted of cognition tests: Card Sort, ToL, N-back, the Stroop Test, Verbal Recall and Social Cognition. Classification tests included

SIGH-AD, CES-D. MINI PLUS, psychiatric and medical questionnaires, and intelligence measure WTAR. High school subject information was also collected. For further information see Section 6.2.2.

10.2.2.2 Blood sample

The blood samples were collected in both gel and heparinised tubes and spun in a centrifuge. A pipette was used to remove the plasma, which was then stored in an industrial freezer at −70°C. Plasma GABA concentration was measured by an enzyme-linked immunosorbent assay, using a commercially available kit and following the manufacturer's instructions (USCN, 2011).

10.2.3 Procedure

10.2.3.1 Cognitive testing

Participants initially undertook the six cognitive tasks: Card Sort, ToL, Verbal Recall, N-back, Social Cognition and the Stroop Test in a counterbalanced order. Participants then completed a series of structured or self-assessed classification tests: SIGH-AD, MINI PLUS, psychiatric and medical questionnaires, CES-D, education information and the WTAR. For further information see 6.2.3.

10.2.3.2 Blood sample

A blood sample was taken from the veins in the antecubital fossa and collected into either gel or heparinised tubes. The blood was stood for 20 minutes and then centrifuged at 2700 rpm for 10 minutes. The plasma and serum were pipetted into containers and stored in an industrial freezer at −70°C. The appropriate conditions for the assay were determined by sample titration and by testing several incubation times for the tetramethylbenzidine reagent. For one hour before addition of the detection antibody, 25 µL plasma/serum was pre-incubated in the plate and addition of the

tetramethylbenzidine was then staggered every 15 seconds, to enable accurate 3.5-minute incubations in each well.

10.3 Statistical analysis

10.3.1 Exclusion including outliers.

As depression was not the main focus, the participants with past post-traumatic stress disorder were not excluded. There were no EF outliers.

10.3.2 Statistical tests.

Means and standard deviations of descriptive variables and cognition scores were calculated and reported. Other data including gender and disorder subgroups was presented in percentages of the sample. To compare two continuous variables (e.g., plasma GABA concentration and cognition scores), the Pearson correlation coefficient (r) was used. For more in-depth information on statistical tests see Section 6.3.2.

10.4 Results

10.4.1 Current and past data combined

The relationship between plasma GABA concentration and cognition was investigated using Pearson correlations (see Table 10.3). Four data sets were analysed: (1) total data, (2) subset primary depression, (3) subset ordinary mathematics and (4) combined subsets primary depression and ordinary mathematics. For the total data set, there was a medium positive correlation between GABA concentration and Stroop B ($p < .01$). There were no other significant correlations between GABA and cognition ($p > .05$). For primary depression, there was a medium positive correlation between plasma GABA concentration and 2-back and Word Recall Trial 4 ($p < .05$). For the subset ordinary mathematics, there was a medium positive correlation between plasma GABA concentration and 2-back, Word Recall Trials 4 and 5 and Total Trials ($p < .05$). Combining both subsets (n = 31), there was a medium positive correlation between

plasma GABA concentration and 1-back, 2-back (p<.05), Word Recall Trial 4 (p < .01), Trial 5 and Total Trials (p < .05). Table 10.3 shows the detailed results.

Table 10.3

Correlations between Plasma GABA Concentration and Cognitive Measures for Combined Current and Past Data

Combined current and past	r correlation coefficient			
Neuropsychological domains	Total data set n = 53	Primary depression n = 21	Ordinary maths n = 23	Subgroups combined n = 31
Social cognition				
Affect naming	.158	.373	.072	.133
Prosody face matching	−.014	−.057	−.219	−.134
Prosody pair matching	.015	−.060	−.161	−.066
Social perception pairs	.173	.227	.156	.217
Social perception	.102	.132	−.104	−.002
Social perception prosody	−.002	−.062	−.222	−.117
Stroop				
Golden Stroop	−.105	.149	−.007	.044
Stroop A	.237	.123	.182	.110
Stroop B	.446**	.422	.354	.319
Stroop C	.246	.489*	.286	.279
N-back				
N-back: 1-back % accuracy	.127	.379	.349	.371*
N-back: 2-back % accuracy	.186	.482*	.416*	.403*
N-back: 3-back % accuracy	.210	.329	.327	.328
Card sort				
Perseverative errors	.131	.133	.290	.214
Non-perseverative errors	−.045	−.202	.207	.051
Total errors	.008	−.103	.270	.118
Categories	.042	.178	−.213	−.049
ToL				
ToL3 ring	.019	.002	.055	−.016
ToL4 ring	.163	.155	.209	.153
ToL5 ring	.109	.014	.111	.022
ToL total	.110	.056	.126	.031
Word Recall				
Trial 1	.037	.393	.317	.315

Trial 2	.030	.321	.162	.227
Trial 3	−.078	.160	.143	.199
Trial 4	.171	.494*	.476*	.484**
Trial 5	.233	.413	.455*	.448*
Total	.098	.432	.436*	.438*

* $p<.05$, ** $p<.001$ (two tailed).

10.4.2 Current data only

Correlation results for *current* data only is shown in Table 10.4. Similar to *combined current and past* data (see Table 10.3), for *current* data (n = 38) there was a medium positive correlation between plasma GABA and Stroop B ($p < .01$), as well as Stroop C ($p < .05$). For the *current* combined subsets of primary depression and ordinary mathematics data, there was a medium positive correlation between plasma GABA concentration and Word Recall Trial 4 and Total Trials ($p<.05$).

Table 10.4

Correlations between Plasma GABA Concentration and Cognitive Measures for Current Data Only

Current only	r correlation coefficient	
	Total data set n = 38	Subgroups combined n = 23
Neuropsychological domains		
Social cognition		
Affect naming	.373*	.301
Prosody face matching	.054	−.052
Prosody pair matching	.034	−.033
Social perception pairs	.292	.293
Social perception	.251	.125
Social perception prosody	.052	−.049
Stroop		
Golden Stroop	−.122	−.051
Stroop A	.315	.200
Stroop B	.485**	.368
Stroop C	.356*	.330
N-back		
N-back: 1-back % accuracy	.185	.396[a]

N-back: 2-back % accuracy	.254	.381[b]
N-back: 3-back % accuracy	.260	.331
Card sort		
Perseverative errors	.054	.177
Non-perseverative errors	−.098	.072
Total errors	−.057	.119
Categories	.122	−.008
ToL		
ToL3 ring	−.043	−.043
ToL4 ring	.182	.206
ToL5 ring	.184	−.048
ToL total	.088	.010
Word Recall		
Trial 1	.116	.363
Trial 2	.025	.245
Trial 3	−.080	.127
Trial 4	.198	.464*
Trial 5	.189	.397[c]
Total	.104	.438*

* $p<.05$, ** $p<.001$ (two tailed); a) $p=.061$, b) $p=.073$, c) $p=.061$.

10.5 Discussion

This part of the thesis investigated the relationships between plasma GABA concentration and cognition. Although no specific hypotheses were specified, significant correlations were found for the overall data set and for the subgroups primary depression and ordinary mathematics.

10.5.1 Overall data set

For the *current and past* data set, there was a significant medium positive correlation between plasma GABA concentration and Stroop B. Similarly, for the *current* data set, there was a medium positive correlation with Stroop B and Stroop C. Both tasks, Stroop A and Stroop B, were similar and involved naming the colour of the stimuli as fast as possible, with the stimuli for Stroop A being coloured dots and for Stroop B, congruent words. For Stroop A there was a small positive correlation for the

current and past data set and a positive medium correlation for the *current* data set; however, these results were not significant. Looking at the Stroop B results, given that lower plasma GABA concentration equated to faster completion time for the task, perhaps this relationship was, in fact, indicative of a measure of psychometric speed. This disagrees with past research that has linked low plasma GABA concentration to psychomotor retardation in males (Petty, Kramer, Gullion et al., 1992). However, whether this result actually indicates a relationship with GABA and inhibition can be questioned because of the lack of relationship with Stroop A and the overall measure Golden Stroop. Also of note is that the significant effect disappears with both subgroups. Therefore, the most likely explanation for the relationship between plasma GABA concentration and inhibition is that it was a statistical anomaly.

10.5.2 Subtypes: Primary depression and ordinary mathematics

For the discussion for the subgroups primary depression and ordinary mathematics, the combined *current and past* data set is mostly used (see Section 10.5.3 for the discussion regarding the *current* data set). For the subgroup primary depression, there was a significant medium positive correlation between plasma GABA concentration and 2-back (updating) and Word Recall Trial 4 (verbal learning and memory). For the subgroup ordinary mathematics, the result was similar, with plasma GABA concentration showing a significant medium positive correlation with 2-back and Word Recall Trials 4 and 5 and Total Trials. The similarity of the two subgroups was not unexpected, as 57% (13 out of 23) of the young adults in the ordinary mathematics subgroup were also in the primary depression subgroup. While not all trials in the N-back and Word Recall tasks were significant, this did not detract from the result and could be explained by using previous studies. For the N-back task, the 2-back maybe the best measure of updating, with the 1-back a simpler task and the 3-back a

very difficult task (see Section 6.2.2.1.3). Studies such as Fitzgerald et al. (2008), who conducted an fMRI study, used only the 2-back as a measure of updating (for meta-analysis, see Owen et al., 2005). Regarding the Word Recall task, the pattern whereby deficits were significant only in the latter trials is evident in the literature (Bearden et al., 2006; Smith et al., 2006) where differences occurred in the later trials as the healthy control group continued to improve while the depression group plateaued.

Significant correlations between plasma GABA concentration and the N-back and Word Recall tasks may reflect a relationship with working memory capacity. The N-back task is a commonly used measure of working memory capacity (Owen et al., 2005), while the Word Recall task significantly correlates with another working memory measure, backward digit span (Khosravi Fard et al., 2016). Set-shifting and inhibition, which were not significant in this current study, have been shown in other studies to have significant relationships with working memory capacity (Lehto, 1996; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Vogel, McCollough, & Machizawa, 2005). The lack of significant results in this study with set-shifting and inhibition may simply reflect that working memory capacity plays a more pivotal role in updating (N-back) and verbal learning and memory (Word Recall) than either set-shifting or inhibition.

10.5.3 Comparison of current versus current and past data sets

The biological component of this thesis was only added towards the end of the data collection period. Participants who had completed the cognitive aspects previously were invited to provide a blood sample. The collection of *past* data were included, as plasma GABA concentration levels have been found to be relatively stable over long periods (Petty Kramer, Fulton et al., 1995; Petty, Steinberg et al., 1993), with the exception for people taking SSRI medications (Kucukibrahimoglu et al., 2009;

Sanacora, Mason, Rothman & Krystal, 2002). Of the 15 participants who had completed the cognitive tests previously, only two were taking antidepressant medication currently and one other had taken medication in the past.

Regarding the differences in results for the combined subgroups in comparing *current* versus the *current and past* data sets, visual comparisons can be noted between Table 10.3 and Table 10.4. In Table 10.4 *current* data set, 1-back and 2 back are not significant (in comparison to Table 10.3, where they are); however, note that the change in *r* from the complete data set to that in the combined subgroups. For both the *current* and *current and past* data sets *r* increases from a small to medium strength correlation. Comparisons for the Word Recall task show that both the *current* and the *current and past* data sets showed significant correlations for Word Recall Trial 4 and Total Trials. Word Recall Trial 5 for the *current* data set was also approaching significance (p=.061), with a similar increase in *r*. In conclusion, the results observed in the *current* data set were comparable to the results for the *current and past* data set, providing no reason to discount the *past* data set.

10.5.4 Examining the dual nature (state and trait) of EF deficits

The significant relationship between plasma GABA concentration and verbal learning and memory and updating, may explain the dual nature of EF deficits in terms of categorising them as state and trait deficits (see Section 1.4). Cognitive deficits are generally regarded either as state deficits, which vary with disorder severity, or as trait deficits, which do not.

Verbal learning and memory demonstrated state-like qualities owing to its significant relationship with disorder severity (Porter et al., 2003). However, in other studies, deficits in verbal learning and memory have shown trait-like qualities, such as remaining beyond clinical recovery (Neu et al., 2005; Preiss et al., 2009; Smith et al.,

2006) or in familial studies (Mannie, Harmer et al., 2009). Similarly, updating has demonstrated a significant relationship with disorder severity factors (state deficit) (Harvey et al., 2004), although evidence of trait-like qualities is less clear. In a familial study, Mannie, Harmer et al. (2009) showed no significant difference between the familial and healthy control groups in the updating task. However, the familial group showed over-activation of brain areas that support working memory compared to the control group, which could demonstrate a trait vulnerability marker for depression.

Trait-like properties of both verbal learning and memory and updating, could be explained by altered brain function due to cellular changes (see Section 1.5), as indicated in this study through reduced plasma GABA concentration. Therefore, the trait-like properties of verbal learning and memory and updating could be explained by a biological basis, while the effects of depression severity would still be responsible for state-like properties. The results from the above study were then applied to propose a new Executive Function Depression Pathway, as described in the next section.

10.5.5 Executive Function Depression Pathway (EF Pathway)

The proposed EF Pathway encapsulates developmental or environmental deficiencies, biological abnormalities in the PFC and cognitive deficits leading to decreased problem-solving and flexible thinking skills, resulting in negative life events that lead to depression onset (see Figure 10.1). Rajkowska, Miguel-Hidalgo et al.'s (1999) histopathological analysis comparing the brain tissue of post mortem depression patients and healthy matched tissue found brain abnormalities in the dlPFC and OFC, including differences in neuronal size, cortical thickness and glial density. According to Rajkowska, Miguel-Hidalgo et al., the reduction in glial density, for example, could result in altered metabolism (performance) of those areas (see Section 1.5 for more details). Blood activation studies have shown that the dlPFC and OFC are pivotal to EF

(Birrell & Brown, 2000; Buckley et al., 2009; Killgore et al., 2007; Owen et al., 2000; Wagner et al., 2006) and therefore, altered metabolism in these areas could contribute to EF deficits. However, no studies have made this link directly.

Biological changes in the PFC have been suggested to be due to developmental or environmental factors rather than the course of depression (Rajkowska, Miguel-Hidalgo et al., 1999; Sheridan & McLaughlin, 2014). This has been demonstrated in animal studies where developmental deficiencies in the form of early adverse life events, result in EF deficits and cellular changes in brain areas that are key to EF (Baarendse et al., 2013; Fone & Porkess, 2008; Makinodan et al., 2012; Stamatakis et al., 2016) However while cellular changes in the above animal studies correspond to brain areas associated with the human dlPFC and OFC whether the PFC of rats and mice can be generalised to the human PFC is debatable (Uylings et al., 2003). Developmental or environmental deficiencies leading to cellular changes and EF deficits forms the initial stages of the EF Pathway (see Figure 10.1).

To observe a possible link between biological abnormalities and cognition, a relevant subgroup such as primary depression was required. As shown in Study 5 of this research (see Table 10.3), a significant correlation between GABA and working memory (N-back, Word Recall) occurred only in the subgroups primary depression and ordinary mathematics. A rationale for this result is firstly explored in terms of the subgroup primary depression.

Primary depression, depression onset not due to a non-depressive disorder or medical condition, has already demonstrated some form of biological basis with a relationship with low plasma GABA concentration. Petty, Kramer and Feldman (1987) showed that participants with primary depression had significantly lower plasma GABA concentration than the healthy control group or those with secondary depression. As

glial cells affect the uptake of glutamate, which is a precursor to GABA (Öngür et al., 1998), low GABA concentration may simply be an indicator of cellular changes such as reduced glial density in the PFC. If low GABA concentration is an indicator of cellular changes in the PFC then corresponding EF deficits should be evident.

The results of the current study were partially consistent with this. For the primary depression subgroup, there was a significant medium positive correlation for plasma GABA concentration and EF tests 2-back (updating) and Word Recall Trial 4 (verbal learning and memory). In addition, note there is an increase in Table 10.3 in *r* for Word Recall Trial 5 for the primary depression subgroup. As explained in the above discussion (see Section 10.5.2), 2-back and Word Recall Trials 4 and 5 are adequate measures of updating and verbal learning and memory, and both these EF function measures have a significant working memory component.

The relationship between low GABA concentration and poor performance in the updating and verbal learning and memory tasks was also evident in the ordinary mathematics subgroup (see Table 10.3). Due to the overlap in participants in the two subgroups, this result was not unexpected. In Study 5, the results showed that for the ordinary mathematics subgroup, plasma GABA concentration significantly correlated with 2-back, Word Recall Trials 4 and 5, and Total Trials. Whether young adults who study ordinary mathematics is an indicator of higher probability of cellular abnormalities in the PFC, reflected in lower mathematical ability, can be considered for future investigations.

The above results for the subgroups primary depression and ordinary mathematics indicate a link between a biological measure, plasma GABA concentration, and EF. Equating low concentration of plasma GABA to cellular deficits is speculative even though there is a literary basis (Gos et al., 2009; Karolewicz et al., 2010; Öngür et

al., 1998; Rajkowska, O'Dwyer et al., 2007). This demonstrates one of the hurdles with investigating the relationship between cognition and human PFC cellular abnormalities as past cellular studies are restricted to post mortem brain tissue. Measuring brain activity using non-evasive techniques such as an electroencephalogram (EEG) or fMRI may provide a stronger link in the relationship between GABA, cellular abnormalities and cognition (See Section 11.9.2.1).

The final stages of the EF Pathway state that deficits in EF, which essentially aid in successfully navigating new and unforeseen challenges, result in negative outcomes, that could include stressful or negative life events, which have been demonstrated to contribute to depression onset (Brown, 1993; Kendler et al., 1993; Phelan et al., 1991). Life events also play a role in depression onset in the Prosodic Pathway (see Figure 8.1), except it is assumed that the life events would be non-severe. There are mixed results regarding whether non-severe life events could result in the onset of an initial depressive episode, rather than only in depression reoccurrence (Brown, 1993; Kendler et al., 1993; Phelan et al., 1991; Stegenga et al., 2012). However, this argument does not apply for the EF Pathway, because life events resulting from an inability to successfully navigate unforeseen challenges could be severe.

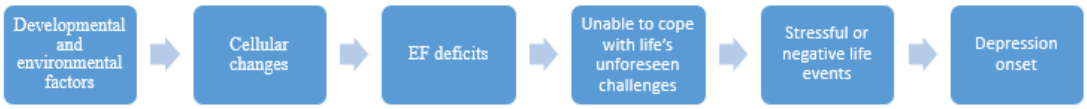

Figure 10.1. Executive Function Depression Pathway

In summary, the EF Pathway extends the proposed biological basis for EF deficits model (see Figure 6.1) by suggesting that EF deficits lead to difficulties in coping with unforeseen challenges, result in stressful or negative life events, leading to depression onset (Kendler et al., 1993; Phelan et al., 1991). Both the subgroups primary depression and ordinary mathematics demonstrated a significant relationship between

plasma GABA concentration and working memory, demonstrating a possible link between cellular abnormalities and cognitive deficits. The EF Pathway forms a model for future research.

10.6 Conclusion

This study has examined the relationship between plasma GABA concentration and cognition. It has found that for subgroups primary depression and ordinary mathematics, plasma GABA concentration significantly correlated with updating and verbal learning and memory. It was suggested that this result represents a relationship between plasma GABA concentration and working memory capacity. The significant result highlighted the importance of recognising subgroups relevant to the 'pathway' of the depression that is being researched. It was also suggested a biological basis for cognitive deficits, indicated by low plasma GABA concentration, provides an explanation for the trait-like properties of cognitive deficits such as verbal learning and memory. The EF Pathway was proposed, postulating that suboptimal developmental and environmental factors can lead to cellular changes and corresponding EF deficits. It was further proposed that these EF deficits would negatively affect skills such as problem-solving and flexible thinking, resulting in stressful or negative life events, which could lead to depression onset. The EF Pathway is suggested as a model for future research.

Chapter 11: Conclusion

This chapter summarises the main aims and findings of this thesis. It includes comments regarding the new depression pathways and research limitations, as well as an outline for future research. The aim of this thesis was to explore the cognitive deficits associated with young adults with depression and anxiety disorders. Previous literature, mostly conducted with young to middle-aged adults, had demonstrated that cognitive deficits in the domains of EF are especially relevant to this field (Castaneda, Tuulio-Henriksson et al., 2008; Snyder, 2013). The sample for the current research was subclinical and the majority of participants were recruited from first- and second-year university psychology classes.

11.1 Study 1: Depression and Anxiety in Young Adults

Study 1 (Chapter 6) first compared young adults with mild to moderate depression to a healthy control group. The aim was to identify cognitive deficits between the two groups. However, the results showed no significant differences. Results from previous literature had been mixed, with several studies also finding no significant differences in cognition between depression and healthy control groups (Castaneda, Suvisaari et al., 2008; Fossati et al., 1999; Hill et al., 2004), or finding only moderate differences in some forms of EF and no significant differences in others (Grant et al., 2001). The use of a subclinical sample, with its low to moderate depression severity, could have accounted for the non-significant results in cognitive tasks associated with state deficits, such as verbal learning and memory (Grant et al., 2001; Porter et al., 2003). However, the use of a subclinical sample did not explain the non-significant differences in EF domains applicable to trait deficits such as set-shifting.

Study 1 also compared an 'anxiety disorder only' group with the healthy control group, predicting there would be significant differences between the groups in verbal learning and memory. While the anxiety disorder only group remembered fewer words in four out of five trials (tied for Trial 5), the differences were not significant. The small sample size for the anxiety disorder only group (n = 26) may have contributed to the non-significant result because of a Type II error.

Despite the non-significant results, several points of interest were raised from Study 1, mostly regarding the healthy control group. Approximately one-third of the healthy control group were shown to be susceptible to future depressive episodes, owing to first-degree relatives having a psychiatric diagnosis of depression, BPD, or schizophrenia and participants themselves having subclinical symptoms of depression. In terms of depression susceptibility, age and gender may have also confounded the healthy control group, as young adults are yet to experience many depression triggers, such as financial and relationship stressors (Airaksinen et al., 2007). Further, given that a high proportion of the disorder sample were female and a matching percentage was required in the healthy control group, simply being female was a predictor of future depressive episodes (Airaksinen et al., 2007; Klein et al., 2013; Lewinsohn et al., 1994). These factors highlighted the difficulties in assembling a healthy control group in the young adult age range, especially when investigating trait deficits.

In addition, mathematical ability was raised as a possible confounding variable for the healthy control group. The experimenter observed a cohort of athletic male participants who had no history of depression or anxiety, but performed poorly on the cognitive tests. It was surmised that these participants were sports science students and suggested that mathematical ability may account for their poor performance in cognitive

testing. Therefore, Study 4 Mathematical Ability was added to the thesis, to measure whether the level of mathematics studied in high school had an effect on EF skills.

Possible solutions for a valid control comparison group are conducting a separate healthy control participant search that includes financial incentives, and having non-healthy control comparison groups. A separate healthy control group search is common in the literature; however, it was not successful in this project, most likely due to a lack of financial incentives. As healthy control participants who are not enrolled in psychology classes do not receive course credits for participation in research studies, financial incentives such as a $30 shopping voucher per participant are recommended. As approximately 30 to 50 healthy control participants are required, an expenditure of $1000 to $2000 could be justified. Other problems of creating a healthy control group, such as age and gender, cannot be overcome easily. Therefore, an alternative form of comparison is comparing depression subtypes, which was explored in Study 2 with the comparison of primary and secondary depression, and in Study 3, in which cognitive differences were compared between recurrent and non-recurrent depression.

Finally, a possible biological basis regarding the lack of EF deficits was suggested. Histopathological evidence had shown that abnormalities in the dlPFC and OFC included decreased glial density in the brain tissue of depression patients compared to healthy matched tissue (Rajkowska, Miguel-Hidalgo et al., 1999). These cellular abnormalities could result in altered metabolism of the dlPFC and OFC, which are pivotal for EF (Birrell & Brown, 2000; Buckley et al., 2009; Killgore et al., 2007; Owen et al., 2000; Wagner et al., 2006). Whether cellular abnormalities are due to the course of depression or other factors such as development deficiencies is an area of interest. Several animal studies have shown that developmental deficiencies result in not only deficits in EF, but also cellular abnormalities in depression related brain areas

(Baarendse et al., 2013; Fone & Porkess, 2008; Makinodan et al., 2012; Stamatakis et al., 2016). Therefore, if cellular abnormalities play a role in the causation of EF deficits, then identification of EF deficits in a depression group would be dependent on whether the depression group had significantly more participants with relevant cellular abnormalities than the healthy control group. This is especially relevant for subclinical samples, in which the low depression severity essentially negates clinical state deficits. The concept of identifying subgroups with a high likelihood of depression onset due to PFC abnormalities provided a secondary aim for Study 2.

11.2 Study 2: Primary and Secondary Depression

In Study 2 (Chapter 7), the cognitive differences between young adults with primary depression and the healthy control group from Study 1 were investigated. Further, this part of the research compared young adults with primary depression and secondary depression. Rather than study the differences between young adults with depression versus young adults with depression and a comorbid disorder, examining primary and secondary depression offered information regarding whether depression and the comorbid disorder were interacting. Primary depression was defined as when the onset is not due to a non-depressive disorder or medical condition, whereas for secondary depression onset was most probably due to a non-depressive disorder (see definitions in Section 7.2.1).

The rationale for this part of the study was twofold. First, from a depression onset perspective, if the secondary depression was caused by a non-depressive disorder, then cognition would be independent of depression onset. Therefore, when attempting to identify trait cognitive deficits that may be implicated in depression onset, participants with secondary depression may confound the results. Second, if a non-depressive disorder was not the causal agent for primary depression, then it could be

questioned whether cognitive deficits contributed to depression onset. Therefore, primary depression was identified as a depression subgroup whereby EF deficits are more likely to play a role in depression onset than in secondary depression.

The results of Study 2 showed that young adults with primary depression committed significantly more perseverative and non-perseverative errors than those with secondary depression. Consistent with the literature, this highlighted the possible role of set-shifting as a cognition of interest in depression. However, the primary depression group was not significantly different from the healthy control group, leaving three possible outcomes: (1) primary depression is not a subtype of depression that could be used to identify relevant cognitive deficits of depression; (2) in this study, the secondary depression group were simply very good at cognitive tests; or (3) the healthy control was not a valid control group, owing to issues such as familial depression and subclinical symptoms, as reported in Study 1.

Reanalysis of depression/cognition research was unable to confirm whether the proportion of comorbid anxiety in depression samples was a significant factor to explain previous mixed results. Two conclusions can be drawn from this study. First, differences in EF between primary and secondary depression highlight the need for further comparison between these groups in future studies. Second, comparing two depression subtypes eliminates issues with a healthy control group such as whether the healthy control participants are vulnerable to future depressive episodes. Further, primary depression was highlighted as a subgroup of interest and plays a role in Study 5 when comparing probable biological and cognitive markers of depression.

11.3 Study 3: Non-recurrent and Recurrent Depression

The aim of Study 3 (Chapter 8) was to examine cognitive differences between young adults who had one or two episodes of depression and no further episodes,

compared to a person who continued to experience episodes of depression. The groups were labelled as ‘non-recurrent depression’ (one or two MDEs only) and ‘recurrent depression’ (three or more MDEs). Research on depression reoccurrence has indicated that social cognition, rather than EF, is the main type of cognition of interest (Bouhuys et al., 1999; Geerts & Bouhuys, 1998; Hale, 1998; Inoue, Yamada et al., 2006).

The results of Study 3 showed that young adults with recurrent depression made significantly more errors in the prosody matching task when statements were read in a sarcastic or sad tone. This is the first study to show deficits in sarcasm in a depression population. The Prosodic Uncertainty Depression Pathway (Prosodic Pathway) was proposed to examine a possible mechanism behind the prosodic deficits (sarcasm) and a pathway to the onset of depressive episodes.

11.3.1 The Prosodic Uncertainty Depression Pathway (Prosodic Pathway)

The Prosodic Pathway (see Figure 8.1) proposes that anxiety, mediated by uncertainty, results in egocentric behaviour (Todd et al., 2015), which causes a person to negate prosodic cues such as a sarcastic tone. It is also proposed that negating prosodic information results in a negative interpretation of a situation, resulting in an increase in negative affect and/or non-severe life events, which contribute to the onset of a depressive episode (Beck, 1991; Hankin et al., 2007; Lenze et al., 2008; Stroud et al., 2011). Previously, depression onset due to a non-depressive disorder was thought to be due solely to stress resulting from the persistence of that non-depressive disorder (Bech, 2010; Kessler & Walters, 1998). The Prosodic Pathway provides an alternative explanation of the mechanism involved in a person progressing from a non-depressive disorder to depression, as well as providing a model for future research.

11.4 Study 4: Mathematical Ability

The aim of Study 4 (Chapter 9) was to investigate cognitive differences depending on the scholastic pathways taken during high school. Participants were divided in terms of mathematical ability: advanced mathematics (or physics) and ordinary mathematics. Previous research has demonstrated a relationship between EF and mathematical ability (Cragg & Gilmore, 2014). This current study found that the advanced mathematics group performed better than the ordinary mathematics group in the initial trial of the verbal learning and memory task and in all the set-shifting task variables. The EF domains of inhibition, updating and planning were not significantly different between the groups. In the first trial of the verbal learning and memory task, participant feedback suggested better memory techniques, such as visualisation, rather than a larger memory span. Differences in set-shifting are interesting, as this domain of EF has been identified as being especially relevant to depression studies (Channon, 1996; Grant et al., 2001; Harvey et al., 2004; Merriam et al., 1999). While it is not suggested that being proficient at mathematics will provide some form of protection against depression onset, it does highlight that the deficits in set-shifting that have been identified in depression cognition studies (Channon, 1996; Grant et al., 2001; Harvey et al., 2004; Merriam et al., 1999) are also in deficit in students who studied ordinary mathematics. A longitudinal study would be required to investigate whether the skills learned in advanced mathematics play a role in helping to solve situations encountered in life that may trigger a depressive episode. The comparison of cognitive differences based on mathematical ability in Study 4 was fortuitous, as the subgroup of young adults who studied ordinary mathematics played a pivotal role in Study 5.

11.5 Study 5 GABA and cognition

Low concentrations of plasma and brain GABA have been proposed as a biological marker for depression (Petty, Kramer, Fulten et al., 1995; Sanacora, Gueorguieva et al., 2004). The aim of Study 5 (Chapter 10) was to investigate whether there was a relationship between GABA and EF, which is also associated with depression (Castaneda, Tuulio-Henriksson et al., 2008; Snyder, 2013). This was the first study to investigate the relationship between GABA and cognition. To date, research has shown (1) that people with depression have a lower GABA concentration than healthy control participants (Kosel et al., 2004; Kucukibrahimoglu et al., 2009; Kugaya et al., 2003; Petty, Kramer, Gullion et al., 1992; Petty & Sherman, 1984; Sanacora, Mason, Rothman, Behar et al., 1999), (2) that GABA concentration has been shown to stable over time, with the exception of treatments involving SSRIs, and ECT (Kucukibrahimoglu et al., 2009; Petty, Fulton, Moeller et al., 1993; Petty, Kramer, Fulten et al., 1995; Petty, Kramer, Gullion et al., 1992; Sanacora, Gueorguieva et al., 2004; Sanacora, Mason, Rothman, Hyder et al., 2003; Sanacora, Mason, Rothman, & Krystal, 2002), and (3) participants with primary depression show significantly lower plasma GABA concentrations than participants with secondary depression or healthy control participants (Petty, Kramer & Feldman, 1987).

In Study 5, when analysing the data from the subgroup primary depression compared to the complete data set, a relationship began to form between plasma GABA concentration and working memory. Both EF domains with large working memory components, updating and verbal learning and memory, correlated significantly with plasma GABA concentration. (See Section 10.4.1for a full discussion regarding working memory indicators in updating and verbal memory and learning tests.) Specifically, this means that participants with primary depression and low plasma

GABA concentration demonstrated poor working memory. If decreased GABA is an indicator of cellular abnormalities, due to its relationship with glial density (Öngür et al., 1998), then this result links cellular abnormalities with decreased working memory capacity.

To examine this relationship between low GABA concentration and deficits in working memory, another subgroup, ordinary mathematics, was tested. The ordinary mathematics group was originally selected due to similarities in EF deficits with the primary depression group (Study 2 and 4). As per Section 10.4, the ordinary mathematics group displayed a similar relationship between GABA and working memory than the primary depression group. This result was not unexpected due to a large overlap of participants in the two subgroups. Future studies should consider ordinary mathematics as a subgroup of interest, as low mathematical ability may be a stable indicator of EF deficits, possibly due to cellular abnormalities in the PFC. The significant result demonstrates the importance of targeting relevant subgroups associated with the depression 'pathway' being investigated. A model to test future research regarding the relationship between biological deficits, cognitive deficits and depression is summarised in the next section.

11.5.1 Executive Function Depression Pathway (EF Pathway)

The EF Pathway (see Figure 10.1) proposed that sub-optimal developmental or environmental factors lead to biological abnormalities in the PFC resulting in EF deficits (Baarendse et al., 2013; Fone & Porkess, 2008; Makinodan et al., 2012; Stamatakis et al., 2016). It is further proposed that these EF deficits, negatively affect problem solving and flexible thinking skills, resulting in stressful or negative life events that contribute to depression onset (Kendler et al., 1993; Phelan et al., 1991). It is hoped

that this pathway will provide a model for future research, which may help to prevent depression before the formation of depression onset triggers.

11.6 The Role of Uncertainty

It is unknown whether the two proposed depression pathways, if found to be valid, will have a significant effect on society. One way to examine this is to look at the triggers of both pathways. The trigger for the Prosodic Pathway is uncertainty (see Figure 8.1), which may also play a significant role in the EF Pathway. The aetiology of the EF Pathway is based on the formation of cellular abnormalities, which then affect EF. The role of EFs is to manage unforeseen or novel situations, or in essence, uncertain situations. While uncertainty plays a mediating role in the Prosodic Pathway, it would also play a moderating role in the EF Pathway. Therefore, to examine whether the Prosodic and EF Pathways could play a significant role in the future, a measure of uncertainty over time would need to be examined.

11.7 Clinical Applications

This section explores the clinical applications of first, the cognitive deficits identified and second, of the proposed Prosodic and EF Pathways.

11.7.1 Clinical solutions

In Study 3, the recurrent depression group was shown to have deficits in understanding sarcasm compared to the non-recurrent depression group. While deficits in sarcasm have been seen in other disorders such as Huntington disease (Larsen et al., 2016), this is the first study to identify deficits in young adults with depression and there are clinical implications of this finding. First, making a person aware that they have deficits in sarcasm would be of benefit and allow them to begin to re-evaluate situations that they may have misinterpreted previously. Second, clinical techniques, such as cognitive reappraisal, could be applied to situations involving sarcasm to assist

the person in altering the emotional impact of a situation (Zhang, Li, Qin, & Luo, 2012). Cognitive reappraisal can lead to greater positive emotion, less negative emotion and is associated with better interpersonal functioning and well-being (Gross & John, 2003). However, while being aware of the deficit and applying clinical tools such as cognitive reappraisal may lead to positive outcomes, these are only short-term solutions. Therefore, a pathway model showing precursors of the deficit may offer a long-term solution.

11.7.2 Pathway models

In the introduction, it was stated that identifying cognitive deficits relevant to depression would allow effective treatment in the disorder's infancy. This concept also works for depression pathways, in which treatment can be aimed at precursors of the cognitive deficits. Cummings et al. (2014) proposed three depression pathways that equated, essentially, to primary depression (i.e., depression that is not due to a non-depressive disorder), secondary depression (i.e., depression that is due to a non-depression disorder) and the situation whereby depression and the non-depressive disorders occur simultaneously. Secondary depression is an example of a pathway in which treatment of the primary non-depressive disorder may offer benefits in terms of positive depression outcomes. For example, studies have shown that treatment of the primary non-depressive disorder (Lesser et al., 1989; Norton et al., 2004) or primary medical condition (Hurst, 2010) resulted in decreased depression severity. Other depression pathways have also provided valuable information without necessarily improving depression outcomes at this stage. Non-severe life events have been identified as causal factors for depression reoccurrence (Lenze et al., 2008; Stroud et al., 2011), while also providing an explanation for females experiencing more depressive events than males (Hankin et al., 2007). Clinical solutions focusing on reducing stress

and the occurrence of stressful life events could have a positive impact on depression (for meta-analysis, see Grossman, Niemann, Schmidt, & Walach, 2004). Pathways can provide a useful tool in explaining the mechanisms behind depression onset and thereby providing clinical suggestions for treatment focusing on the precursors, rather than on the depression itself.

The two pathways proposed in this thesis are yet to be validated; however, they are examined briefly here. The first step for the Prosodic Pathway (see Figure 8.1) is anxiety mediated by uncertainty, while for the EF Pathway (see Figure 10.1), it is developmental or environmental deficiencies. If these pathways were validated, then goals and plans could be set to address the initial stages of each pathway. For example, for the Prosodic Pathway initial goals would be to identify and treat the anxiety disorder, while taking steps to address the issue of uncertainty. For the EF Pathway negative developmental and environmental situations that contribute to EF deficits have been linked to poverty, neglect and institutionalisation (Sheridan & McLaughlin, 2016). Goals and action plans directed at evidenced based parenting programs would be an initial and positive step forward (Sanders, 2010).

11.8 Limitations

Several limitations were noted in this thesis. The first was in relation to the validity of the healthy control group. Although the total number of participants recruited for the healthy control group was sufficient for the necessary comparisons, issues arose as to whether approximately one-third of the healthy control participants were susceptible to future depressive episodes, owing to the presence of subclinical symptoms or family members with a psychiatric diagnosis. However, these limitations exist for any study involving young adults. While attempts in this study to recruit healthy control participants in different domains in which course credits were not

offered had a zero success rate, it was recommended for future studies that financial compensation be considered to assist in recruiting a healthy control group.

A second limitation was the sample size of Study 5, GABA and cognition. As this study was added to the thesis after the majority of data had been collected, the total sample size was 53. This small sample size did not allow for comparisons such as healthy control versus depression group, or comparisons of subgroups such as primary and secondary depression. Further, in this study, participants who had completed the cognitive testing up to two years previously were allowed to give a blood sample and to be labelled '*past*'. As noted in Section 10.4.2, a visual inspection shows that the combined *current and past* results did not differ from the *current* results. For future studies, a separately recruited healthy control group that is financially rewarded and beginning the blood sample collection at the start of the research would allay these limitations.

In both the Prosodic and EF Pathways this thesis has proposed a role for cognition in depression onset to the exclusion of other factors. Factors such as the role of neurochemicals (for example dopamine and serotonin), which are beyond the scope of this thesis, are a further limitation. The EF Pathway (see Figure 10.1) examines how developmental deficiencies result in EF deficits and biological abnormalities in depression related brain areas. Development deficiencies such as isolation, also result in long term changes in neurochemical systems (for a review see Fone et al., 2008). What is unknown is whether the resultant changes in neurochemical systems either mediate or modulate the onset of depression proposed in the EF Pathway, including possibly negating the effects of cognition.

11.9 Future Studies

The future studies that are recommended from the results of this thesis can be achieved by testing the two proposed pathways: the Prosodic Pathway and the EF Pathway.

11.9.1 The Prosodic Pathway

11.9.1.1 Egocentrism–prosody relationship

The first part of the Prosodic Pathway study would be to test the relationship between anxiety, egocentrism and prosody. In Todd et al. (2015), participants with anxiety displayed egocentric behaviours when completing perspective-taking tasks. Aspects of Todd et al.'s study could be extended by including a measure of prosody. The prosody task should include statements that are read in a sarcastic or ironic tone, making the meaning of the statements ambiguous. The main difference in the Prosodic Pathway study and Todd et al.'s study would be in way the participants experience anxiety. In Todd et al., a state of anxiety was induced temporarily, using an emotional manipulation task. However, in this proposed study, purposeful sampling would be undertaken, recruiting young adults (aged 17 to 35 years) who have experienced symptoms of anxiety within the past six months. (The period six months was chosen as it is the period for GAD in the MINI PLUS.) Participants would complete perspective-taking tasks and cognitive tests measuring social perception, including prosody matching, set-shifting and verbal learning and memory. Classification measures would include the SIGH-AD, CES-D and the MINI PLUS. Todd et al. noted that the resultant egocentric behaviour might be mediated by uncertainty. In Todd et al., a simple Likert scale was used to measure uncertainty after the emotional manipulation task. A similar task could be implemented with the CES-D Scale, or a specific measure of uncertainty, such as the Mishel Uncertainty in Illness Scale (Mishel, 1981), could be implemented.

Also included in the test battery would be the Life Events and Difficulties Schedule Interview and a measure of negative bias such a facial affect, which is part of the social perception tests. The two EF tests, set-shifting and verbal learning and memory, are not time consuming and had implications in the second part of this study so should be included (see Section 11.9.1.2). In addition, a matched healthy control group would be included as a comparison group and comparisons between the disorder groups if possible should be utilised. A further aspect that could be explored in a purposefully designed study would be whether deficits in sarcasm extend to the written word. Given the high usage of social media as a form of communication, this would be a worthy future research question.

The aim of this study would be to investigate the relationship between anxiety, egocentric behaviours and prosodic deficits. Several hypotheses have been proposed: (1) young adults with anxiety who display egocentric behaviours will display significant prosodic deficits compared to young adults who do not display egocentric behaviour; (2) the egocentric behaviour/prosodic deficit relationship will be mediated by uncertainty; and (3) young adults with anxiety will display significantly more egocentric behaviours and prosodic deficits than a matched healthy control group.

Figure 11.1. Egocentrism-prosody relationship

11.9.1.2 Prosody deficits–depressive episodes relationship

The second part of the Prosodic Pathway study would be to determine whether factors such as anxiety, uncertainty, egocentric behaviour or prosodic deficits play a role in depression onset or reoccurrence. To investigate this, a longitudinal aspect would be

introduced. One and two years after the initial testing, the participants would be invited back to repeat the testing procedure. As the majority of recruitment should be done through first- and second-year university psychology courses, high retention of participants should be possible by testing in consecutive years of their university degrees.

Two measures that have been shown to predict either depression onset or depression relapse, number of non-severe life events and negative bias, would be the focus of this part of the study, as well as the incidence of MDEs. As there are several different versions of each test, they can be rotated each year, to avoid the problem of practice effects. Including the EF tests set-shifting and verbal learning and memory as probable trait deficits of depression (Grant et al., 2001; Harvey et al., 2004; Neu et al., 2005; Purcell et al., 1997; Smith et al., 2006) would be important in a longitudinal cognition study to determine whether deficits in cognition play a role in depression onset or relapse. Another confounding variable in this experiment would be that other factors might contribute to depression onset or relapse, such as persistence of the non-depressive disorder, or ongoing medical conditions. A qualitative aspect of the study would be to create a timeline of the year, including stressful life events and incidences of depression, to record the participants' beliefs regarding the causal factors in depression onset. The primary aim of this study would be to investigate the relationship between anxiety, prosody, stressful life events, and depression onset. The secondary aim of the study would be to investigate whether prosodic deficits mediate negative bias effects, which in turn have a moderation effect on rates of depression relapse. The following hypotheses have been proposed: (1) young adults with anxiety who display deficits in prosody will experience a greater number of stress life events than young adults with anxiety with no deficits in prosody; (2) young adults who experience

cumulative stressful life events will experience a greater number of depressive episodes than young adults who do not experience stressful life events; and (3) young adults with anxiety who display deficits in prosody and who experience negative bias will experience a greater rate of depression occurrence compared to young adults with anxiety with no deficits in prosody.

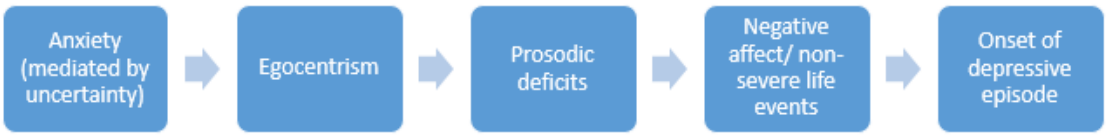

Figure 11.2. Anxiety, egocentrism-prosody deficits, depressive episodes pathway

11.9.2 Executive Function Depression Pathway (EF pathway)

11.9.2.1 Brain activity, plasma GABA concentration and cognition

The proposed EF Pathway states that developmental or environmental factors result in chnages in the PFC which further results in diminished EF, leading to poor decision making, which leads to negative factors such as stressful life events that may result in, or contribute to, depressive episode onset. The proposed study would incorporate purposive sampling, with the aim to replicate the depression subgroups from Study 5 in this research; that is, young adults (aged 17 to 35) with depression that can be classified as primary depression (see Section 7.2.1) or who have studied ordinary mathematics (see Section 9.2.1). Participants would complete EF tests in set-shifting and verbal learning and memory. Classification measures would include the SIGH-AD, CES-D and the MINI PLUS. Also included in the test battery would be the Life Events and Difficulties Schedule Interview and a measure of negative bias. A matched healthy control group would be included as a comparison group. During cognitive testing, the participants would undergo electroencephalography (EEG) testing, focusing on the dlPFC and OFC. In addition, brain GABA concentrations could be measured using MR

Spectroscopy (Levy & Degnan, 2013), or if that is not feasible then participants could provide a blood sample to measure plasma GABA concentration.

The aim of this study would be to investigate the possible relationships between electrical activity in the PFC, GABA concentration and cognition. Proposed hypotheses are that young adults with either primary depression or depression and have studied ordinary mathematics will (1) show a significant correlation between brain activity, GABA concentration and cognition scores; (2) show lower brain activity in the PFC than the healthy control group; (3) have lower GABA concentration than the healthy control group; and (4) commit significantly more errors on EF tests than the healthy control group. Other issues of interest would include (5) comparison of brain activity in the dlPFC for low and high non-perseverative errors in the set-shifting task and (6) comparison of brain activity in the OFC for low and high perseverative errors in the set-shifting task.

Figure 11.3. Brain activity, GABA concentration, EF deficits pathway

11.9.2.2 EF Pathway and depressive episodes

The second part of the EF Pathway study would be to investigate whether brain activity, GABA concentration and cognitive deficits play a role in depressive episode onset. As for the Prosodic Pathway study, participants would be retested one and two years after the initial testing period. Factors such as number of stressful life events, degree of negative bias and number of depressive episodes since the preceding testing period would be recorded. As for the Prosodic Pathway study, a timeline of the year, including stressful life events and incidences of depression, would be recorded as well as participants' beliefs regarding the causal factors in the depression onset.

The aim of the study would be to investigate the relationship between brain activity, GABA concentration, cognition, stressful life events and depressive episode onset. Proposed hypotheses are that (1) brain activity, GABA concentration and cognitive deficits predict the number of stressful life events; (2) brain activity, GABA concentration and cognitive deficits predict depression relapse; and (3) GABA concentration is stable over all testing periods.

Figure 11.4. Brain activity, GABA concentration, EF deficits, depressive episodes pathway

11.9.3 Combining the prosodic and biological studies

Because of the large number of factors in common between the Prosodic Pathway and EF Pathway studies, there is merit in combining both studies. Working from the Prosodic Pathway study to form a common methodology, participants would have to undergo an EEG during the cognitive testing and would be required to provide a measure of GABA. Combining these studies would allow a greater number of comparisons involving disorder subgroups such as anxiety versus depression. However, the EEG and MR Spectroscopy processes can be quite lengthy, adding on to an already time-consuming testing phase. To keep the time to test each participant under three hours, a reliable, computerised, self-rating measure of depression (for example CES-D), anxiety severity and disorder classification would be advantageous. Given that the main forms of targeted cognition would be trait deficits, an exact measure of disorder severity is less important than correct disorder classification. Because of the time commitments involved for the combined studies, if participants could obtain class credits, I would recommend an additional compensation to the value of $20 to $30, in the form of

money or a shopping voucher. This would be especially important for retention in the longitudinal aspects of the study, as class credits may no longer be offered in later stages.

11.9.4 Matched healthy control group

A matched healthy control group would be needed for both the Prosodic Pathway and the EF Pathway studies. Owing to the similarity of both studies, the matched healthy control group could be used for both studies. The recruitment of the healthy control group should be independent from the disordered participant search. Several factors should be taken into account when recruiting the heathy control group, such as gender and mathematical ability. As the occurrence of anxiety and depression in young adults is much higher in females (NHS, 2014), a ratio of approximately three females to one male is required. In the EF Pathway study, one of the subgroups was young adults who studied ordinary mathematics in high school; therefore, this should also be reflected in the healthy control group. A healthy control group would be of great importance for both Pathway studies to investigate the effect of all variables on initial depressive episode onset, rather than depression reoccurrence. A compensation package for participants of around $50 per testing period is recommended. As for the disorder groups, focusing on first- or second-year students would ensure greater retention during the longitudinal aspect of the studies.

11.10 Concluding Remarks

This thesis has explored cognitive deficits in young adults with depression and/or anxiety. Though no significant differences were found between depression, anxiety disorder only and the healthy control groups, important methodological issues were highlighted regarding healthy control group design. Significant differences were found between depression subgroups, including between young adults with primary

depression who committed more errors in the set-shifting task than those with secondary depression. Primary depression was identified as a subgroup of interest and suggested to have a biological basis. Young adults with recurrent depression committed more errors in the prosody task, than those with non-recurrent depression. This formed the basis of the proposed Prosodic Pathway. Young adults who studied ordinary mathematics committed more errors in the set-shifting task than those who studied advanced mathematics. Ordinary mathematics proved to be an important subgroup in the investigation of plasma GABA concentration and cognition. By focusing on subgroups suggested to encompass a biological component, a significant correlation between plasma GABA concentration and working memory emerged. This led to the proposed EF Pathway, with GABA concentration suggested to be an indicator of cellular chnages in the PFC. It is recommended that both pathways be used to model future research and treatments based on precursors of depression triggers.

References

Aalto-Setälä, T., Marttunen, M., Tuulio-Henriksson, A., Poiklainen, K., & Lönnqvist, J. (2002). Psychiatric treatment seeking and psychosocial impairment among young adults with depression. *Journal of Affective Disorders, 70*(1), 35–47. doi:10.1016/s0165-0327(01)00316-0

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic memory dysfunction. *Journal of Psychiatric Research, 39*(2), 207–214. doi:10.1016/j.jpsychires.2004.06.001

Airaksinen, E., Wahlin, A., Forsell, Y., & Larsson, M. (2007). Low episodic memory performance as a premorbid marker of depression: Evidence from a 3-year follow-up. *Acta Psychiatrica Scandinavica, 115*(6), 458–465. doi:10.1111/j.1600-0447.2006.00932.x

Anderson, R. J., Simpson, A. C., Channon, S., Samuel, M., & Brown, R. G. (2013). Social problem solving, social cognition, and mild cognitive impairment in Parkinson's disease. *Behavioral Neuroscience, 127*(2), 184–192. doi:10.1007/s10608-007-9169-3 http://dx.doi.org/10.1037/a0030250

Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57–87. doi:10.1111/1469-7610.00424

Ardila, A., Pineda, D., & Rosselli, M. (2000). Correlation between intelligence test scores and executive function measures. *Archives of Clinical Neuropsychology, 15*(1), 31–36. doi:http://dx.doi.org/10.1016/S0887-6177(98)00159-0

Arffa, S. (2007). The relationship of intelligence to executive function and non-executive function measures in a sample of average, above average, and gifted

youth. *Archives of Clinical Neuropsychology, 22*(8), 969–978. doi:http://dx.doi.org/10.1016/j.acn.2007.08.001

Arffa, S., Lovell, M., Podell, K., & Goldberg, E. (1998). Wisconsin Card Sorting Test Performance in Above Average and Superior School Children: Relationship to Intelligence and Age. *Archives of Clinical Neuropsychology, 13*(8), 713–720. doi:http://dx.doi.org/10.1016/S0887-6177(98)00007-9

Asmundson, G., Stein, M. B., Larsen, D., & Walker, J. (1995). Neurocognitive function in panic disorder and social phobia patients. *Anxiety, 1*, 200–206.

Australian Bureau of Statistics (ABS). (2012). 4433.0.55.004—Psychological Disability, 2012. *Australian Bureau of Statistics.*

Baarendse, P. J. J., Counotte, D. S., O'Donnell, P., & Vanderschuren, L. J. M. J. (2013). Early Social Experience Is Critical for the Development of Cognitive Control and Dopamine Modulation of Prefrontal Cortex Function. Neuropsychopharmacology, 38(8), 1485-1494. doi:10.1038/npp.2013.47

Baune, B. T., Czira, M. E., Smith, A. L., Mitchell, D., & Sinnamon, G. (2012). Neuropsychological performance in a sample of 13–25 year olds with a history of non-psychotic major depressive disorder. *Journal of Affective Disorders, 141*(2–3), 441448. doi:http://dx.doi.org/10.1016/j.jad.2012.02.041

Bearden, C. E., Glahn, D. C., Monkul, E. S., Barrett, J., Najt, P., Villarreal, V., & Soares, J. C. (2006). Patterns of memory impairment in bipolar disorder and unipolar major depression. *Psychiatry Research, 142*(2–3), 139–150.

Bech, P. (2010). Struggle for subtypes in primary and secondary depression and their mode-specific treatment or healing. *Psychotherapy and Psychosomatics, 79*(6), 331–338. doi:http://dx.doi.org/10.1159/000320118

Beck, A. T. (1991). Cognitive therapy: A 30-year retrospective. *American Psychologist, 46*(4), 368–375. doi:http://dx.doi.org/10.1037/0003-066X.46.4.368

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*(1), 77–100. doi:http://dx.doi.org/10.1016/0272-7358(88)90050-5

Beevers, C. G., Keitner, G. I., Ryan, C. E., & Miller, I. W. (2003). Cognitive predictors of symptom return following depression treatment. *Journal of Abnormal Psychology, 112*(3), 488–496. doi:http://dx.doi.org/10.1037/0021-843X.112.3.488

Bench, C. J., Friston, K. J., Brown, R. G., Frackowiak, R. S. J., & Dolan, R. J. (1993). Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychological Medicine, 23*(3), 579–590. doi:10.1017/S0033291700025368

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology, 39*(1), 15–22. doi:10.1080/00221309.1948.9918159

Berg, W. K., & Byrd, D. L. (2002). The Tower of London spatial problem-solving task: Enhancing clinical and research implementation. *Journal of Clinical and Experimental Neuropsychology, 24*(5), 586–604.

Berman, K. F., Doran, A. R., Pickar, D., & Weinberger, D. R. (1993). Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. *British Journal of Psychiatry, 162*, 183–192. doi:10.1192/bjp.162.2.183

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *The Journal of Neuroscience, 20*(11), 4320–4324.

Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., … Lotstra, F. (1994). Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry, 36*(6), 381–388. doi:http://dx.doi.org/10.1016/0006-3223(94)91213-0

Boldrini, M., Del Pace, L., Placidi, G. P. A., Keilp, J., Ellis, S. P., Signori, S., … Cappa, S. F. (2005). Selective cognitive deficits in obsessive-compulsive disorder compared to panic disorder with agoraphobia. *Acta Psychiatrica Scandinavica, 111*(2), 150–158.

Bos, E. H., Bouhuys, A. L., Geerts, E., Van Os, T. W. D. P., Van der Spoel, I. D., Brouwer, W. H., & Ormel, J. (2005). Cognitive, physiological, and personality correlates of recurrence of depression. *Journal of Affective Disorders, 87*(2–3), 221–229.

Bouhuys, A. L., Geerts, E., & Gordijn, M. C. M. (1999). Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: A longitudinal study. *Journal of Nervous and Mental Disease, 187*(10), 595–602. doi:http://dx.doi.org/10.1097/00005053-199910000-00002

Brady, E. U., & Kendall, P. C. (1992). Comorbidity of anxiety and depression in children and adolescents. *Psychological Bulletin, 111*(2), 244–255. doi:10.1037/0033-2909.111.2.244

Brambilla, P., Perez, J., Barale, F., Schettini, G., & Soares, J. C. (2003). GABAergic dysfunction in mood disorders. *Molecular Psychiatry, 8*(8), 721–737.

Bremner, J., Innis, R. B., Salomon, R. M., Staib, L. H., Ng, C. K., Miller, H. L., … Charney, D. S. (1997). Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion—induced depressive relapse. *Archives of General Psychiatry, 54*(4), 364–374. doi:10.1001/archpsyc.1997.01830160092012

Brown, G. W. (1993). Life events and affective disorder: Replications and limitations. *Psychosomatic Medicine May/June, 55*(3), 248–259.

Buckley, M. J., Hassan, H., Mahboubi, M., Browning, P. G. F., Kwok, S. C., Phillips, A., & Tanaka, K. (2009). Dissociable components of rule-guided behavior depend on distinct medial and prefrontal regions. *Science, 325*(5936), 52–58. doi:http://dx.doi.org/10.1126/science.1172377

Cai, H.-L., Zhu, R.-H., Li, H.-D., Zhang, X.-H., Hu, L., Yang, W., & Ye, H.-S. (2010). Elevated plasma gamma-aminobutyrate/glutamate ratio and responses to risperidone antipsychotic treatment in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34*(7), 1273–1278.

Carder, H. P., Handley, S. J., & Perfect, T. J. (2004). Deconstructing the Tower of London: Alternative moves and conflict resolution as predictors of task performance. *The Quarterly Journal of Experimental Psychology A: Human Experimental Psychology, 57A*(8), 1459–1483.

Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders, 106*(1–2), 1–27. doi:10.1016/j.jad.2007.06.006

Castaneda, A. E., Suvisaari, J., Marttunen, M., Perälä, J., Saarni, S. I., Aalto-Setälä, T., … Tuulio-Henriksson, A. (2008). Cognitive functioning in a population-based

sample of young adults with a history of non-psychotic unipolar depressive disorders without psychiatric comorbidity. *Journal of Affective Disorders, 110*(1-2), 36–45. doi:10.1016/j.jad.2007.12.239

Channon, S. (1996). Executive dysfunction in depression: The Wisconsin Card Sorting Test. *Journal of Affective Disorders, 39*(2), 107–114.

Channon, S., & Green, P. S. S. (1999). Executive function in depression: The role of performance strategies in aiding depressed and non-depressed participants. *Journal of Neurology, Neurosurgery & Psychiatry, 66*(2), 162–171.

Chudasama, Y. (2011). Animal models of prefrontal-executive function. *Behavioral Neuroscience, 125*(3), 327–343. doi:http://dx.doi.org/10.1037/a0023766

Corrigan, P., & Penn, D. (2001). *Introduction: Framing models of social cogntion and schizphrenia*. Washington DC: American Psychological Association.

Coryell, W., Zimmerman, M., & Pfohl, B. (1985). Short-term prognosis in primary and secondary major depression. *Journal of Affective Disorders, 9*(3), 265–270.

Costello, C. G., & Scott, C. B. (1991). Primary and secondary depression: A review. *Canadian Journal of Psychiatry, 36*(3), 210-217.

Cotter, D., Mackay, D., Landau, S., Kerwin, R., & Everall, I. (2001). Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch. Gen. Psychiatry, 58*(6), 545–553.

Cragg, L., & Gilmore, C. (2014). Skills underlying mathematics: The role of executive function in the development of mathematics proficiency. *Trends in Neuroscience and Education, 3*(2), 63–68. doi:http://dx.doi.org/10.1016/j.tine.2013.12.001

Csukly, G., Telek, R., Filipovits, D., Takács, B., Unoka, Z., & Simon, L. (2011). What is the relationship between the recognition of emotions and core beliefs:

Associations between the recognition of emotions in facial expressions and the maladaptive schemas in depressed patients. *Journal of Behavior Therapy and Experimental Psychiatry, 42*(1), 129–137. doi:http://dx.doi.org/10.1016/j.jbtep.2010.08.003

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological Bulletin, 140*(3), 816–845. doi:10.1016/j.janxdis.2009.07.024 10.1023/A:1021351722364 http://dx.doi.org/10.1037/a0034733

Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neuroscience & Biobehavioral Reviews, 28(7), 771-784. doi:http://dx.doi.org/10.1016/j.neubiorev.2004.09.006

Davidson, J. R., Turnbull, C. D., & Miller, R. D. (1980). A comparison of inpatients with primary unipolar depression and depression secondary to anxiety. *Acta Psychiatrica Scandinavica, 61*(5), 377–386. doi:http://dx.doi.org/10.1111/j.1600-0447.1980.tb00876.x

de Graaf, R., Bijl, R. V., ten Have, M., Beekman, A. T. F., & Vollebergh, W. A. M. (2004). Pathways to comorbidity: The transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *Journal of Affective Disorders, 82*(3), 461–467. doi:http://dx.doi.org/10.1016/j.jad.2004.03.001

Dent, J., & Teasdale, J. D. (1988). Negative cognition and the persistence of depression. *Journal of Abnormal Psychology, 97*(1), 29–34. doi:http://dx.doi.org/10.1037/0021-843X.97.1.29

Dias, R., Robbins, T. W., & Roberts, A. C. (1996a). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature, 380*(6569), 69–72. doi:http://dx.doi.org/10.1038/380069a0

Dias, R., Robbins, T. W., & Roberts, A. C. (1996b). Primate analogue of the Wisconsin card sorting test: Effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behavioral Neuroscience, 110*(5), 872–886. doi:10.1037/0735-7044.110.5.872

Dykiert, D., & Deary, I. J. (2013). Retrospective validation of WTAR and NART scores as estimators of prior cognitive ability using the Lothian Birth Cohort 1936. *Psychological Assessment, 25*(4), 1361–1366. doi:10.1037/a0033623

Emerson, C. S. P. D., Harrison, D. W. P. D., & Everhart, D. E. P. D. (1999). Investigation of receptive affective prosodic ability in school-aged boys with and without depression. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 12*(2), 102–109.

Espejo, E. P., Hammen, C. L., Connolly, N. P., Brennan, P. A., Najman, J. M., & Bor, W. (2007). Stress sensitization and adolescent depressive severity as a function of childhood adversity: A link to anxiety disorders. *Journal of Abnormal Child Psychology, 35*(2), 287–299. doi:10.1007/s10802-006-9090-3

Feighner, J. P., Woodruff, R. A., Winokur, G., Munoz, R., Robins, E., & Guze, S. B. (1972). Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry, 26*(1), 57–63. doi:10.1001/archpsyc.1972.01750190059011.

Fichter, M. M., Quadflieg, N., Fischer, U. C., & Kohlboeck, G. (2010). Twenty-five-year course and outcome in anxiety and depression in the Upper Bavarian Longitudinal Community Study. *Acta Psychiatrica Scandinavica, 122*(1), 75–85. doi:10.1111/j.1600-0447.2009.01512.x

Field, A. (2013). *Discovering statistics using IBM SPSS statistics* (Vol. 4th edition). London: Sage.

Fitzgerald, P. B., Srithiran, A., Benitez, J., Daskalakis, Z. Z., Oxley, T. J., Kulkarni, J., & Egan, G. F. (2008). An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Human Brain Mapping, 29*(4), 490–501.

Fone, K. C., & Porkess, M. V. (2008). Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neurosci Biobehav Rev, 32(6), 1087-1102. doi:10.1016/j.neubiorev.2008.03.003

Fossati, P., Amar, G., Raoux, N., Ergis, A. M., & Allilaire, J. F. (1999). Executive functioning and verbal memory in young patients with unipolar depression and schizophrenia. *Psychiatry Research, 89*(3), 171–187. doi:10.1016/s0165-1781(99)00110-9

Garber, J., & Weersing, V. R. (2010). Comorbidity of anxiety and depression in youth: Implications for treatment and prevention. *Clinical Psychology: Science and Practice, 17*(4), 293–306. doi:10.1111/j.1468-2850.2010.01221.x

Gaudreau, G., Monetta, L., Macoir, J., Laforce, R., Jr., Poulin, S., & Hudon, C. (2013). Verbal irony comprehension in older adults with amnestic mild cognitive impairment. *Neuropsychology, 27*(6), 702–712. doi:http://dx.doi.org/10.1037/a0034655

Geary, D. C. (2011). Cognitive predictors of achievement growth in mathematics: A 5-year longitudinal study. *Developmental Psychology, 47*(6), 1539–1552. doi:10.1037/a0025510

Geerts, E., & Bouhuys, N. (1998). Multi-level prediction of short-term outcome of depression: Non-verbal interpersonal processes, cognitions and personality traits. *Psychiatry Research, 79*(1), 59–72. doi:http://dx.doi.org/10.1016/S0165-1781(98)00021-3

Golden, C. J. (1978). *Stroop color and word test manual*. Odessa, FL: Psychological Assessment Resources.

Gollan, J. K., Pane, H. T., McCloskey, M. S., & Coccaro, E. F. (2008). Identifying differences in biased affective information processing in major depression. *Psychiatry Research, 159*(1–2), 18–24. doi:http://dx.doi.org/10.1016/j.psychres.2007.06.011

Gos, T., Günther, K., Bielau, H., Dobrowolny, H., Mawrin, C., Trübner, K., … Bogerts, B. (2009). Suicide and depression in the quantitative analysis of glutamic acid decarboxylase-Immunoreactive neuropil. *Journal of Affective Disorders, 113*(1–2), 45–55. doi:http://dx.doi.org/10.1016/j.jad.2008.04.021

Goto, N., Yoshimura, R., Kakeda, S., Moriya, J., Hori, H., Hayashi, K., … Nakamura, J. (2010). No alterations of brain GABA after 6 months of treatment with atypical antipsychotic drugs in early-stage first-episode schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34*(8), 1480–1483. doi:http://dx.doi.org/10.1016/j.pnpbp.2010.08.007

Grant, M. M., Thase, M. E., & Sweeney, J. A. (2001). Cognitive disturbances in outpatient depressed younger adults: Evidence of modest impairment. *Biological Psychiatry, 50*(1), 35–43. doi:10.1016/s0006-3223(00)01072-6

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of*

Personality and Social Psychology, 85(2), 348–362. doi:http://dx.doi.org/10.1037/0022-3514.85.2.348

Grossman, P., Niemann, L., Schmidt, S., & Walach, H. (2004). Mindfulness-based stress reduction and health benefits: A meta-analysis. *Journal of Psychosomatic Research*, *57*(1), 35–43. doi:http://dx.doi.org/10.1016/S0022-3999(03)00573-7

Gur, R. C., Erwin, R. J., Gur, R. E., Zwil, A. S., Heimberg, C., & Kraemer, H. C. (1992). Facial emotion discrimination: II. Behavioral findings in depression. *Psychiatry Research, 42*(3), 241–251. doi:http://dx.doi.org/10.1016/0165-1781(92)90116-K

Guy, W., National Institute of Mental Health (U.S.), Psychopharmacology Research Branch, Early Clinical Drug Evaluation Programs. (1976). *ECDEU assessment manual for psychopharmacology*. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Haaga, D. A., Dyck, M. J., & Ernst, D. (1991). Empirical status of cognitive theory of depression. *Psychological Bulletin, 110*(2), 215–236. doi:http://dx.doi.org/10.1037/0033-2909.110.2.215

Hale, W. W., III. (1998). Judgment of facial expressions and depression persistence. *Psychiatry Research, 80*(3), 265–274. doi:http://dx.doi.org/10.1016/S0165-1781(98)00070-5

Halvorsen, M., Wang, C. E., Eisemann, M., & Waterloo, K. (2010). Dysfunctional attitudes and early maladaptive schemas as predictors of depression: A 9-year

follow-up study. *Cognitive Therapy and Research, 34*(4), 368–379. doi:http://dx.doi.org/10.1007/s10608-009-9259-5

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32*(1), 50–55. doi:10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*(1), 56–62.

Hammen, C., Brennan, P. A., Keenan-Miller, D., & Herr, N. R. (2008). Early onset recurrent subtype of adolescent depression: Clinical and psychosocial correlates. *Journal of Child Psychology and Psychiatry, 49*(4), 433–440. doi:10.1111/j.1469-7610.2007.01850.x

Hankin, B. L. (2008). Cognitive vulnerability–stress model of depression during adolescence: Investigating depressive symptom specificity in a multi-wave prospective study. *Journal of Abnormal Child Psychology, 36*(7), 999–1014. doi:10.1007/s10802-008-9228-6

Hankin, B. L., Mermelstein, R., & Roesch, L. (2007). Sex differences in adolescent depression: Stress exposure and reactivity models. *Child Development, 78*(1), 279–295. doi:http://dx.doi.org/10.1111/j.1467-8624.2007.00997.x

Harvey, P. O., Le Bastard, G., Pochon, J. B., Levy, R., Allilaire, J. F., Dubois, B., & Fossati, P. (2004a). Executive functions and updating of the contents of working memory in unipolar depression. *Journal of Psychiatric Research, 38*(6), 567–576. doi:http://dx.doi.org/10.1016/j.jpsychires.2004.03.003

Hennion, S., Delbeuck, X., Duhamel, A., Lopes, R., Semah, F., Tyvaert, L., … Szurhaj, W. (2015). Characterization and prediction of theory of mind disorders in temporal lobe epilepsy. *Neuropsychology, 29*(3), 485–492. doi:http://dx.doi.org/10.1037/neu0000126

Hezel, D. M., & McNally, R. J. (2014). Theory of mind impairments in social anxiety disorder. *Behavior Therapy, 45*(4), 530–540. doi:http://dx.doi.org/10.1016/j.beth.2014.02.010

Hidaka, B. (2012). Depression as a disease of modernity: Explainations for increasing prevalence. *J. Affect Disord, 140*(3), 305–214. doi:10.1016/j.jad.2011.12.036

Hill, S. K., Keshavan, M. S., Thase, M. E., & Sweeney, J. A. (2004). Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. *American Journal of Psychiatry, 161*(6), 996–1003. doi:10.1176/appi.ajp.161.6.996

Horan, W. P., Pogge, D. L., Borgaro, S. R., Stokes, J. M., & Harvey, P. (1997). Learning and memory in adolescent psychiatric inpatients with major depression: A normative study of the California Verbal Learning Test. *Archives of Clinical Neuropsychology, 12*(6), 575–584.

Hünefeldt, T., Laghi, F., Ortu, F., & Belardinelli, M. O. (2013). The relationship between 'theory of mind' and attachment-related anxiety and avoidance in Italian adolescents. *Journal of Adolescence, 36*(3), 613–621. doi:http://dx.doi.org/10.1016/j.adolescence.2013.03.012

Hurst, K. (2010). Primary hyperparathyroidism as a secondary cause of depression. *Journal of the American Board of Family Medicine, 23*(5), 677–680.

Ilonen, T., Taiminen, T., Lauerma, H., Karlsson, H., Helenius, H. Y. M., Tuimala, P., … Salokangas, R. K. R. (2000). Impaired Wisconsin Card Sorting Test performance in first-episode schizophrenia: Resource or motivation deficit? *Comprehensive Psychiatry, 41*(5), 385–391. doi:http://dx.doi.org/10.1053/comp.2000.9017

Inoue, Y., Yamada, K., & Kanba, S. (2006). Deficit in theory of mind is a risk for relapse of major depression. *Journal of Affective Disorders, 95*(1–3), 125–127.

Inoue, Y., Tonooka, Y., Yamada, K., & Kanba, S. (2004). Deficiency of theory of mind in patients with remitted mood disorder. *Journal of Affective Disorders, 82*(3), 403–409.

Jones, G. H., Marsden, C. A., & Robbins, T. W. (1991). Behavioural rigidity and rule-learning deficits following isolation-rearing in the rat: neurochemical correlates. Behav Brain Res, 43(1), 35-50.

Kaller, C. P., Rahm, B., Spreer, J., Weiller, C., & Unterrainer, J. M. (2010). Dissociable contributions of left and right dorsolateral prefrontal cortex in planning. cerebral cortex. doi:10.1093/cercor/bhq096

Kalueff, A. V. P. D., & Nutt, D. J. M. D. (2007). Role of gaba in anxiety and depression. *Depression and Anxiety, 24*(7), 495–517.

Kaplan, J. S., Erickson, K., Luckenbaugh, D. A., Weiland-Fiedler, P., Geraci, M., Sahakian, B. J., … Neumeister, A. (2006). Differential performance on tasks of affective processing and decision-making in patients with Panic Disorder and Panic Disorder with comorbid Major Depressive Disorder. *Journal of Affective Disorders, 95*(1–3), 165–171. doi:10.1016/j.jad.2006.04.016

Karolewicz, B., Maciag, D., O'Dwyer, G., Stockmeier, C. A., Feyissa, A. M., & Rajkowska, G. (2010). Reduced level of glutamic acid decarboxylase-67 kda in the prefrontal cortex in major depression. *The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 13*(4), 411–420. doi:10.1017/S1461145709990587

Kendler, K., Kessler, R., Neale, M., Heath, A., & Eaves, L. (1993). The prediction of major depression in women: Toward an integrated etiologic model. *American Journal of Psychiatry, 150*(8), 1139–1148. doi:doi:10.1176/ajp.150.8.1139

Kessing, L. V. (1998). Cognitive impairment in the euthymic phase of affective disorder. *Psychological Medicine, 28*(05), 1027–1038. doi:doi:null

Kessler, R. C., & Walters, E., E. (1998). Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the national comorbidity survey. *Depression and Anxiety, 7*(1), 3–14.

Khosravi Fard, E., Keelor, J. L., Akbarzadeh Bagheban, A., & Keith, R. W. (2016). Comparison of the Rey Auditory Verbal Learning Test (RAVLT) and Digit Test among typically achieving and gifted students. *Iranian Journal of Child Neurology, 10*(2), 26–37.

Killgore, W. D. S., Gruber, S. A., & Yurgelun-Todd, D. A. (2007). Depressed mood and lateralized prefrontal activity during a Stroop task in adolescent children. *Neuroscience Letters, 416*(1), 43–48. doi:http://dx.doi.org/10.1016/j.neulet.2007.01.081

Kirk, S. A., & Hsieh, D. K. (2004). Diagnostic consistency in assessing conduct disorder: An experiment on the effect of social context. *American Journal of Orthopsychiatry, 74*(1), 43–55. doi:http://dx.doi.org/10.1037/0002-9432.74.1.43

Klein, D. N., Glenn, C. R., Kosty, D. B., Seeley, J. R., Rohde, P., & Lewinsohn, P. M. (2013). Predictors of first lifetime onset of major depressive disorder in young adulthood. *Journal of Abnormal Psychology, 122*(1), 1–6. doi:http://dx.doi.org/10.1037/a0029567

Koren, D., Seidman, L. J., Harrison, R. H., Lyons, M. J., Kremem, W. S., Caplan, B., … Tsuang, M. T. (1998). Factor structure of the Wisconsin Card Sorting Test:

Dimensions of deficit in schizophrenia. *Neuropsychology, 12*(2), 289–302. doi:http://dx.doi.org/10.1037/0894-4105.12.2.289

Kosel, M., Rudolph, U., Wielepp, P., Luginbühl, M., Schmitt, W., Fisch, H. U., & Schlaepfer, T. E. (2004). Diminished GABAA receptor-binding capacity and a DNA base substitution in a patient with treatment-resistant depression and anxiety. *Neuropsychopharmacology, 29*(2), 347–350. doi:http://dx.doi.org/10.1038/sj.npp.1300353

Kruijshaar, M. E., Hoeymans, N., Bijl, R. V., Spijker, J., & Essink-Bot, M. L. (2003). Levels of disability in major depression: Findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Journal of Affective Disorders, 77*(1), 53–64. doi:http://dx.doi.org/10.1016/S0165-0327(02)00099-X

Kucukibrahimoglu, E., Saygin, M. Z., Caliskan, M., Kaplan, O. K., Unsal, C., & Goren, M. Z. (2009). The change in plasma GABA, glutamine and glutamate levels in fluoxetine- or S-citalopram-treated female patients with major depression. *European Journal of Clinical Pharmacology, 65*(6), 571–577.

Kugaya, A., Sanacora, G., Verhoeff, N. P. L. G., Fujita, M., Mason, G. F., Seneca, N. M., … Innis, R. B. (2003). Cerebral benzodiazepine receptors in depressed patients measured with [123i]iomazenil SPECT. *Biological Psychiatry, 54*(8), 792–799. doi:http://dx.doi.org/10.1016/S0006-3223(02)01788-2

Kupfer, D. J. (1976). REM latency: A psychobiologic marker for primary depressive disease. *Biol Psychiatry, 11*(2), 159–174.

Kuriyama, K., & Sze, P. Y. (1971). Blood-brain barrier to H3-γ-aminobutyric acid in normal and amino oxyacetic acid-treated animals. *Neuropharmacology, 10*(1), 103–108. doi:http://dx.doi.org/10.1016/0028-3908(71)90013-X

Kuyken, W., Kurzer, N., DeRubeis, R. J., Beck, A. T., & Brown, G. K. (2001). Response to cognitive therapy in depression: The role of maladaptive beliefs and personality disorders. *Journal of Consulting and Clinical Psychology, 69*(3), 560–566. doi:http://dx.doi.org/10.1037/0022-006X.69.3.560

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2016). Do I misconstrue? Sarcasm detection, emotion recognition, and theory of mind in Huntington disease. *Neuropsychology, 30*(2), 181–189. doi:http://dx.doi.org/10.1037/neu0000224

Lautenbacher, S., Spernal, J., & Krieg, J.-C. (2002). Divided and selective attention in panic disorder. *European Archives of Psychiatry and Clinical Neuroscience, 252*(5), 210–213.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., … Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry, 12*(5), 224–231. doi:http://dx.doi.org/10.1016/S0924-9338(97)83296-8

Lehto, J. (1996). Are executive function tests dependent on working memory capacity? *The Quarterly Journal of Experimental Psychology Section A, 49*(1), 29–50. doi:10.1080/713755616

Lenze, S. N., Cyranowski, J. M., Thompson, W. K., Anderson, B., & Frank, E. (2008). The cumulative impact of nonsevere life events predicts depression recurrence during maintenance treatment with interpersonal psychotherapy. *Journal of Consulting and Clinical Psychology, 76*(6), 979–987. doi:http://dx.doi.org/10.1037/a0012862

Leppänen, J. M., Milders, M., Bell, J. S., Terriere, E., & Hietanen, J. K. (2004). Depression biases the recognition of emotionally neutral faces. *Psychiatry Research, 128*(2), 123–133. doi:http://dx.doi.org/10.1016/j.psychres.2004.05.020

Lesser, I. M., Rubin, R. T., Rifkin, A., Swinson, R. P., Ballenger, J. C., Burrows, G. D., … Pecknold, J. C. (1989). Secondary depression in panic disorder and agoraphobia: II. Dimensions of depressive symptomatology and their response to treatment. *Journal of Affective Disorders, 16*(1), 49–58.

Levy, L. M., & Degnan, A. J. (2013). GABA-Based Evaluation of Neurologic Conditions: MR Spectroscopy. American Journal of Neuroradiology, 34(2), 259-265. doi:10.3174/ajnr.A2902

Lewinsohn, P. M., Roberts, R. E., Seeley, J. R., Rohde, P., Gotlib, I. H., & Hops, H. (1994). Adolescent psychopathology: II. Psychosocial risk factors for depression. *Journal of Abnormal Psychology, 103*(2), 302–315.

Li, N., Wu, X., & Li, L. (2007). Chronic administration of clozapine alleviates reversal-learning impairment in isolation-reared rats. Behav Pharmacol, 18(2), 135-145. doi:10.1097/FBP.0b013e3280d3ee83

Lieb, R., Isensee, B., Höfler, M., Pfister, H., & Wittchen, H. (2002). Parental major depression and the risk of depression and other mental disorders in offspring: A prospective-longitudinal community study. *Archives of General Psychiatry, 59*(4), 365–374. doi:10.1001/archpsyc.59.4.365

Liu, Z., Zhao, J., & Tam, W. C. C. (2003). Attention and executive function impairments in unaffected siblings of patients with schizophrenia. *Hong Kong Journal of Psychiatry, 13*(2), 8–11.

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science, 337(6100), 1357-1360. doi:10.1126/science.1220845.

Mannie, Z. N., Harmer, C. J., Cowen, P. J., & Norbury, R. (2009). A functional magnetic resonance imaging study of verbal working memory in young people at increased familial risk of depression. *Biological Psychiatry, 67*(5), 471–477.

Mannie, Z. N., Barnes, J., Bristow, G. C., Harmer, C. J., & Cowen, P. J. (2009). Memory impairment in young women at increased risk of depression: Influence of cortisol and 5-HTT genotype. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences, 39*(5), 757–762.

Mannie, Z. N., Norbury, R., Murphy, S. E., Inkster, B., Harmer, C. J., & Cowen, P. J. (2008). Affective modulation of anterior cingulate cortex in young people at increased familial risk of depression. *The British Journal of Psychiatry, 192*(5), 356–361. doi:10.1192/bjp.bp.107.043398

Mansouri, F. A., Matsumoto, K., & Tanaka, K. (2006). Prefrontal cell activities related to monkeys' success and failure in adapting to rule changes in a Wisconsin Card Sorting Test Analog. *The Journal of Neuroscience, 26*(10), 2745–2756. doi:http://dx.doi.org/10.1523/JNEUROSCI.5238-05.2006

McCabe, D. P., Roediger, H. L., III, McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: Evidence for a common executive attention construct. *Neuropsychology, 24*(2), 222–243. doi:http://dx.doi.org/10.1037/a0017619

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive

disorder: A review and synthesis. *Neuropsychology, 24*(1), 9–34. doi:http://dx.doi.org/10.1037/a0017336

McFarland, C., & Miller, D. T. (1994). The framing of relative performance feedback: Seeing the glass as half empty or half full. *Journal of Personality and Social Psychology, 66*(6), 1061–1073. doi:http://dx.doi.org/10.1037/0022-3514.66.6.1061

Merriam, E. P., Thase, M. E., Haas, G. L., Keshavan, M. S., & Sweeney, J. A. (1999). Prefrontal cortical dysfunction in depression determined by Wisconsin Card Sorting Test performance. *American Journal of Psychiatry, 156*(5), 780–782.

Mishel, M. H. (1981). The measurement of uncertainty in illness. *Nurs. Res., 30*(5), 258–263.

Moilanen, D. L. (1993). Depressive information processing among nonclinic, nonreferred college students. *Journal of Counseling Psychology, 40*(3), 340–347. doi:http://dx.doi.org/10.1037/0022-0167.40.3.340

National Health Survey (NHS). (2014). National Health Survey: First Results: 2014–2015. Canberra: Australian Bureau of Statistics.

Neu, P., Bajbouj, M., Schilling, A., Godemann, F., Berman, R. M., & Schlattmann, P. (2005). Cognitive function over the treatment course of depression in middle-aged patients: Correlation with brain MRI signal hyperintensities. *Journal of Psychiatric Research, 39*(2), 129–135. doi:10.1016/j.jpsychires.2004.06.004

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology, 109*(3), 504–511. doi:10.1037/0021-843X.109.3.504

Norton, P. J., Hayes, S. A., & Hope, D. A. (2004). Effects of a transdiagnostic group treatment for anxiety on secondary depression. *Depression & Anxiety, 20*(4), 198–202.

Nunes, T., Bryant, P., Barros, R., & Sylva, K. (2012). The relative importance of two different mathematical abilities to mathematical achievement. *British Journal of Educational Psychology, 82*(1), 136–156. doi:10.1111/j.2044-8279.2011.02033.x

Olino, T. M., Klein, D. N., Lewinsohn, P. M., Rohde, P., & Seeley, J. R. (2010). Latent trajectory classes of depressive and anxiety disorders from adolescence to adulthood: Descriptions of classes and associations with risk factors. *Comprehensive Psychiatry, 51*(3), 224–235. doi:http://dx.doi.org/10.1016/j.comppsych.2009.07.002

Öngür, D., Drevets, W. C., & Price, J. L. (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. In *Proceedings of the National Academy of Sciences of the United States of America, 95*(22), 13290–13295.

Owen, A. M., Lee, A. C. H., & Williams, E. J. (2000). Dissociating aspects of verbal working memory within the human frontal lobe: Further evidence for a 'process-specific' model of lateral frontal organization. *Psychobiology, 28*(2), 146–155. doi:10.3758/bf03331974

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping, 25*(1), 46–59. doi:10.1002/hbm.20131

Pallant, J. (2013). *SPSS survival manual* (5th ed.). Sydney, NSW: Allen & Unwin.

Paradiso, S., Lamberty, G. J., Garvey, M. J., & Robinson, R. G. (1997). Cognitive impairment in the euthymic phase of chronic unipolar depression. *Journal of Nervous and Mental Disease, 185*(12), 748–754.

Park, R. J., Goodyer, I. M., & Teasdale, J. D. (2005). Self-devaluative dysphoric experience and the prediction of persistent first-episode major depressive disorder in adolescents. *Psychological Medicine, 35*(4), 539–548.

Pehrson, A. L., & Sanchez, C. (2015). Altered gamma-aminobutyric acid neurotransmission in major depressive disorder: A critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug Des Devel Ther, 9*, 603–624. doi:10.2147/dddt.s62912

Pell, M. D., Monetta, L., Rothermich, K., Kotz, S. A., Cheang, H. S., & McDonald, S. (2014). Social perception in adults with Parkinson's disease. *Neuropsychology, 28*(6), 905–916. doi:http://dx.doi.org/10.1037/neu0000090

Petty, F., & Sherman, A. D. (1984). Plasma GABA levels in psychiatric illness. *Journal of Affective Disorders, 6*(2), 131–138. doi:10.1016/0165-0327(84)90018-1

Petty, F., Kramer, G. L., & Feldman, M. (1987). Is plasma GABA of peripheral origin? *Biological Psychiatry, 22*(6), 725–732. doi:10.1016/0006-3223(87)90204-6

Petty, F., Kramer, G. L., Gullion, C. M., & Rush, A. J. (1992). Low plasma γ-aminobutyric acid levels in male patients with depression. *Biological Psychiatry, 32*(4), 354–363. doi:10.1016/0006-3223(92)90039-3

Petty, F., Kramer, G. L., Fulton, M., Davis, L., & Rush, A. J. (1995). Stability of plasma GABA at four-year follow-up in patients with primary unipolar depression. *Biological Psychiatry, 37*(11), 806–810. doi:10.1016/0006-3223(94)00226-s

Petty, F., Steinberg, J., Kramer, G. L., Fulton, M., & Moeller, F. G. (1993). Desipramine does not alter plasma GABA in patients with major depression. *Journal of Affective Disorders, 29*(1), 53–56.

Petty, F., Fulton, M., Kramer, G. L., Kram, M., Davis, L. L., & Rush, A. J. (1999). Evidence for the segregation of a major gene for human plasma GABA levels. *Molecular Psychiatry, 4*(6), 587–589.

Petty, F., Fulton, M., Moeller, F. G., Kramer, G., Wilson, L., Fraser, K., & Isbell, P. (1993). Plasma gamma-aminobutyric acid (GABA) is low in alcoholics. *Psychopharmacology Bulletin, 29*(2), 277–281.

Phelan, J., Schwartz, J. E., Bromet, E. J., Dew, M. A., Parkinson, D. K., Schulberg, H. C., … Curtis, E. C. (1991). Work stress, family stress and depression in professional and managerial employees. *Psychological Medicine, 21*(4), 999–1012. doi:10.1017/S0033291700029998

Pinninti, N. R., Madison, H., Musser, E., & Rissmiller, D. (2003). MINI International Neuropsychiatric Schedule: Clinical utility and patient acceptance. *European Psychiatry, 18*(7), 361–364. doi:http://dx.doi.org/10.1016/j.eurpsy.2003.03.004

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *British Journal of Psychiatry, 182*(3), 214–220. doi:10.1192/bjp.182.3.214

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology. *Am. J. Psychiatry, 149*, 999–1010.

Preiss, M., Kucerova, H., Lukavsky, J., Stepankova, H., Sos, P., & Kawaciukova, R. (2009). Cognitive deficits in the euthymic phase of unipolar depression. *Psychiatry Research, 169*(3), 235–239.

Purcell, R., Maruff, P., Kyrios, M., & Pantelis, C. (1997). Neuropsychological function in young patients with unipolar major depression. *Psychological Medicine, 27*(6), 1277–1285.

Queensland Studies Authority (QSA). (2014a). Mathematics A syllabus. Spring Hill, Queensland: Author.

Queensland Studies Authority (QSA). (2014b). Mathematics B syllabus. Spring Hill, Queensland: Author.

Queensland Studies Authority (QSA). (2014c). Mathematics C syllabus. Spring Hill: Queensland: Author.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385–401. doi:10.1177/014662167700100306

Rajkowska, G., O'Dwyer, G., Teleki, Z., Stockmeier, C. A., & Miguel-Hidalgo, J. J. (2007). GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology, 32*(2), 471–482.

Rajkowska, G., Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., … Stockmeier, C. A. (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression∗. *Biological Psychiatry, 45*(9), 1085–1098. doi:http://dx.doi.org/10.1016/S0006-3223(99)00041-4

Rey, A. (1964). *L'examen clinique en psychologie*. Paris, France: Presses Universitaires de France.

Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin Card Sorting Test: A meta-analytic review. *Psychology and Aging, 19*(3), 482–494. doi:http://dx.doi.org/10.1037/0882-7974.19.3.482

Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1994). Are adolescents changed by an episode of major depression? *Journal of the American Academy of Child & Adolescent Psychiatry, 33*(9), 1289–1298. doi:10.1097/00004583-199411000-00010

Rose, E. J., & Ebmeier, K. P. (2006). Pattern of impaired working memory during major depression. *Journal of Affective Disorders, 90*(2–3), 149–161.

Rubin, R. T., & Lesser, I. M. (1990). Secondary depression in panic patients. *Journal of Psychiatric Research, 24*, Supplement 1(0), 78–79. doi:http://dx.doi.org/10.1016/0022-3956(90)90096-9

Rush, A. J., Weissenburger, J., & Eaves, G. (1986). Do thinking patterns predict depressive symptoms? *Cognitive Therapy and Research, 10*(2), 225–235. doi:10.1007/bf01173727

Salvadore, G., Nugent, A. C., Lemaitre, H., Luckenbaugh, D. A., Tinsley, R., Cannon, D. M., Drevets, W. C. (2011). Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. Neuroimage, 54(4), 2643-2651. doi:10.1016/j.neuroimage.2010.11.011

Sanacora, G., Mason, G. F., Rothman, D. L., & Krystal, J. H. (2002). Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *American Journal of Psychiatry, 159*(4), 663–665. doi:doi:10.1176/appi.ajp.159.4.663

Sanacora, G., Fenton, L. R., Fasula, M. K., Rothman, D. L., Levin, Y., Krystal, J. H., & Mason, G. F. (2006). Cortical γ-aminobutyric acid concentrations in depressed patients receiving cognitive behavioral therapy. *Biological Psychiatry, 59*(3), 284–286. doi:http://dx.doi.org/10.1016/j.biopsych.2005.07.015

Sanacora, G., Gueorguieva, R., Epperson, C. N., Wu, Y., Appel, M., Rothman, D. L., … Mason, G. F. (2004). Subtype-specific alterations of [gamma]-aminobutyric acid and glutamate in patients with major depression. *Archives of General Psychiatry, 61*(7), 705–713.

Sanacora, G., Mason, G. F., Rothman, D. L., Behar, K. L., Hyder, F., Petroff, O. A. C., … Krystal, J. H. (1999). Reduced cortical γ-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 56*(11), 1043–1047. doi:http://dx.doi.org/10.1001/archpsyc.56.11.1043

Sanacora, G., Mason, G. F., Rothman, D. L., Hyder, F., Ciarcia, J. J., Ostroff, R. B., … Krystal, J. H. (2003). Increased cortical GABA concentrations in depressed patients receiving ECT. *American Journal of Psychiatry, 160*(3), 577–579. doi:doi:10.1176/appi.ajp.160.3.577

Sanders, M. R. (2010). Adopting a public health approach to the delivery of evidence-based parenting interventions. Canadian Psychology/Psychologie canadienne, 51(1), 17-23. doi:http://dx.doi.org/10.1037/a0018295

Schenkel, L. S., Marlow-O'Connor, M., Moss, M., Sweeney, J. A., & Pavuluri, M. N. (2008). Theory of mind and social inference in children and adolescents with bipolar disorder. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences, 38*(6), 791–800.

Schlipf, S., Batra, A., Walter, G., Zeep, C., Wildgruber, D., Fallgatter, A., & Ethofer, T. (2013). Judgment of emotional information expressed by prosody and semantics in patients with unipolar depression. *Frontiers in Psychology, 4*. doi:http://dx.doi.org/10.3389/fpsyg.2013.00461

Schrijver, N. C., & Würbel, H. (2001). Early social deprivation disrupts attentional, but not affective, shifts in rats. Behavioral Neuroscience, 115(2), 437-442. doi:http://dx.doi.org/10.1037/0735-7044.115.2.437

Schrijver, N. C. A., Pallier, P. N., Brown, V. J., & Würbel, H. (2004). Double dissociation of social and environmental stimulation on spatial learning and reversal learning in rats. Behavioural Brain Research, 152(2), 307-314. doi:http://dx.doi.org/10.1016/j.bbr.2003.10.016

Shallice, T. (1982). Specific impairments of planning: Philosophical transactions of the Royal Society of London B. *Biological Sciences, 298*(1089), 199–209. doi:10.1098/rstb.1982.0082

Shear, M. K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W., … Frank, D. M. (2001). Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depression and Anxiety, 13*(4), 166–178. doi:10.1002/da.1033

Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*(S20), 22–33.

Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., … Dunbar, G. C. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry, 12*(5), 232–241. doi:http://dx.doi.org/10.1016/S0924-9338(97)83297-X

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: Deprivation and threat. *Trends in Cognitive Sciences, 18*(11), 580–585. doi:http://dx.doi.org/10.1016/j.tics.2014.09.001

Sheridan, M. A., & McLaughlin, K. A. (2016). Neurobiological models of the impact of adversity on education. *Current Opinion in Behavioral Sciences, 10*, 108–113. doi:http://dx.doi.org/10.1016/j.cobeha.2016.05.013

Shiah, I. S., Yatham, L. N., Gau, Y.-C., & Baker, G. B. (2003). Effect of lamotrigine on plasma GABA levels in healthy humans. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(3), 419–423. doi:http://dx.doi.org/10.1016/S0278-5846(03)00028-9

Siegman, A. W., & Boyle, S. (1993). Voices of fear and anxiety and sadness and depression: The effects of speech rate and loudness on fear and anxiety and sadness and depression. *Journal of Abnormal Psychology, 102*(3), 430–437. doi:10.1037/0021-843x.102.3.430

Smith, D. J., Muir, W. J., & Blackwood, D. H. R. (2006). Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. *Bipolar Disorders, 8*(1), 40–46.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin, 139*(1), 81–132. doi:10.1016/j.eurpsy.2006.03.0081681499310.1016/j.eurpsy.2006.03.0082006-12445-003

St Clair-Thompson, H. L., & Gathercole, S. E. (2006). Executive functions and achievements in school: Shifting, updating, inhibition, and working memory.

The Quarterly Journal of Experimental Psychology, 59(4), 745–759. doi:10.1080/17470210500162854

Stange, J. P., Alloy, L. B., Flynn, M., & Abramson, L. Y. (2013). Negative inferential style, emotional clarity, and life stress: Integrating vulnerabilities to depression in adolescence. *Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53, 42*(4), 508–518. doi:10.1080/15374416.2012.743104

Steele, A., Karmiloff-Smith, A., Cornish, K., & Scerif, G. (2012). The multiple subfunctions of attention: Differential developmental gateways to literacy and numeracy. *Child Development, 83*(6), 2028–2041. doi:10.1111/j.1467-8624.2012.01809.x

Stegenga, B. T., King, M., Grobbee, D. E., Torres-Gonzalez, F., Svab, I., Maaroos, H. I., … Geerlings, M. I. (2012). Differential impact of risk factors for women and men on the risk of major depressive disorder. *Ann. Epidemiol., 22*(6), 388–396. doi:10.1016/j.annepidem.2012.04.011

Stordal, K. I., Lundervold, A. J., Egeland, J., Mykletun, A., Asbjornsen, A., Landro, N. I., … Lund, A. (2004). Impairment across executive functions in recurrent major depression. *Nordic Journal of Psychiatry, 58*(1), 41–47. doi:10.1080/08039480310000789

Stroud, C. B., Davila, J., Hammen, C., & Vrshek-Schallhorn, S. (2011). Severe and nonsevere events in first onsets versus recurrences of depression: Evidence for stress sensitization. *Journal of Abnormal Psychology, 120*(1), 142–154. doi:http://dx.doi.org/10.1037/a0021659

Surguladze, S. A., Young, A. W., Senior, C., Brébion, G., Travis, M. J., & Phillips, M. L. (2004). Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology, 18*(2), 212–218. doi:http://dx.doi.org/10.1037/0894-4105.18.2.212

Swanson, H. L. (2011). Working memory, attention, and mathematical problem solving: A longitudinal study of elementary school children. *Journal of Educational Psychology, 103*(4), 821–837. doi:10.1037/a0025114

Szöke, A., Schürhoff, F., Golmard, J.-L., Alter, C., Roy, I., Méary, A., … Leboyer, M. (2006). Familial resemblance for executive functions in families of schizophrenic and bipolar patients. *Psychiatry Research, 144*(2–3), 131–138. doi:http://dx.doi.org/10.1016/j.psychres.2005.11.013

Thorell, L. B. (2007). Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. *Journal of Child Psychology and Psychiatry, 48*(11), 1061–1070. doi:10.1111/j.1469-7610.2007.01777.x

Todd, A. R., Forstmann, M., Burgmer, P., Brooks, A. W., & Galinsky, A. D. (2015). Anxious and egocentric: How specific emotions influence perspective taking. *Journal of Experimental Psychology: General, 144*(2), 374–391. doi:http://dx.doi.org/10.1037/xge0000048

Troyer, A. K., Leach, L., & Strauss, E. (2006). Aging and response inhibition: Normative data for the Victoria Stroop Test. *Aging, Neuropsychology, and Cognition, 13*(1), 20–35. doi:10.1080/138255890968187

Twenge, J. (2000). The age of anxiety? Birth cohort change in anxiety and neuroticism, 1952–1993. *Journal of Personality and Social Psychology, 76*(6), 1007–1021. doi:10.1O37//OO22-3514.79.6.1007

Twenge, J. (2015). Time period and birth cohort differences in depressive symptoms in the U.S., 1982–2013. *Soc. Indic. Res., 121*, 437–454. doi:10.1007/s11205-014-0647-1

Uekermann, J., Abdel-Hamid, M., Lehmkämper, C., Vollmoeller, W., & Daum, I. (2008). Perception of affective prosody in major depression: A link to executive functions? *Journal of the International Neuropsychological Society, 14*(4), 552–561. doi:http://dx.doi.org/10.1017/S1355617708080740

Uekermann, J., Channon, S., Lehmkämper, C., Abdel-Hamid, M., Vollmoeller, W., & Daum, I. (2008). Executive function, mentalizing and humor in major depression. *Journal of the International Neuropsychological Society, 14*(1), 55–62.

USCN. (2011). Enzyme-linked Immunosorbent Assay Kit For Gamma-Aminobutyric Acid (gABA) Organism: General Instruction manual. In U. L. S. Inc. (Ed.). Houston TX.

Uylings, H. B. M., Groenewegen, H. J., & Kolb, B. (2003). Do rats have a prefrontal cortex? Behavioural Brain Research, 146(1–2), 3-17. doi:http://dx.doi.org/10.1016/j.bbr.2003.09.028

Van der Ven, S. H. G., Kroesbergen, E. H., Boom, J., & Leseman, P. P. M. (2012). The development of executive functions and early mathematics: A dynamic relationship. *British Journal of Educational Psychology, 82*(1), 100–119. doi:10.1111/j.2044-8279.2011.02035.x

van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernández, G. (2009). From specificity to sensitivity: How acute stress affects amygdala processing of biologically salient stimuli. *Biological Psychiatry, 66*(7), 649–655. doi:http://dx.doi.org/10.1016/j.biopsych.2009.05.014666

Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*(7067), 500–503.

Wagner, G., Koch, K., Reichenbach, J. R., Sauer, H., & Schlösser, R. G. M. (2006). The special involvement of the rostrolateral prefrontal cortex in planning abilities: An event-related fMRI study with the Tower of London paradigm. *Neuropsychologia, 44*(12), 2337–2347. doi:http://dx.doi.org/10.1016/j.neuropsychologia.2006.05.014

Walsh, N. D., Williams, S. C. R., Brammer, M. J., Bullmore, E. T., Kim, J., Suckling, J., … Fu, C. H. Y. (2007). A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. *Biological Psychiatry, 62*(11), 1236–1243.

Wang, C. E., Halvorsen, M., Sundet, K., Steffensen, A. L., Holte, A., & Waterloo, K. (2006). Verbal memory performance of mildly to moderately depressed outpatient younger adults. *Journal of Affective Disorders, 92*(2–3), 283–286. doi:10.1016/j.jad.2006.02.008

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdeli, H. (2006). Offspring of depressed parents: 20 years later. *American Journal of Psychiatry, 163*(6), 1001–1008. doi:10.1176/appi.ajp.163.6.1001

Welsh, J. A., Nix, R. L., Blair, C., Bierman, K. L., & Nelson, K. E. (2010). The development of cognitive skills and gains in academic school readiness for children from low-income families. *Journal of Educational Psychology, 102*(1), 43–53. doi:10.1037/a0016738

Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A normative-developmental study of executive function: A window on prefrontal function in children.

Developmental Neuropsychology, 7(2), 131–149. doi:10.1080/87565649109540483

Weniger, G., Lange, C., Rüther, E., & Irle, E. (2004). Differential impairments of facial affect recognition in schizophrenia subtypes and major depression. *Psychiatry Research, 128*(2), 135–146. doi:http://dx.doi.org/10.1016/j.psychres.2003.12.027

Whitney, K. A., Shepard, P. H., Mariner, J., Mossbarger, B., & Herman, S. M. (2010). Validity of the Wechsler Test of Adult Reading (WTAR): Effort considered in a clinical sample of U.S. military veterans. *Applied Neuropsychology, 17*(3), 196–204. doi:10.1080/09084282.2010.499787

Williams, J. B. W. (1988). A structured interview guide for the Hamilton Depression Rating Scale. *Archives of General Psychiatry, 45*(8), 742–747. doi:10.1001/archpsyc.1988.01800320058007

Williams, J. B. W. (2005). *Structured interview guide for the Hamilton Depression and Anxiety Scales (SIGH-AD)*. Retrieved from

Willoughby, M. T., Blair, C. B., Wirth, R. J., & Greenberg, M. (2012). The measurement of executive function at age 5: Psychometric properties and relationship to academic achievement. *Psychological Assessment, 24*(1), 226–239. doi:10.1037/a0025361

Winokur, G. (1990). The concept of secondary depression and its relationship to comorbidity. *Psychiatric Clinics of North America, 13*(4), 567–583.

World Heath Organization (WHO). (2012). Depression fact sheet No. 369. Retrieved from http://www.who.int/mediacentre/factsheets/fs369/en/index.html

Wright, S. L., Langenecker, S. A., Deldin, P. J., Rapport, L. J., Nielson, K. A., Kade, A. M., … Zubieta, J.-K. (2009). Gender-specific disruptions in emotion processing

in younger adults with depression. *Depression and Anxiety, 26*(2), 182–189. doi:http://dx.doi.org/10.1002/da.20502

Zhang, W., Li, F., Qin, S., & Luo, J. (2012). The integrative effects of cognitive reappraisal on negative affect: Associated changes in secretory immunoglobulin A, unpleasantness and ERP activity. *PLOS ONE, 7*(2), e30761. doi:10.1371/journal.pone.0030761

Appendix A

Patient initials: _____ Patient code: P __ __

Visit date: _____

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION AND ANXIETY SCALES (SIGH-AD)

Janet B.W. Williams, D.S.W.

This is an interview guide for the Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A), combined.

Items from the HAM-A are shaded

Items from the HAM-D are not.

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

HAM-A ITEMS

For some of the HAM-A items, you will find you have already asked about some of the symptoms. You do not need to repeat questions about these symptoms unless you need additional information to rate their severity. Symptoms that have been asked about previously, are underlined (in the right-hand column) as a reminder to consider them in assigning the final item severity score.

All of the items in the HAM-A have the same anchor points. The following may be useful as guides to rating item severity:

MILD:	Occurs irregularly and for short periods of time.
MODERATE:	Occurs more constantly and of longer duration, requiring considerable effort on the part of the subject to cope with it.
SEVERE:	Continuous and dominates the subject's life.
VERY SEVERE:	Incapacitating.

Interviewers may find it helpful to ask the patient the following questions to help clarify the severity of a symptom: How much time does [the symptom] take up? Has [the symptom] been irregular or constant? Has it been easily manageable? How severe has it been when you get it? How much time over the last week has it been bothering you?

Panic attacks. If the patient has panic attacks, this will affect the ratings of many of the symptoms. It is recommended that you consider the total amount of time during the past week that the panic attack symptoms occurred, as well as their severity. Therefore, for example, a patient who has a few severe but short-lived panic attacks during the week, but who otherwise does not have many anxiety symptoms, would probably not have a very high total HAM-A score.

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION AND ANXIETY SCALES (SIGH-AD)

Janet B.W. Williams, D.S.W.

NOTES:

Time period. The interview questions indicate that the ratings should be based on the patient's condition in the past week.

HAM-D loss of weight item. It is recommended that this item be rated positively whenever the patient has lost weight relative to their baseline weight (i.e., before their current episode of depression), provided that they have not begun to gain back lost weight. Once the patient has begun to gain weight, however, even if they are still below their baseline, they should no longer be rated positively on this item.

Referent of "usual" or "normal" condition. Several of the interview questions in the HAM-D refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks. Items on the HAM-A are rated positively if the symptoms are present, regardless of whether or not the symptoms represent a change from the patient's usual condition.

Attribution. In general, symptoms should be rated regardless of attribution, i.e. “rate it as you see it.” For example, a patient who does not have insomnia but says it is because they are taking sleeping pills, should not be rated positively on the insomnia items. This relieves the rater of having to guess whether or not the patient would have insomnia if they were not taking sleeping pills. An exception is when the interviewer is certain that this symptom can be *unambiguously* attributed to a source other than the depression, such as a known medication or a medical condition. Then the symptom may be rated as absent.

This instrument provides an interview guide for both the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960) and the Hamilton Anxiety Scale (Hamilton, Max: The assessment of anxiety states by rating. Brit J Med Psychol 32:50-55, 1959). The anchor point descriptions for both scales, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747).

This work was supported in part by Biomedical Research Support Grant #903-E759S and Psychiatric Institute Research Support Grant #903-8517A from the Research Foundation for Mental Hygiene, Inc. and NIMH Grant #1 P50 MH 43520.

For further information contact Dr. Williams at 1051 Riverside Drive, Unit 60, N.Y., N.Y. 10032 (Tel: 212-543-5524; fax: 212-543-5525; E-mail: jbw5@columbia.edu). 4/30/96 - v. 2

Revised for GSK Study NKF 100092, 6/16/04, Janet B. W. Williams & Kenneth A. Kobak

3

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION AND ANXIETY SCALES (SIGH-AD)*

PT'S INITIALS: _____

TIME BEGAN SIGH-AD: _____

SUBJECT IDENTIFIER: _____

DATE: __ __ __ __ __ __

INTERVIEWER: _____

OVERVIEW: **I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?**

What's your mood been like this past week (compared to when you feel OK)? Have you been feeling down or depressed? (if yes): Can you describe what this feeling has been like for you? How bad is the feeling? Does the feeling lift at all if something good happens? How are you feeling about the future? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**1. DEPRESSED MOOD** (sadness, hopeless, helpless, worthless): 0 - absent 1 - indicated only on questioning*(occasional, mild depression)* 2 - spontaneously reported verbally *(persistent, mild to moderate depression)* 3 - communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep *(persistent, moderate to severe depression,)* 4 - VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication *(persistent, very severe depression, with extreme hopelessness or tearfulness)*

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

NOTES:

* Janet B.W. Williams, DSW, Unit 60, 1051 Riverside Drive, New York, NY 10032
f:\institut\cultadap\project\ma2787\final-versions\sighadoriq.doc-11/10/2005

How have you been spending your time this past week (when not at work)? Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? How much less interested in these things have you been this past week compared to when you're not depressed? How hard to do you have to push yourself to do them? Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why? About how many hours a day do you spend doing things that interest you? Is there anything you look forward to? IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? How much less productive or efficient are you compared to before you were depressed?	**2. WORK AND ACTIVITIES:** 0 - no difficulty 1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies *(Mild reduction in interest or pleasure; no clear impairment in functioning)* 2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities; (*Clear reduction in interest, pleasure or functioning)* 3 - decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (hospital job or hobbies) exclusive of ward chores (*Profound reduction in interest, pleasure, or functioning)* 4 - stopped working bec. of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (*Unable to work or fulfill primary role because of illness, and total loss of interest)*
Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began? **When have you been falling asleep and waking up over the past week?**	
Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep? Have you changed the time at which you try to get to sleep since you've been depressed?	**3. INSOMNIA EARLY (INITIAL INSOMNIA):** 0 - no difficulty falling asleep 1 - complains of occasional difficulty falling asleep – (i.e., more than 1/2 hour, *2-3 nights)* 2 - complains of nightly difficulty falling asleep *(i.e., more than ½ hour, 4 or more nights)*
During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep? Do you wake up more than once during the night? (If yes: How long does it take for you to fall back to sleep each time?) Have you felt your sleeping has been restless or disturbed some nights? How many nights this week have you had that kind of trouble?	**4. INSOMNIA MIDDLE:** 0 - no difficulty 1 - complains of being restless and disturbed during the night (or *Occasional difficulty, i.e., 2-3 nights, more than ½ hr)* 2 - waking during the night - any getting out of bed (except to void) (*Often i.e., 4 or more nights of difficulty, more than ½ hr)*

What time have you been waking up in the morning for the last time, this past week? IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)? How many mornings this past week have you awakened early?	**5. INSOMNIA LATE (TERMINAL INSOMNIA):** 0 - no difficulty 1 - waking in early hours of morning but goes back to sleep *(occasional i.e., 2-3 nights) difficulty)* 2 - unable to fall asleep again if gets out of bed *(often i.e., 4 or more nights difficulty)*

In the last week, have you had broken sleep or unsatisfying sleep and felt tired when you woke up? How about having bad dreams or nightmares? FOR EACH SX: How bad has that been? How often has this happened in the past week?	**6. INSOMNIA** (difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

This past week, have you been feeling better or worse at any particular time of day - morning or evening? IF VARIATION: How much worse do you feel in the (MORNING OR EVENING)? IF UNSURE: A little bit worse or a lot worse? **NOTE: MOST OF THE INFORMATION NEEDED TO RATE THIS ITEM HAS ALREADY BEEN OBTAINED.**	**7. DEPRESSED MOOD** (loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the last week, have you had trouble concentrating, or trouble remembering things? (How much?)	**8. INTELLECTUAL** (difficulty in concentrating; poor memory): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.) Has there been any change in your interest in sex (from when you were feeling OK)? IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)	**9. GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances): 0 - absent 1 - mild (*Somewhat less interest than usual)* 2 - severe (*A lot less interest than usual)*

FOR WOMEN: When some women feel nervous or anxious, they are unable to have an orgasm, although they have had them in the past. Has that happened to you since you started feeling bad? IF YES: How bad has that been? (When did that start?) **Have you had your period in the last month or so?** IF NOT: Do you know why not? IF YES: Has it been especially heavy? **In the past week, have you had to urinate frequently? Have you had the urge to?** **FOR MEN: Sometimes when men feel nervous or anxious, they find they have trouble with premature ejaculation, or they have trouble keeping an erection. Has that happened to you since you started feeling bad?** IF YES: How bad has that been? (When did that start?) **In the past week, have you had to urinate frequently? Have you had the urge to?**	**10. GENITOURINARY SYMPTOMS** (frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

How has your appetite been this past week? (What about compared to your usual appetite?) IF LESS: How much less than usual? Have you had to force yourself to eat? Have other people had to urge you to eat? (Have you skipped meals?)	**11. SOMATIC SYMPTOMS GASTROINTESTINAL:** 0 - none 1 - loss of appetite but eating without encouragement (*Appetite somewhat less than usual)* 2 - difficulty eating without urging (or *Appetite significantly less than usual)*

Have you lost any weight since this (DEPRESSION) began? IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back? IF YES: How much? **NOTE: RATE 1 TO 3 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.**	**12. LOSS OF WEIGHT (Rate either A or B):** A. When rating by history: 0 - no weight loss 1 - probable weight loss due to current depression 2 - definite (according to patient) weight loss due to depression 3 - not assessed B. On weekly ratings by ward staff, when actual weight changes are measured: 0 - less than 1 lb. loss in week 1 - more than 1 lb. loss in week 2 - more than 2 lb. loss in week 3 - not assessed **NOTE: AVOID CODING "3" IF POSSIBLE**

How has your energy been this past week? IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?) This week, have you had any aches or pains? (What about backaches, headaches, or muscle aches?) (How much of the time? How bad has it been?) Have you felt any heaviness in your limbs, back, or head?	**13. SOMATIC SYMPTOMS GENERAL:** 0 - none 1 - heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatiguability. *(Somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)* 2 - any clear-cut symptoms *(Persistent, significant loss of energy or muscle aches/heaviness)*

Have you been putting yourself down this past week, feeling you've done things wrong, or let others down? IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? IF YES: What have your thoughts been? What about things that happened a long time ago? (if unknown) How often have you thought about this the past week? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? (Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)	**14. FEELINGS OF GUILT:** 0 - absent 1 - self-reproach, feels he has let people down 2 - ideas of guilt or rumination over past errors or sinful deeds *(feelings of guilt, remorse or shame)* 3 - present illness is a punishment. Delusions of guilt. *(severe, pervasive feelings of guilt)* 4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

This past week, have you had thoughts that life is not worth living? IF YES: What about thinking you'd be better off dead? Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?	**15. SUICIDE:** 0 - absent 1 - feels life is not worth living 2 - wishes he were dead or any thoughts of possible death to self 3 - suicidal ideas or gesture 4 - attempts at suicide

In the last week, how much have you been worrying? **How much have you been thinking about the worst that can happen, or been afraid of what's going to happen?** **Have you been especially irritable this past week?**	**16. ANXIOUS MOOD** (worries, anticipation of the worst, fearful anticipation, irritability): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

Have you been feeling especially tense this past week? IF YES: Is this more than is normal for you? Have you been unusually argumentative or impatient? Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How often have you felt this way the past week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**17. ANXIETY PSYCHIC:** 0 - no difficulty 1 - subjective tension and irritability *(Mild, occasional)* 2 - worrying about minor matters (*Moderate, causes some distress)* 3 - apprehensive attitude apparent in face or speech (*Severe; significant impairment in functioning due to anxiety)* 4 - fears expressed without questioning (*Symptoms incapacitating)*

In the past week, how much have you felt tired? **How much have you been bothered by any of these things: being startled easily, crying easily, trembling, feeling restless, not being able to relax?** FOR EACH SX: How bad has that been this past week?	**18. TENSION** (feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the last week, have you been bothered by muscle twitching, stiffness, or sudden muscle jerks? **How about grinding your teeth, having an unsteady voice, or your muscles being tight?** IF YES: How bad has that been? (How much has it bothered you?)	**19. SOMATIC (MUSCULAR)** (pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the past week, have you had ringing in your ears, blurred vision, hot or cold flashes, feelings of weakness, or pricking sensations? IF YES: How bad has that been? (How much has it bothered you?)	**20. SOMATIC (SENSORY)** (tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

This past week, have you been afraid of the dark, of strangers, of being left alone, of animals, of traffic, or of crowds? IF YES: How afraid? Do you have any other special fears? **NOTE: INCLUDE ANY IRRATIONAL ANXIETY ABOUT OBJECTS OR SITUATIONS.**	**21. FEARS** (of dark, of strangers, of being left alone, of animals, of traffic, of crowds): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the last week, have you had trouble swallowing? Have you had stomach pain or fullness, nausea, vomiting, burning or rumbling in your stomach, or constipation? FOR EACH SX: How bad has that been this past week?	**22. GASTROINTESTINAL SYMPTOMS** (difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the past week, have you had any flushing in your face, or have you been pale? Have you felt lightheaded, or had any tension headaches, or felt the hair rise on your arms, the back of your neck, or your head? FOR EACH SX: How bad has that been this past week?	**23. AUTONOMIC SYMPTOMS** (dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the past week, has your heart skipped or pounded? Have you had pain in your chest, throbbing blood vessels, or fainting feelings? FOR EACH SX: How bad has that been this past week?	**24. CARDIOVASCULAR SYMPTOMS** (tachycardia, palpitations, pain in chest, throbbing vessels, fainting feelings): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

In the last week, have you had pressure or tightness in your chest, or choking feelings? What about shortness of breath? FOR EACH SX: How bad has that been this past week?	**25. RESPIRATORY SYMPTOMS** (pressure or constriction in chest, choking feelings, sighing, dyspnea): 0 - not present 1 - mild 2 - moderate 3 - severe 4 - very severe

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST) FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? (How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?) NOTE: DO NOT RATE SXS THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.	**26. ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating): 0 - not present 1 - mild *(Symptom(s) present only infrequently, no impairment, minimal distress)* 2 - moderate (*Symptom(s) more persistent, or some interference with usual activities, moderate distress)* 3 - severe *(Significant impairment in functioning)* 4 - incapacitating

In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?) Have you worried a lot that you had a specific medical illness? Do you complain much about how you feel physically? Have you seen a doctor about these problems? What did the doctor say?	**27. HYPOCHONDRIASIS:** 0 - not present 1 - self-absorption (bodily) (*Some inappropriate worry about his/her health OR slightly concerned despite reassurance)* 2 - preoccupation with health *(Often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance)* 3 - frequent complaints, requests for help, etc. *(Is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health)* 4 - hypochondriacal delusions

RATING BASED ON OBSERVATION DURING INTERVIEW	**28. INSIGHT:** 0 - acknowledges being depressed and ill OR not currently depressed 1 - acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc. 2 - denies being ill at all

RATING BASED ON OBSERVATION DURING INTERVIEW	**29. AGITATION:** 0 - none 1 - fidgetiness 2 - playing with hands, hair, etc. 3 - moving about, can't sit still 4 - hand-wringing, nail biting, hair-pulling, biting of lips
RATING BASED ON OBSERVATION DURING INTERVIEW	**30. BEHAVIOR AT INTERVIEW** (fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos, etc.): 0 - absent 1 - mild 2 - moderate 3 - severe 4 - very severe

RATING BASED ON OBSERVATION DURING INTERVIEW	**31. RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity): 0 - normal speech and thought 1 - slight retardation at interview 2 - obvious retardation at interview 3 - interview difficult 4 - complete stupor

TIME ENDED SIGH-AD:	_____
TOTAL 17-ITEM HAMILTON DEPRESSION SCORE (NON-SHADED ITEMS):	___ ___
TOTAL 14-ITEM HAMILTON ANXIETY SCORE (SHADED ITEMS):	___ ___

Appendix B

FIGURE 1. The Center for Epidemiologic Studies Depression Scale

Experts who treat and study depression use a wide variety of tests and rating systems to determine a person's level of depression. The Center for Epidemiologic Studies Depression Scale (CES-D) is one of the most common methods for allowing an individual to determine his or her depression quotient, because it easy to understand, take, and score. This quick self-test measures a patient's depressive feelings and behaviors during the past week. The CES-D - developed by Lenore Radloff, while she was a researcher at the National Institute of Mental Health - is an effective, time-honored tool that has become a standard for identifying depression.

For the following 20 items, please select the choice that best describes how you have felt over the past week:	Rarely or none of the time (<1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with the help from my family and friends.				
4. I felt that I was not as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeless about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was unhappy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I did not enjoy life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not get "going".				

TO SCORE:

Step 1: For each answer, assign the following value:

0-Rarely or none of the time (<1 day)
1-Some or a little of the time (1-2 days)
2-Occasionally or a moderate amount of the time (3-4 days)
3-Most or all of the time (5-7 days)

Step 2: Add the total scores and refer to this scale:

- *If the score is 22 or higher, the patient may be suffering from a major depression.*
- *If the score is 15 to 21, the patient may be suffering from mild to moderate depression.*
- *If the score is below 15, this test does not indicate that the patient is depressed.*

Reference: Radloff, L.S. (1977). The CES-D scale: A self report depression scale for research in the general population. Applied Psychological Measurement, 1, 385-401.

Appendix C

M.I.N.I. PLUS

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

USA: D. Sheehan, J. Janavs, R. Baker, K.Harnett-Sheehan, E. Knapp, M. Sheehan
University of South Florida - Tampa

FRANCE: Y. Lecrubier, E. Weiller, T. Hergueta, P. Amorim, L.I. Bonora, J.P. Lépine,
Hôpital de la Salpétrière - Paris

M.I.N.I. Plus 5.0.0 (July 1, 2006)

Appendix D

Cognitve Function Study
Interview questionnaire 1

VISIT 1, Baseline

Patient initials: ..... **Patient code: P __ __**

Visit date: _____ **Informed Consent date: _____**

PSYCHIATRIC HISTORY

Please note:
**This proforma is intended as a checklist of mandatory questions* in addition to *Investigators' standard psychiatric history questions.*
** If an exact answer cannot be elicited, please provide an estimate and note "approx." next to value.*

1. Year of first known depressed episode: _____

2. Year of first diagnosis of MDD: _____

3. Total number of depressed episodes over lifetime (NOT including current episode):

_____

4. Total number of prior depressed episodes over past year: _____

5. Onset of present MDD (date): _____

6. Total number of hospitalisations for depression over lifetime: _____

7. Date of last inpatient psychiatric hospitalisation: _____

8. Has the patient ever attempted suicide (YES or NO)? _____
If answer to Q8 is NO, go to Q11.

9. Total number of suicide attempts over lifetime: _____

10. Has the patient been hospitalised for a suicide attempt (YES or NO)? _____

11. Any family members with known diagnosis of MDD (YES or NO)? _____
If answer to Q11 is NO, go to Q15.

12. Total number of family members with known diagnosis of MDD: _____

13. Does biological mother have diagnosis of MDD? _____

14. Does biological father have diagnosis of MDD? _____

Cognitve Function Study
Interview questionnaire 1

15. Number of biological brothers, sisters (NOT half-brothers and half-sisters) and children:

→ Brothers: _____ Number with known diagnosis of MDD: _____

→ Sisters: _____ Number with known diagnosis of MDD: _____

→ Children: _____ Number with known diagnosis of MDD: _____

Investigator Signed: _____ Date: _____

Appendix E

ADC-Study
Interview questionnaire 2

VISIT 1 (Baseline)

Patient initials: _____ **Patient code: P __ __**

Visit date: _____

MEDICAL HISTORY, Past and Current

Please note:
**This proforma is intended as a checklist of mandatory questions* in addition to *Investigators' standard medical history questions.*
** If an exact answer cannot be elicited, please provide an estimate and note "approx." next to value.*

Has subject any relevant (past and/or current) medical conditions? No ☐ Yes ☐

'Relevant' here excludes lessor conditions with no obvious importance for the purposes of this study, such as:

- *Common diseases of childhood;*
- *Accidental fractures unless resulting in sequelae;*
- *Minor symptomatic conditions.*

Condition	Past	Current	Current Medication taken
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....
.....	☐	☐	.....

Investigator Signed: _____ Date: _____