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**The Blue Brain: Hemispheric Asymmetry in Depression as
an Explanation for Working Memory Impairment**

A thesis presented in partial fulfilment of the requirements for the degree of

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*"If you immediately know the candlelight is fire, then the meal was cooked a long time ago."
– Oma Desala*

To Colin, my rock, for always helping me to see the big picture.

Abstract

Due to substantial variability in past research regarding the cognitive and neurobiological correlates of depression, the current study investigated whether taking the possible relationship between asymmetric brain activity and cognitive impairment into account would help to clarify the matter. A total of 78 participants including 36 currently depressed, 11 previously depressed, and 31 never depressed participants, completed three mood questionnaires (Beck Depression Inventory, Hamilton Depression Inventory Short-Form, and the State-Trait Anxiety Inventory), and four working memory tasks (a spatial and verbal variant of both the N-back and complex span task). All participants had their resting brain activity recorded using an electroencephalogram. It was hypothesised that depressed participants would show relatively reduced left frontal activity, since left frontal activity is linked to positive affect and approach motivation, and that participants with depression but low levels of anxiety would show reduced right parietal activity while those with high anxiety would show increased right parietal activity due to the role of the right parietal area in arousal. These hypotheses were not supported as there were no differences in asymmetry scores between the currently depressed and the never depressed groups. However, investigation of this hypothesis was hindered by the high comorbidity of anxiety and depression making it impossible to disentangle the effects of depression and anxiety on parietal activity. It was also hypothesised that participants with depression would show impaired working memory with disproportionate impairment in the verbal working memory tasks that are thought to utilise left frontal brain activity. There was no clear support for this hypothesis. In fact, there was a trend toward improved performance possibly related to increased attention to detail due to activation of stress systems signalling a potential threat in the environment. A final hypothesis was that there would be an association between different patterns of brain activity and WM impairment but no association was found. These results highlight problems with research in this field including the conceptualisation and measurement of depression and cognitive performance as well as problems distinguishing between anxiety and depression. Future research needs to address these issues.

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Introduction

Depression is a common disorder that affects approximately 25% of New Zealanders during their lifetime (Browne, Wells, Scott, & McGee, 2006). Although depression is typically characterised by negative affect, there is also a prominent cognitive component (Hammar & Ardal, 2009; Ravnkilde et al., 2002; Rose & Ebmeier, 2006). Cognitive deficits, such as memory loss or reduced attention span, may have a severe impact on depressed individuals' ability to function in their everyday lives (Austin, Mitchell, & Goodwin, 2001; Rose & Ebmeier, 2006). A better understanding of cognitive deficits may assist in improving the quality of life for individuals with depression (Gualtieri, Johnson, & Benedict, 2006). Depression is heterogeneous with respect to the nature and severity of the symptoms experienced by its sufferers (Porter, Bourke, & Gallagher, 2007). In particular, the specific profile of cognitive impairment appears to be highly variable (Baune, McAfoose, Leach, Quirk, & Mitchell, 2009; Porter, Gallagher, Thompson, & Young, 2003; Rose & Ebmeier, 2006). Despite abundant research in the field, no single profile of cognitive deficits in depression has emerged (Baune, Fuhr, Air, & Hering, 2014; Weiland-Fiedler et al., 2004). This may indicate that depression is not a unitary construct and may consist of subtypes (Abramson, Alloy, & Hogan, 1997; Shenal, Harrison, & Demaree, 2003). Proposed subtypes of depression have been associated with their own biological or social basis which could result in unique profiles of cognitive impairment. For example, depressive subtypes characterised by left hypofrontality may result in specific impairments in tasks typically associated with left-sided brain activity (Austin et al., 2001; Porter et al., 2007; Shenal et al., 2003). However, such possibilities are poorly understood. The current study aimed to further investigate asymmetric brain activity and cognitive impairments in depression and how they might be related.

Chapter One

A Brief Review of Depression

Depression, also known as Major Depressive Disorder (MDD), Clinical Depression, and Unipolar depression, is a highly heterogeneous clinical impairment characterised by negative affect (Beck & Alford, 2009; Sharpley & Bitsika, 2014; Shenal et al., 2003). Individuals with depression often suffer from a reduced ability to function in their everyday lives (Beck & Alford, 2009). The nature and extent of the symptoms of depression are extremely variable which may indicate that clinical depression is not a homogenous construct and may consist of a number of subtypes (Abramson et al., 1997; Chen, Yu, Zhang, Li, & Zhang, 2014; Merikangas, Wicki, & Angst, 1994; Sharpley & Bitsika, 2014). However, no single classification system has become universally accepted and little is known about the cause of symptomatic variation. Different underlying causes may help to explain why depression is difficult to treat successfully (Gaynes et al., 2008; Van Loo, De Jonge, Romeijn, Kessler, & Schoevers, 2012). Resistance to treatment is of particular concern when the high prevalence of depression amongst the general population is considered (Browne et al., 2006; Moffitt et al., 2010). Prevalence within families is significantly higher than the general population, even when raised in separate environments, pointing to a genetic component in depression (Merikangas et al., 1994; Milne et al., 2009). A corollary of this is that depression may have specific biological markers such as altered patterns of brain activity (Hahn et al., 2011; Stewart, Bismark, Towers, Coan, & Allen, 2010). Variation in the underlying biological basis of depression may help to account for symptomatic heterogeneity (Shenal et al., 2003).

Symptoms of Depression

The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) states that in order for an individual to be diagnosed with depression they must meet five or more of the following criteria: persistent sad mood or loss of pleasure in usual activities, significant weight loss or gain, sleep disturbances, psychomotor agitation or retardation, fatigue, feelings of worthlessness and/or guilt, reduced concentration, and suicidal ideation. The symptoms need to have been present for most of the day, the majority of the time in the two weeks prior to diagnosis. It is also important that the symptoms are not better explained by drug use, medical conditions such as hypothyroidism, or the recent loss of a loved-one. Although the criteria for diagnosis seem unambiguous, there is often disagreement between clinicians on what constitutes depression and what is better explained by other mental disorders (Beck & Alford, 2009). Furthermore, the nature and severity of the symptoms varies greatly among patients (Gruenberg, Goldstein, & Pincus, 2005; Porter et al., 2007).

The symptoms of depression can be broadly grouped into affective, cognitive, motivational, and physical symptoms. The affective symptoms tend to be the most salient and include symptoms such as depressed mood, negative feelings towards self, and reduced experience of pleasure (Beck & Alford, 2009; Nutt et al., 2007). These symptoms are frequently accompanied by cognitive symptoms such as negative thought processes, low self-esteem, pessimism, self-criticism, and indecisiveness (Brown, Bifulco, Veiel, & Andrews, 1990; Carver & Ganellen, 1983). Sufferers of depression also experience motivational symptoms such as avoidance, dependency on others, suicidal ideation, and paralysis of will or reduced motivation to complete even basic, everyday tasks (Beck & Alford, 2009). Finally, many patients with depression also experience physical symptoms such as changes in appetite and sleep patterns, loss of libido, and fatigue (Beck & Alford, 2009; Wenzel, Steer, & Beck,

2005). However, not all patients suffer from the same array of symptoms making diagnosis and treatment of depression difficult (Beck & Alford, 2009; Sharpley & Bitsika, 2014). For example, what if an individual reports physical symptoms of depression but does not report the subjective experience of depressed mood? Should a clinician diagnose this individual as having a physical/medical condition or could this patient be suffering from depression and be unable or unwilling to express their emotional difficulties? The aforementioned pattern of symptoms has been found and has sometimes been termed ‘atypical depression’ or ‘concealed depression’ (Beck & Alford, 2009; Bruder et al., 2002).

Despite the prominent mood component of depression, there is an increasing tendency to place a greater emphasis on the cognitive symptoms associated with depression such as impaired memory and decision making (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lonnqvist, 2008; Hammar & Ardal, 2009; Ravnkilde et al., 2002; Rose & Ebmeier, 2006). Patients with depression frequently report impaired cognitive functions with complaints of impaired short and long-term memory, reduced decision making capabilities, and slower reaction times (Gualtieri et al., 2006). Functional deficits have been observed in short-term memory (e.g., Porter et al., 2003), decision making (e.g., Taylor-Tavares et al., 2007), attention (e.g., Ravnkilde et al., 2002), and working memory (e.g., Rose & Ebmeier, 2006). The findings have been inconsistent and as a result, no single profile of cognitive impairment in depression has been compiled (Hammar & Ardal, 2009). Chapter 3 contains more information on cognitive impairment in depression.

Although the symptoms associated with depression are highly variable, one observation remains constant: the cognitive and affective symptoms of depression can severely impair patients’ ability to function in their daily lives (Austin et al., 2001). The substantial variability suggests that depression may not be a unitary construct and may consist of a number of subtypes, each associated with its own symptom profile.

Subtypes of Depression

As a result of symptom variability, a multitude of classification systems for depression have been proposed. Five key approaches have been used to develop these classification systems: the clinical/symptom based approach, the course and severity approach, the statistical approach, the neurobiological approach, and theory-driven approaches.

One of the most accessible and commonly used approaches to classifying depression is based on the clinical observation of symptoms. For example, an early approach described two symptom-based subtypes of depression: neurotic and endogenous depression (Kiloh & Garside, 1963). Endogenous depression was said to stem from an internal source and was characterised by somatic symptoms such as psychomotor retardation, weight loss, early waking, and a tendency for sufferers to feel more depressed in the morning. In contrast, neurotic depression was characterised by emotional reactivity with hysteria, irritability, and could often be linked to a psychological stressor. Further research regarding these subtypes suggested that endogenous depression could be easily diagnosed using somatic symptoms such as weight disturbance, dry mouth, reduced pulse, and reduced body temperature (Pollitt, 1965). This set of somatic symptoms was described as representing a 'functional shift' that resulted from hypothalamic dysfunction (Pollitt, 1965). Kiloh and Garside (1963) argued for the utility of this classification system by providing evidence that endogenous depression was more responsive to pharmacological intervention than neurotic depression. This system of classifying depression into two subtypes has been labelled the 'binarian' approach (Parker, 2000). In more recent years, this approach has been abandoned in favour of a 'unitarian' approach in which all depression, regardless of the specific symptom profile, has been grouped together and is thought to only vary based on symptom severity (Parker, 2000). This type of approach is still seen in the most recent version of the DSM.

In an extension of the idea that all depression is a single disorder that only varies in terms of severity, a number of researchers have attempted to classify depression based on the severity and course of the illness. For example, Merikangas et al. (1994) proposed that depression should be classified by the time-course and recurrence of depressive episodes. Depression was split into four subtypes: single episode major depression, multiple episode major depression, recurrent brief depression, and a combination of major depression and recurrent brief depression. Each of these subgroups was found to differ with respect to the symptoms experienced, the impact on daily functioning, and demographic make-up. Despite the success of this technique in classifying depression, Merikangas et al. noted that differences between the subgroups probably did not reflect different aetiology. Therefore, these proposed subtypes may represent an artificial distinction and may not be of practical use in the diagnosis and treatment of depression.

Although the last two decades have seen a tendency towards considering depression a unitary construct, recent research still suggests that depression can be categorised into symptom-based subtypes. For instance, Singh and Rais (2007) discussed a number of symptom-based subtypes including atypical depression, melancholic depression, seasonal affective disorder (SAD), dysthymic disorder, and agitated depression. Each subtype is characterised by a distinct set of symptoms. For example, atypical depression is characterised by reverse vegetative symptoms (e.g., increased sleep and increased appetite), mood reactivity and interpersonal rejection sensitivity (Beck & Alford, 2009; Bruder et al., 2002). However, a number of the subtypes proposed by Singh and Rais, SAD being one, are not generally considered to be distinct syndromes of depression and may be better named as 'descriptors' characterising the nature of an individual's depression. Singh and Rais argued against this showing that each subtype was responsive to different treatments and associated with different demographic characteristics providing evidence for distinct syndromes.

Although symptom-based subtypes may be useful in predicting treatment outcomes, they are subjective and diagnosis may differ between clinicians. To reduce subjectivity, researchers have employed statistical methods to group the symptoms of depression into clusters representative of distinct subtypes. A number of approaches have been employed including, grade of membership analysis (GOM), cluster analysis, factor analysis, and discriminant function analysis. Studies using factor analysis to classify the symptoms assessed with various depression inventories have found evidence of four factors possibly indicative of subtypes (e.g., Blumenthal, 1975; Ross & Mirowsky, 1984). However, there is little agreement regarding the content of each factor. For example, Pichot and Lempriere (1964) defined the factors as vital depression, self-abasement, pessimism/suicide, and indecision/inhibition (as cited in Blazer et al., 1989). In contrast, Ross and Mirowsky (1984) defined the factors as depressive affect, enervation, poor life satisfaction/lack of positive affect, and interpersonal problems. This approach has been criticised as it creates distinct, homogenous symptom clusters and does not allow for any within factor variability, failing to take into account individual differences unrelated to depression.

In an effort to correct this problem, Blazer et al. (1989) employed GOM analysis, a statistical method in which symptom clusters are not assumed to be homogenous and individuals are able to be characterised by the degree to which they fit into each of the categories. Evidence of five symptom-based groups was found: depression with symptoms of anxiety, depression with anxiety and no evidence of mania, old-age depression with cognitive dysfunction and psychomotor retardation, stress-related depression with anxiety and sleep disturbances, and a depressed mood group characterised by weight gain and sleep disturbances. Considerable overlap between these groups makes using this system to diagnose subtypes of depression difficult and of limited utility. Despite the theoretical attractiveness of statistically-based subtypes, little agreement exists amongst research using

different methods suggesting that an essential element may be being overlooked. Statistical classification methods are unlikely to produce valid results if not used in combination with strong theoretical underpinnings (Maxwell, 1971).

Due to the limitations of symptom and statistically-based subtypes of depression, some researchers have adopted a more theory-driven approach. For example, Abramson et al. (1997) used a theory-driven approach to define three cognitive subtypes of depression. The first subtype, hopelessness depression, is characterised by a cognitive style causing individuals to attribute negative events to stable, global, and internal causes. The second subtype, termed the dependent/sociotropic subtype, was found to occur in individuals who displayed an overwhelming need for interpersonal relationships. The final subtype discussed by Abramson et al. was the self-critical/autonomous subtype in which sufferers tend to set unobtainable goals for themselves and as a result label themselves as failures. Abramson et al. noted that each of these subtypes could be used to assess the cause of depression, the symptoms, and to predict the best treatment approach. That said, such subtypes may be difficult to assess as cognitions are highly internalised and it may be difficult to gain enough information about individuals' internal thought processes to classify them and test the feasibility of such theory-based subtypes.

Although symptom-based approaches, whether observational, statistical, or theoretical, seem appealing, similar symptom profiles may result from different neurobiological causes. Therefore, classifying depression using neurobiological markers may be more useful in predicting response to treatment and could lead to less diagnostic heterogeneity (Gruenberg et al., 2005; Schmidt, Shelton, & Duman, 2011). For example, Shenal et al. (2003) theorised that depression could be separated into four subtypes based on abnormal patterns of brain activity. Shenal et al. proposed dividing the brain into four quadrants: left frontal, right frontal, left posterior, and right posterior. Dysfunction in each of

these regions was theorised to lead to a different subtype of depression. For example, left frontal regions have been associated with the experience and processing of positive/approach-motivated emotions while right frontal regions have been associated with the experience of negative/withdrawal-motivated emotions (Davidson, 1992; Debener et al., 2000). If an individual was to suffer from reduced activity in the left frontal region they may suffer from reduced experience of positive emotion. In contrast, right frontal dysfunction could lead to increased experience of negative emotion and withdrawal, while right posterior dysfunction could lead to impaired emotional processing and reduced arousal. Support for different patterns of brain activity in depression has been found in imaging and electroencephalographic (EEG) research (e.g., Bruder et al., 1989; Bruder et al., 1997; Heller, & Nitschke, 1998; Pizzagalli et al., 2002). However, little research has been conducted regarding left posterior dysfunction in depression. Although further research regarding the quadrant approach to classifying depression is required, this approach is promising as it could explain symptom variability as different symptoms could be associated with different patterns of abnormal brain activity. Other neurobiological approaches to classifying depression have included abnormalities in levels of growth factors, cytokines, and neurotransmitters (e.g., Schmidt et al., 2011). Different underlying biology may explain why symptom-based approaches have not been able to accurately predict treatment outcomes as similar symptoms could result from different underlying patterns of brain activity and, as a result, may require different treatment (Bruder et al., 2008; Iosifescu et al., 2009).

The aforementioned classification systems are just a sample of the numerous subtype proposals and no single system has been agreed upon or received strong support. In fact, Abramson et al. (1997) described this area of research as particularly problematic due to 'General MacArthur Syndrome' (GMS). Numerous theories are developed and limited or conflicting support is found for them. As a result, it is common for theories to fade away as

researchers become disinterested, a fate similar to what General MacArthur described as happening to old generals, never dying, never going away but instead gradually fading away (Abramson et al., 1997). Little progress has been made in developing a unifying theory of the subtypes of depression. Subtype research is important as accurate subtype classification could improve treatment and prevention programmes.

Comorbidity of Anxiety and Depression

One of the core debates regarding depression is whether anxiety and depression can be distinguished from each other or whether they are different presentations of the same condition (e.g., Burns & Eidelson, 1998; Feldman, 1993; Kocovski, Endler, Cox, & Swinson, 2004). Approximately 50% of all individuals with depression also suffer from a comorbid anxiety disorder (Bruder et al., 1997; Kessler et al., 2003; Zimmerman, McDermet, & Mattia, 2014). High comorbidity may suggest that anxiety and depression are dimensional aspects of the same condition. On the other hand, anxiety and depression may be separable conditions but they may share common symptoms and vulnerability factors accounting for the high overlap (Burns & Eidelson, 1998; Kocovski et al., 2004; Nitschke, Heller, Imig, McDonald, & Miller, 2001). The relationship between depression and anxiety is dependent on the specific type of depression and anxiety disorder (Watson, 2009). For example, Generalised Anxiety Disorder (GAD) seems to be more strongly associated with dysthymic disorder and major depression than other anxiety disorders such as social phobia and panic disorder.

The Tripartite model (Clark & Watson, 1991) explains the high overlap due to the shared symptoms of negative affect/general distress. The Tripartite model describes depression and anxiety in terms of three factors, positive affect, negative affect, and physiological arousal (Clark & Watson, 1991). Anxious individuals can be differentiated by high physiological arousal and the intact experience of positive affect. In contrast, depressed

individuals' experience reduced positive affect, anhedonia, and low arousal levels. Although the Tripartite model has received much support, in some types of anxiety disorder, such as social phobia, sufferers experience low positive arousal which does not fit with the Tripartite model (Anderson & Hope, 2008). Subtle variations in the negative affect component may be better markers to help distinguish anxiety and depression (Burns & Eidelson, 1998). For example, hypersomnia seems to be specific to depression while insomnia seems to be a more general symptom common to both depression and anxiety (Watson, 2009).

A key concern with research on depression is how to distinguish between anxiety and depression. If the two are separate conditions, not accounting for the presence of anxiety could introduce extra variance. Even if anxiety and depression are separate conditions, can they be separated in a research setting or is the symptom overlap too high to reliably distinguish between them? High correlations between scores on anxiety and depression inventories are often put forward as evidence that depression and anxiety are not independent entities but Burns and Eidelson (1998) argued that the high correlations are not problematic and instead represent strong convergent validity. Since depression and anxiety both involve general distress, relatively high correlations between depression and anxiety inventories are not surprising but detailed analysis of inventories usually reveals a number of items that distinguish between depression and anxiety (Burns & Eidelson, 1998; Kocovski et al., 2004; Wetherell, Gatz, & Pedersen, 2001). This view is disputed by Feldman (1993) who used factor analysis to determine that depression and anxiety inventories do not measure distinct aspects of mood. On the other hand, Nitschke et al. (2001) found that depression and anxiety could be differentiated using psychometric testing if a large number of tests and items were employed, but such a large set of tests may not always be feasible due to time constraints and extra tests placing a higher demand on participants.

The conflicting evidence regarding whether anxiety and depression are separable is likely to result from the use of different measures for both anxiety and depression. Tanaka-Matsumi and Kameoka (1986) compared a number of commonly used depression and anxiety inventories and only observed weak/moderate correlations between different measures of depression and also found that these correlations were comparable to those between depression and anxiety inventories. For example, the correlation between the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1993) and the Depression Adjective Checklist (DAC; Lubin, 1965) was only weak ($r=.32$) indicating only 10% shared variance. Before further investigation of the anxiety and depression debate can occur, the poor convergent validity of measures to assess the same constructs needs to be addressed.

Prevalence of Depression

The lack of understanding regarding symptom variability and classification of depression is of particular concern when the prevalence of depression is taken into account. In New Zealand approximately 25% of the population will experience depression at some point during their lifetimes (Browne et al., 2006) and up to 14% of patients visiting their doctor for any reason may be diagnosed as having depression (Arroll, Goodyear-Smith, & Lloyd, 2002). These figures are relatively high in comparison to other nationalities (Bromet et al., 2011; Simon, Goldberg, Korff, & Ustun, 2002). Lifetime prevalence has been reported to be as low as 1.6% and 2.5% in parts of Japan and China, respectively. In contrast, South American regions appear to be particularly vulnerable with rates of 18.3% in Rio de Janeiro and 26.3% in Santiago (Bromet et al., 2011; Simon et al., 2002). It is probable that, in regions displaying higher prevalence, cultural differences could lead doctors to diagnose depression more frequently or result in sufferers being more likely to seek assistance for more mild symptoms. Simon et al. (2002) and Bromet et al. (2011) disputed this possibility with

evidence that differences in prevalence were still observed when strict diagnostic criteria were used.

As well as considerable variation of prevalence between nationalities, variation has been found between ethnic groups within a single country. Arroll et al. (2002) found that non-Maori patients visiting their doctor were more likely to be diagnosed as having major depression than Maori patients. However, Maori patients were more likely to be diagnosed with sub-clinical depression or dysthymia. It was also discovered that out of those patients diagnosed as having depression, Maori were less likely to be treated using antidepressant medication. This pattern is not unique to New Zealand. In America, people of European descent are more likely to be diagnosed with major depression while African and Mexican Americans are more likely to be diagnosed with dysthymia (Riolo, Nguyen, Greden, & King, 2005). This may suggest cultural differences in seeking treatment or biases in diagnostic criteria (Riolo et al., 2005).

Gender differences are also apparent in depression (e.g., Angst et al., 2002; Beck & Alford, 2009). World-wide it is estimated that approximately 5-9% of females and 2-3% of males suffer from depression at any one time (Beck & Alford, 2009). Most research, from a wide variety of samples and using different assessment methods, has found that females appear to suffer from depression approximately twice as often as males (Angst et al., 2002). The small number of studies that have not found gender differences in depression prevalence have occurred in specific samples such as Australian university students and the Amish community in the United States of America (Angst et al., 2002). There is considerable debate regarding whether gender differences in depression are a genuine effect or an artefact of treatment and diagnostic procedures (Ross, Frances, & Widiger, 1995). For example, females may be more likely to talk about their symptoms resulting in more frequent diagnoses (Ross et al., 1995).

Depression influences all age groups but considerable debate exists regarding the most at risk age groups with some research indicating depression to be more prevalent in young adults (Wade & Cairney, 2000) and others suggesting high middle-age risk with a steady increase in prevalence from young adults to middle-age (Browne et al., 2006; Kessler, Birnbaum, Bromet et al., 2010). Once comorbid health conditions are controlled for, elderly depression is relatively low which may suggest that age is a protective factor to developing depression (Angst et al., 2002; Jorm, 2000; Wade & Cairney, 2000). It is unclear whether the apparent reduction in prevalence in later life is a cohort effect due to the increasing prevalence of depression as a modern illness (Hidaka, 2012) or whether controlling for comorbid health conditions has artificially reduced depression prevalence in older adults (Kessler, Birnbaum, Shahly et al., 2010).

It is apparent that university students may be at particular risk for developing depression due to the changes in living situation and the psychological stress associated with studying (Stallman, 2010). Point-prevalence of depression in university students ranges from 8-20% (Bayram & Bilgel, 2008; Eisenberg, Gollust, Golberstein, & Hefner, 2007; Stallman, 2010) which could indicate lifetime prevalence in university students to be substantially higher. The specific risk and protective factors have been variable between different research studies. Consistent with research from other samples, symptoms of depression were found to be more prevalent amongst female university students than male students (e.g., Stallman, 2010). On the other hand, Bayram and Bilgel (2008) found no evidence of a gender difference in the prevalence of depression. In general, young, full-time students living alone and/or off campus with high financial stress have been found to be at higher risk for displaying mental illness than students living in university accommodation or those with lower financial stress (Eisenberg et al., 2007; Stallman, 2010). Students from lower socioeconomic backgrounds appear to suffer from increased depression and anxiety

compared to those from higher socioeconomic backgrounds (Bayram & Bilgel 2008; Eisenberg et al., 2007).

Depression also seems to be more common within family groups (Klein, Lewinsohn, Seeley, & Rohde, 2001; Milne et al., 2009; Sullivan, Neale, & Kendler, 2000). Klein et al. (2001) found that relatives of adolescents with major depression were 1.77 times more likely to suffer from depression than relatives of non-depressed adolescents. This pattern appears to be specific to depression as relatives of adolescents with other mental disorders, such as conduct disorder, are no more likely to suffer from depression than relatives of adolescents without mental disorder (Klein et al., 2001). Family history of depression has also been linked to severity of depression measured by factors such as number of recurrences, degree of impairment, and use of mental health services (Milne et al., 2009). Increased prevalence of depression within family groups suggests a genetic basis for depression.

Genetics and Depression

Although higher prevalence of depression within families may suggest a genetic basis, it is also possible that this observation may be due to shared environment. To investigate the possibility of a genetic basis of depression a number of heritability studies have been conducted (e.g., Bierut et al., 1999; Kendler, Gatz, Gardner, & Pedersen, 2006). Heritability has been found to lie between 35 and 45% in studies of community-based samples (Bierut et al., 1999; Kendler et al., 2006). This means that 35-45% of the variation seen in the appearance of depression in the population studied can be attributed to genetic variation. Studies based on clinical populations suggest that heritability may be well above 50% which may be due to the decreased environmental variation in clinical settings (e.g., Kendler, Pedersen, Neale, & Mathe, 1995; McGuffin, Katz, Watkins, & Rutherford, 1996). Several

studies have also observed a higher degree of heritability of depression in females than in males (Bierut et al., 1999; Kendler et al., 2006).

The search for specific genes that may cause or contribute to an individual developing depression has become a key research goal in the last 20 years (e.g., Caspi et al., 2003; Pezawas et al., 2005). The role of environment appears to remain important for the development of depression and depression is likely to result from genetic vulnerability coupled with an unfavourable environment (Bierut et al., 1999; Kendler et al., 1995; Sullivan et al., 2000). For example, Caspi et al. (2003) found that an individual with a particular variant of the promoter region of a gene coding for serotonin transporters (5-HTT) were significantly more likely to develop depression after stressful life events. The gene-environment interaction demonstrated by Caspi et al. shows how a genetic predisposition to developing depression can be 'triggered' by adverse conditions. Genetic changes may alter neurobiological function making an individual vulnerable to developing depression. Pezawas et al. (2005) showed that individuals with a short variation of the 5-HTT gene showed abnormalities in the structure and function of brain regions thought to be critical in emotional reactions, such as the amygdala. Increased activity in the amygdala has been linked to increased vulnerability to developing depression (Ramel et al., 2007; Zhong et al., 2011). In similar research Montag, Weber, Fliessbach, Elger, and Reuter (2009) found that certain forms of the gene coding for Brain Derived Neurotropic Factor (BDNF) resulted in reduced BDNF, reduced parahippocampal and amygdala volumes, and a vulnerability to developing depression.

These findings stimulated research regarding the role of epigenetics in depression. Animal studies have demonstrated that early life stress can lead to epigenetic tags on the arginine vasopressin (AVP) gene leading to increased activity in the hypothalamic-pituitary axis and associated endocrine and behavioural outcomes characteristic of depression

(Murgatroyd, Wu, Bockmühl, & Spengler, 2010). Research on the role of epigenetics in depression has led to the innovation of a novel treatment for depression, the use of histone deacetylase inhibitors to effectively counteract the negative impact of epigenetic tags (Schroeder, Krebs, Bleich, & Frieling, 2010). The role of epigenetics in depression is a research area in its relative infancy and extensive research is required before such treatment options become a reality but the field of epigenetics has provided an exciting avenue for the investigation of the role the gene-environment interaction in the development of depression, and other illnesses, and has essentially rendered the nature-nurture debate obsolete.

It is unlikely that a single gene is responsible for depression. Instead, depression is more likely to result from a combination of genetic factors leading to neurobiological changes that may predispose an individual to developing depression in certain environments (Sullivan et al., 2000; Torgerson, 2008). It is possible that neurobiological changes could be readily measured using biomarkers to highlight individuals at risk for developing depression given certain environmental conditions.

Biomarkers of Depression

Finding simple-to-measure biomarkers to diagnose depression, and highlight those at risk for developing depression, will help to remove uncertainty in diagnosing depression and will also provide an opportunity for preventative measures to be taken to reduce the risk of ever developing depression. One of the most promising avenues is identifying specific patterns of brain activity that indicate those vulnerable to developing depression. For example, numerous imaging studies have implicated abnormal functioning of the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex in depression (Levin, Heller, Mohanty, Herrington, & Miller, 2007; Rogers et al., 2004; Vasic, Walter, Sambataro, & Wolf, 2009). Abnormalities have been observed in those vulnerable to developing

depression, such as those with a strong family history of depression but have never experienced an episode of depression themselves (e.g., Amico et al., 2011), and have been found to predict responsiveness to treatment (Pizzagalli, 2011). Magnetic Resonance Imaging (MRI) could be used to identify those at risk, but MRI is a costly procedure limiting its use as a general screening technique.

A more practical screening measure that is non-invasive and relatively cheap is EEG. Individuals with depression typically show left-hypofrontality, a relative reduction in left frontal lobe activity that persists beyond recovery from the affective symptoms of depression and is present in those at risk for developing depression (Gotlib, Ranganath, & Rosenfeld, 1998; Heller & Nitschke, 1998; Thibodeau, Jorgensen, & Kim, 2006). Therefore, left-hypofrontality may be a useful biomarker for identifying at-risk individuals though not all individuals with depression exhibit left-hypofrontality. Further understanding of abnormal brain activity in depression may help to identify those at-risk for developing depression and enable preventative measures to be taken. Abnormal patterns of brain activity in depression will be reviewed in Chapter 2.

Chapter Two

Brain Activity in Depression

Identifying neurobiological correlates of depression, such as structural and or functional changes in the brain, has become a primary target for research. In order to understand how changes in the brain may be implicated in depression, it is first necessary to understand how emotion is processed in non-depressed individuals. Although early research focussed on subcortical structures such as the limbic system, more recent research has highlighted the importance of the cerebral cortex in the experience of emotion (Davidson, 1993, 1994; Shenal et al., 2003). While an in-depth discussion of the subcortical circuitry of emotion is outside the scope of this review, the cerebral cortex and limbic system appear to have multiple, complex connections suggesting they both function together in the experience of emotion (Davidson, 2004). Cortical regions may not be solely responsible for the experience and processing of emotion but may moderate activity in other parts of the circuit such as the amygdala (Hariri, Bookheimer, & Mazziotta, 2000). Therefore, cortical activity during the experience of emotion may be indicative of activity in subcortical regions so key subcortical regions and connections will be addressed briefly later in this chapter. There are four main models describing how cortical regions are specialised for emotional processing.

Models of Emotion

Right hemisphere model of emotion. One of the earliest models of emotional processing suggests that the right hemisphere preferentially processes emotions. Support for this model comes from perceptual asymmetry research, studies of brain activation during

emotional experiences, and emotional responses of participants with brain damage (e.g., Heller & Levy, 1981; Ley & Bryden, 1979).

Research on perceptual asymmetry in healthy individuals demonstrates which hemisphere is processing certain stimuli by showing enhanced reaction times (RTs) or increased accuracy in response to material presented to either the left visual field (LVF) or the right visual field (RVF) of the participant. Due to contralateral processing, a LVF advantage indicates right hemisphere (RH) dominance while a RVF advantage indicates left hemisphere (LH) dominance. LVF superiority has been demonstrated for identifying facial affect (Heller & Levy, 1981; Landis, Assal, & Perret, 1979; Ley & Bryden, 1979; Suberi & McKeever, 1977) and for recognition of emotional prosody (Ley & Bryden, 1982). Of course, it is possible that these outcomes indicate RH dominance for processing of any material not just emotional stimuli. To eliminate this possibility comparisons between non-emotional and emotional stimuli have been conducted finding a left ear advantage (RH) in identifying non-verbal emotional expression such as laughter (Carmon & Nachshon, 1973; Silberman & Weingartner, 1986). Landis et al. (1979) found that pictures were associated with a RVF advantage while emotional faces were associated with a LVF advantage indicating that the observed RH advantage for emotional processing was not a result of general processing functions. Similarly, Schwartz, Davidson, and Maer (1975) found that right-handed people tend to shift their gaze leftwards during affective tasks suggesting that the RH might play a specialized role in emotional processing. Evoked potential research supports the RH model with comparatively more RH than LH activity when processing facial affect (Kestenbaum & Nelson, 1992; Laurian, Bader, Lanares, & Oros, 1991).

Observations of unilaterally brain damaged individuals supports the view that the RH plays an integral role in emotion processing as individuals with RH damage commonly display an impaired ability to recognise the affective nature of facial expressions, and

emotional prosody (Adolphs, Damasio, Tranel, & Damasio, 1996; Borod et al., 1998; Bowers, Coslett, Bauer, Speedie, & Heilman, 1987; Heilman, Scholes, & Watson, 1975). However, not all people with RH damage show impaired emotional perception and those that do predominantly have parietal lesions which may indicate a specific role for right posterior regions in emotion rather than the RH as a whole (Silberman & Weingartner, 1986).

Despite the findings indicating the role of the RH in emotional processing, there are a number of problems with the research. Firstly, little consideration is given as to the type of emotional stimuli used and no clear comparisons between types of stimuli have been conducted (Silberman & Weingartner, 1986). It is therefore unclear if different regions specialise in different emotions. A second problem is the failure to distinguish arousal from emotion. RH activity is associated with control over the autonomic nervous system and arousal (Spence, Shapiro, & Zaidel, 1996). Heilman and Van Den Abell (1980) showed dominance of RH in arousal through the facilitation of RT following LVF warning lights. Similarly, patients with RH damage show reduced skin conductance responses (Heilman, Schwartz, & Watson, 1978) and reduced autonomic responses to affective stimuli (Morrow, Vrtunskin, Kim, & Boller, 1981; Gainotti, Caltagirone, & Zoccolotti, 1993). Therefore, a number of the results could be interpreted as further evidence of the role of the RH in arousal rather than emotion as a whole. Although arousal is a component of emotion, other components, such as emotional valence, might be processed in different regions. Given the role of the right parietal lobe in arousal (Shenal et al., 2003), and the finding that impaired emotional processing seems to occur predominantly following right parietal damage (Silberman & Weingartner, 1986), not distinguishing between the arousal component of emotion and other components impairs the ability of such research to determine how emotion is processed in the brain.

Valence model of emotion. Problems with research supporting the RH model of emotion led to the development of the valence model (Tucker, 1981). The valence model of emotion, sometimes referred to as the balance model, suggests that the left cerebrum is responsible for the experience and processing of positively valenced emotions such as happiness, while the right cerebrum is involved in negatively valenced emotions such as sadness or fear (Shenal et al., 2003; Tomarken, Davidson, Wheeler, & Doss, 1992). A relative increase in activity in one hemisphere could lead to the increased experience of emotions associated with that side.

Support for the valence model comes from lesion research. Left-sided lesions frequently result in ‘catastrophic reactions’ characterised by excessive crying, guilt, and fear (Gainotti, 1972; Heilman & Bowers, 1990). In contrast, those with right-sided lesions commonly display indifference or inappropriate cheerfulness (Gainotti, 1972; Starkstein et al., 1989). Similarly, Robinson, Kubos, Starr, Rao, and Price (1984) found that reports of depressed affect are more common in those with left frontal lesions than those in other locations, including right frontal or left posterior lesions. From this research, the valence model of emotion was proposed suggesting that the RH is involved in the experience of negatively valenced emotions while the LH is involved in positively valenced emotions.

Not all lesion studies support this association. For example, Aström, Adolfsson, and Asplund (1993) found that left frontal lesions were only associated with depressed symptomology soon after a stroke occurred and that this association disappeared after three years. This may indicate that the observed emotional reactions are a short-term side effect of the stroke rather than a result of the lesion location. Other studies have also failed replicate this association (e.g., Ebrahim, Barer, & Nouri, 1987; House, Dennis, Warlow, Hawton, & Molyneux, 1990). While some of these inconsistencies have been attributed to situational

factors, it seems that the relationship between lesion location and depression/other emotional reactions is less clear cut than originally thought.

Lesion studies have been criticised on the grounds people with lesions have atypical brains. To circumvent this problem, pseudo-lesions have been created using techniques that result in the temporary paralysis of one hemisphere. For example, injecting sodium amobarbital, a sedative, into the left carotid artery effectively inactivates the LH, leading to the experience of crying, guilt, and worrying, a 'catastrophic reaction'. On the other hand, sedating the RH leads to either smiling, laughing, and mimicry, or indifference (Ahern et al., 1994; Lee, Loring, Meader, & Brooks, 1990; Siberman & Weingartner, 1986). These results seem to be congruent with natural lesion research supporting the validity of the findings. However, lesions, whether natural or artificially produced, lack precision. It is likely that multiple regions are influenced and compensatory brain activity may occur.

Further support for the valence model comes from EEG research demonstrating that participants with relatively increased left frontal activity experience increased positive affect compared to participants with relatively higher right frontal activity (Tomarken et al., 1992). Greater left frontal activation is observed during facial expressions indicative of happiness in response to positive film clips (Davidson, Ekman, Saron, Senulis, & Friesen, 1990) and in infants when viewing videos of people with happy facial expressions (Davidson & Fox, 1982). An imbalance of hemispheric activity while resting, resting frontal asymmetry, has been found to predict affective response to film clips (e.g., Tomarken et al., 1988; Tomarken, Davidson, & Henriques, 1990; Wheeler, Davidson, & Tomarken, 1993). The ability of resting EEG asymmetry to predict emotional response to external stimuli, such as videos, even in the absence of differences in pre-test emotion, suggests that frontal asymmetry is a trait-marker indicative of an individual's likelihood to respond to certain situations with positive or negative affect.

Taken together, results from lesion and EEG research suggest that the LH is more involved than the RH in the experience of positively valenced emotions, such as happiness, while the RH is dominant in the experience and processing of negative emotions, such as sadness.

Motivational model of emotion. Some negative emotions, such as anger, do not appear to fit with the valence model. Anger is typically considered a negative emotion but has been linked to left frontal activity (Harmon-Jones & Allen, 1998; Harmon-Jones, Vaughn-Scott, Mohr, Sigelman, & Harmon-Jones, 2004). This led to the formulation of the motivational model of emotion which proposes that right frontal regions are involved in withdrawal-motivated emotions, such as sadness and fear, while left frontal regions are more involved with approach-motivated emotions such as happiness and anger. A large proportion of the relevant research has been unable to provide support for either the valence or motivational model of emotion as the emotions assessed would be expected to show the same findings under either model. Anger is one emotion that can be used to distinguish between the models as it is both negatively valenced and approach-motivated (Harmon-Jones & Sigelman, 2001). Anger is associated with increased left frontal activity in both the trait (Harmon-Jones & Allen, 1998) and state domains (Harmon-Jones & Sigelman, 2001) which supports the motivational model of emotion. One alternative explanation is that individuals high in trait anger might experience anger as a positive emotion, or have a positive attitude towards it, resulting in increased left frontal activity during the experience of anger. Harmon-Jones (2004) investigated this possibility but did not find any evidence to support it.

Trait withdrawal motivation has been associated with relatively greater right than left frontal activity (Sutton & Davidson, 1997). However, Harmon-Jones and Allen (1997) did not observe any relationship between trait withdrawal motivation and frontal asymmetry. This latter finding has been replicated in later research that found that, although increased left

frontal activity was associated with trait approach motivation, right frontal activity did not seem to be related to trait withdrawal motivation (Coan & Allen, 2003). The cause of these inconsistencies has yet to be resolved; as of now there is relatively little research investigating withdrawal-motivated affect and brain activity compared with approach-motivated affect. Conducting research on withdrawal-motivated emotions is limited by difficulty in distinguishing withdrawal from active avoidance which may engage the approach motivation system (Harmon-Jones, Gable, & Peterson, 2010). Another concern is the use of the Behaviour Inhibition Scale (BIS; Jorm et al., 1998) as an operational definition for avoidance motivation. Amodio, Master, Yee, and Taylor (2008) indicated that the BIS might be more related to conflict monitoring than trait avoidance motivation.

Circumplex model of emotion. One striking omission from the aforementioned models of emotion is that none of them address the frontal/posterior distinction. While frontal regions appear to be associated with emotional valence, the right posterior region has been implicated in arousal (Shenal et al., 2003). Given that arousal is a fundamental component of the emotional experience, an all-inclusive model of emotion should consider both valence and arousal. This led Heller (1993) to propose the circumplex model of emotion, defined by both a valence and an arousal axis. Using this model, all emotions can be viewed as a combination of each of these two dimensions rather than emotions falling into discrete categories (Posner, Russell, & Peterson, 2005). For example, fear is typically associated with both heightened arousal and negative valence. Under this model the cortex is essentially divided into quadrants with the frontal regions representing valence as described in the valence model of emotion and the posterior regions representing arousal, specifically, high arousal is linked to increased right posterior activity (Shenal et al., 2003).

Asymmetrical Brain Activity in Depression

Based on the models of emotion discussed above, it has been proposed that people with depression may suffer from an imbalance of brain activity resulting in relatively greater right frontal activity and the increased experience of negative/withdrawal-motivated emotions and the reduced experience of positive/approach-motivated emotions. Since depression is commonly associated with reduced arousal, the circumplex model of emotion would also predict relatively reduced right posterior activity.

Frontal asymmetry. Superimposed on a bilateral reduction in frontal activity, depressed participants appear to experience a relative reduction in left frontal brain activity as measured by EEG (Bruder et al., 1997; Davidson, 1992; Diego, Field, & Hernandez-Reif, 2001; Heller & Nitschke, 1997; Henriques & Davidson, 1991; Kemp et al., 2010; Miller et al., 2002; Thibodeau et al., 2006). This finding has been observed in both depressed samples diagnosed using a clinical interview (e.g., Debener et al., 2000; Henriques & Davidson, 1991; Kemp et al., 2010) and in participants high in self-reported depressive symptomology (e.g., Diego et al., 2001; Schaffer, Davidson, & Saron, 1983). A meta-analysis found a moderate effect size for reduced left frontal activity in depressed adults ($d=.54$) and in at-risk groups such as infants of depressed mothers ($d= .61$) (Thibodeau et al., 2006). Diego et al. (2001) found that EEG asymmetry scores accounted for 36% of the variance in Center for Epidemiological Studies Depression (CES-D; Radloff, 1977) inventory scores. This pattern of brain activity appears to be relatively stable and has been replicated in a wide variety of samples including depressed inpatients (e.g., Debener et al., 2000), community-based depressed participants (e.g., Schaffer et al., 1983), previously depressed participants (e.g., Gotlib et al., 1998; Henriques & Davidson, 1990) and children/infants of depressed mothers (e.g., Dawson, Panagiotides, Klinger, & Spieker, 1997; Field, Fox, Pickens, & Nawrocki, 1995). Frontal asymmetry has also been used to distinguish previously depressed from never

depressed participants indicating it may have some diagnostic value (Allen, Urry, Hitt, & Coan, 2004; Henriques & Davidson, 1990).

These findings are congruent with models of emotion suggesting that left frontal regions of the brain are involved during positive/approach-motivated emotions, while right frontal regions have been linked to negative/withdrawal-motivated emotions (Davidson, 1992). So, an individual experiencing relatively reduced left frontal activity may suffer from an overabundance of negative emotion and/or a reduction in the experience of positive emotion.

A diathesis-stress model has been proposed in which relatively reduced left frontal activity serves as a stable trait-like vulnerability marker for the development of depression (Coan & Allen, 2004). Given certain environmental conditions and stressors, an individual with reduced left frontal activity may be more likely to develop depression than individuals without this pattern of asymmetry. Abramson et al. (2002) helped to integrate cognitive models of depression with frontal asymmetry research by suggesting that the hopelessness model of depression may be a result of reduced activation within the approach system or reduced left frontal activity. Using this model, when an individual with reduced left frontal activity experiences a negative event, they are more likely to generate negative inferences about the occurrence leading to a feeling of hopelessness and withdrawal consistent with the symptoms of depression. Nusslock et al. (2011) found support for this explanation with reduced left frontal activity being associated with increased cognitive vulnerability to depression as measured by the Cognitive Styles Questionnaire (CSQ; Haefffel et al., 2008). This pattern was observed in participants with no previous history of depression indicating that this association is not a result of being depressed and may instead represent a vulnerability factor. Furthermore, after a 3-year follow up period, both reduced left frontal activity and increased scores in the negative events portion of the CSQ predicted an increased

chance of the participant having their first depressive episode during the follow-up period. In contrast, Gotlib et al. (1998) found no such association between frontal asymmetry scores and scores on Dysfunctional Attitudes Scale (DAS; Weissman & Beck, 1978). This may be a result of the specific content of the survey employed or the method of recording the EEG. EEG recordings utilise a reference site to which recordings at other electrode sites are compared and the use of the CZ reference scheme employed by Gotlib et al. has been suggested to be the least reliable reference montage (Allen, Coan, & Nazarian, 2004). Rather than predicting depression itself, frontal asymmetry may be a marker for dispositional differences (Reid, Duke, & Allen, 1998). These differences may represent risk or protective factors for developing depression which could explain previous findings of a relationship between asymmetry and depression. One possible risk factor, maladaptive coping styles (e.g., repressive defensive) have been linked to frontal asymmetry scores (Reid et al., 1998).

Not all researchers agree with the suggestion that depression is characterised by reduced left frontal activity. For instance, House et al. (1990) suggest that depressed individuals with reduced RH activity suffer from reduced ability to communicate emotions. Therefore, it is likely that depressed individuals with dysfunctional right frontal activity are less likely to be diagnosed due to a lack of awareness and inability to communicate their emotional issues (Heilman, Bowers, & Valenstein, 1993).

The results from EEG research have been supported by other imaging methods including glucose metabolism measured using Positron Emission Tomography (PET). Schwartz, Baxter, Mazziotta, Gerner, and Phelps (1987) found reduced left frontal glucose metabolism in depressed participants; a finding that was later replicated (Baxter et al., 1989). Single photon emission tomography (SPECT) research has also demonstrated reduced cortical blood flow in left frontal regions during depression (e.g., Ebert, Feistel, & Barocka, 1991). Drevets et al. (1992) found conflicting evidence with currently depressed participants

actually showing increased left prefrontal metabolism. In contrast, Drevets et al. also found that as depression severity increased, as measured using the Hamilton Depression Rating Scale (HDRS; Williams, 1988), left prefrontal activity decreased. In an effort to explain this unusual finding Drevets et al. suggested that during acute, brief states of depression or sadness the left frontal cortex may become hyperactivated but after prolonged or severe episodes, such as those experienced during clinical depression, this region may become hypoactive. This explanation does not account for why reduced left frontal activity is also seen in those at risk for developing depression (Dawson et al., 1997; Field et al., 1995).

Further support for the role of frontal asymmetry in depression comes from functional Magnetic Resonance Imaging (fMRI) research demonstrating LH hypoactivity in depressed patients (Grimm et al., 2008) and asymmetries in Visual Evoked Potentials studies (e.g., Janocha et al., 2009). The degree of asymmetry has been linked to depression severity (Grimm et al., 2008). There is also evidence of asymmetric brain activity in perceptual asymmetry research. For example, Davidson, Schaffer, and Saron (1985) found that non-depressed participants reported that identical faces displayed in the RVF and LVF were happier when presented to the RVF while depressed individuals displayed the opposing pattern.

Not all EEG research has found that frontal asymmetry and depression are related (e.g., Nitschke, Heller, Palmieri, & Mille, 1999; Reid et al., 1998; Segrave et al., 2011). A meta-analysis of frontal asymmetry in depressed adults revealed significant variation around the mean weighted effect size suggesting substantial heterogeneity and the need to identify potential moderators (Thibodeau et al., 2006). Null findings have also been observed in research using other imaging methods such as SPECT (e.g., Maes et al., 1993) and PET (e.g., Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Silfverskiold & Risberg, 1989), although it is possible that the supine body position required for these testing methods may

interfere with the relationship between trait approach/avoidance and frontal asymmetry (Harmon-Jones et al., 2010).

Explanations for these inconsistent results include the heterogeneity of depression, sampling, and methodological inconsistencies, such as EEG reference selection, insufficient power, and EEG recording time. One likely contributor is the range of approaches to classifying depression with some research using depression inventories to diagnose depression and others utilising clinical interviews structured according to DSM (American Psychiatric Association, 2013) criteria (Stewart et al., 2010). However, atypical findings have been observed using both clinical diagnoses (e.g., Bruder et al., 1997; Kentgen et al., 2000) and self-report methods (e.g., Nitschke et al., 1999). Reid et al. (1998) conducted two studies, one involving clinically depressed participants using DSM diagnosis and one using students with depressive symptomology measured using the BDI. Both studies failed to find a significant association between asymmetry and depression. Thibodeau et al.'s (2006) meta-analysis found that research categorising participants using extreme scores on depression inventories resulted in marginally smaller effects than either studies using clinical diagnoses or those conducting correlational analysis. Focusing solely on whether a participant is depressed or not may be imposing an artificial dichotomy. This approach assumes that depression is an all-or-nothing disorder in which the underlying asymmetry is either present or not. Instead, depression could be a continuum with those at the higher end of the spectrum being able to be diagnosed with clinical depression and displaying more extreme asymmetry scores. Therefore, using two-category diagnoses (depressed/not depressed) may diminish the opportunity to examine the relationship between symptom severity and degree of asymmetry. A two-method approach, utilising dimensional measures of depressed symptom severity and clinical diagnoses would be advantageous in future research to account for both possibilities. Relying on either approach by itself is problematic. Using dimensional measures without

clinical diagnosis cannot exclude alternative explanations of the symptoms such as medical conditions and grieving while using a dichotomous diagnosis approach may obscure the relationship between symptoms and brain activity.

Choice of reference has commonly been touted as a potential source of variability in EEG research (Davidson, 1988; Thibodeau et al., 2006). EEG data, recorded at a particular site, result from recording the difference between activity at that location and a reference site (Davidson, 1988). Ideally, an electrically neutral site would be used but in reality, such a site does not exist. Three of the most commonly used reference schemes are the common vertex (CZ), linked mastoids, and averaged reference. Although commonly used, the CZ reference is problematic as this is a highly electrically active site (Thibodeau et al., 2006). The linked mastoid reference montage averages activity against recordings from both mastoids- a relatively inactive site behind the ear where the majority of electrical activity from the brain is blocked by the thick mastoid bone. The averaged reference method involves making recordings from a large number of electrode locations and using the average recording from these locations as a reference theoretically eliminating noise from the recording. However, this method requires a large number of electrodes. The most accurate reference choice is still a source of much debate but the correlations between frontal EEG recordings using different schemes are moderate so choice of reference is likely to influence the conclusions drawn (Hagemann, Naumann, & Thayer, 2001; Thibodeau et al., 2006). Reid et al. (1998) compared frontal EEG activity recording using linked mastoid, CZ, and averaged reference schemes and found relatively poor convergent validity ($r = -0.33$ to 0.86). The highest convergent validity was observed between the linked mastoid and averaged reference schemes. In Thibodeau et al.'s (2006) meta-analysis, CZ recordings of frontal EEG asymmetry were associated with the largest effect sizes but also showed the most inconsistency. The other reference schemes were more reliable but yielded smaller effect

sizes. In contrast, Hagemann et al. (2001) found good convergent validity between the reference schemes for posterior recordings. Given the low convergent validity of EEG data obtained using different reference schemes, reference choice is a likely contributor to the inconsistencies observed in this field.

Medication status of depressed individuals is another potential source of variability. Different types of medication may have different impacts on brain activity and not all depressed individuals are medicated. Due to the wide range of medications available, it is virtually impossible to control for the possible impact of each type of medication. Thibodeau et al.'s (2006) meta-analysis did not find any evidence that medication was related to effect size for frontal asymmetry in depressed adults. Similar observations were made by Henriques and Davidson (1991) who compared frontal asymmetry in both medicated and non-medicated depressed participants and found no differences. Low sample size in such studies does limit the ability to find significant effects and larger sample replications of this finding are still required.

It has also been suggested that EEG asymmetry may be indicative of depression in women and not in men (e.g., Smit, Posthuma, Boomsma, & De Geus, 2007) but findings regarding sex differences have been inconclusive. For instance, Miller et al. (2002) found depression was associated with increased left frontal activity in a male sample while other studies have found reduced left frontal activity (e.g., Jacobs & Snyder, 1996). Stewart et al. (2010) found that although females with increased symptoms of depression tended to show reduced left frontal activity, the pattern for males was weak and inconsistent. Men with moderate levels of depression showed reduced left frontal activity, but not those with high levels of depression when using a CZ reference. When using the linked mastoid reference scheme, men with high levels of depression showed *increased* left frontal activity while results for the average reference were non-significant. Such inconsistencies make it difficult

to determine whether there is any stable relationship between frontal asymmetry and depression in males, and identify the need to investigate potential moderating factors such as choice of reference and depression subtype. Different subtypes of depression may be more prevalent for one or the other gender, with male depression often associated with bouts of anger and aggression (Winkler, Pjrek, & Kasper, 2005). Given the motivational model of emotion, this type of depression would likely be associated with increased left frontal activity. Not accounting for such variants of depression could account for some of the observed inconsistencies. Inconsistencies in the presence of depression-related brain asymmetry in males may also result from problems diagnosing depression as males may be less likely to seek help and may not present with the classic symptoms of depression as their key complaint (Piccinelli & Wilkinson, 2000).

Quinn, Harris, Felmingham, Boyce, and Kemp (2014) and Reid et al. (1998) proposed that the reason for the aforementioned conflicting results regarding the strength and presence of reduced left frontal activity is heterogeneity within the construct of depression. More specifically, Quinn et al. proposed that not taking into account different subtypes of depression, such as melancholic and non-melancholic depression, could account for some of the inconsistent findings. While melancholic depression is characterised by anxious arousal, non-melancholic depression is characterised by worry or anxious apprehension (Quinn et al., 2014). Research suggests these two distinct types of anxiety might be associated with different patterns of brain activity (Heller, Nitschke, Etienne, & Miller, 1997; Mathersul, Williams, Hopkinson, & Kemp 2008). Mathersul et al. (2008) found that participants with high anxious arousal showed increased right frontal activity while those with anxious apprehension displayed increased left frontal and increased right parietal brain activity. Quinn et al. investigated the possibility of different patterns of brain activity for different variants of depression and found that only participants with non-melancholic depression

showed brain activity that was different from that of healthy control participants. Non-melancholic participants displayed increased left frontal activity compared with controls, a finding that conflicts with previous research indicating reduced left frontal activity in depression, highlighting the need to consider subtypes of depression. Increased left frontal activity has been linked with anger and aggression (Harmon-Jones, 2004) which have been found to be prevalent in patients with non-melancholic depression (e.g., Parker, Fletcher, & Hadzi-Pavlovic, 2012). This finding may help to explain the unusual results of Quinn et al. Not surprisingly, given the considerable debate regarding the existence and nature of depressive subtypes (see Chapter 1), no clear association between different subtypes and asymmetrical brain activity has been found, though based on the aforementioned findings, subtypes should be considered as a possible source of inconsistency.

The presence of comorbid anxiety may also be a significant contributor to the inconsistent findings. Bruder et al. (1997) found that participants with comorbid anxiety and depression showed the typical finding of reduced left frontal activity compared with controls, while participants with depression only did not significantly differ from the control group. Interestingly, in a meta-analysis, studies involving participants with comorbid anxiety and depression revealed only a weak effect size ($d=0.16$) (Thibodeau et al., 2006). However, the anxiety only studies showed a moderate effect size ($d=0.35$). Thibodeau et al. noted that this result might be due to the small number of studies specifically addressing comorbid anxiety and depression. Intuitively, it seems unlikely that both depression and anxiety could be related to relatively reduced left frontal activity but not when they occur together. Different subtypes of anxiety (e.g., worry vs. panic) might have different influences on frontal asymmetry (Heller et al., 1997). Theoretically, most types of anxiety involve primarily negative/withdrawal motivated emotions which would indicate increased right frontal activity given current models of emotion. This hypothesis has been supported in research with social

phobia and panic disorder (e.g., Davidson, Marshall, Tomarken, & Henriques, 2000; Kemp et al., 2010; Metzger et al., 2004). Null findings (e.g., Kentgen et al., 2000) and opposing results (Heller et al., 1997; Kimbrell et al., 1999) have also emerged. Therefore, some of the inconsistencies may be due to variation in exclusion criteria as some studies exclude participants with comorbid psychiatric diagnosis, such as anxiety, while others do not. Additionally, depending on the sample drawn, varying proportions of comorbid anxious and depressed participants could influence the outcomes.

Posterior asymmetry. Although the frontal lobe is primarily implicated in the experience of emotion, changes in arousal during depression have been associated with parietal lobe activity. There is a relative lack of literature regarding the role that parietal asymmetry may play in depression. One of the most common findings is that of reduced right parietal activity in depression (e.g., Davidson, Chapman, & Chapman, 1987; Henriques & Davidson, 1990). It is thought that reduced right parietal activity may reflect decreased arousal and a reduced ability to process emotional material (Bruder, 2003; Heller & Nitschke, 1997; Stewart, Towers, Coan, & Allen, 2011). Reid et al. (1998) found significant group differences in parietal activity (in the absence of differences in frontal activity). The results were interpreted as evidence of reduced arousal in the depressed participant group but this finding was only observed in one of the three reference schemes used, linked mastoids. Support for EEG research of reduced parietal activity has been found in perceptual asymmetry research (e.g., Heller, Etienne, & Miller, 1995; Keller et al., 2000), and in event-related potential studies of emotional perception (e.g., Sumich, Kumari, Heasman, Gordon, & Brammer, 2006). Other research has not been able to replicate reduced right parietal activity (e.g., Diego et al., 2001; Henriques & Davidson, 1991).

The presence of comorbid anxiety may help to explain some of the conflicting evidence regarding the role of the parietal lobe (Bruder et al., 1997; Bruder, Wexler, Stewart,

Price, & Quitkin, 1999; Heller et al., 1995). As noted earlier, approximately one half of all individuals with depression also suffer from a comorbid anxiety disorder (Bruder et al., 1997; Kessler et al., 2003). Anxiety is associated with an increase in arousal while depression is typically associated with reduced arousal (Bruder et al., 1999). Therefore, if increased right parietal activity is associated with increased arousal, and reduced right parietal activity is associated with decreased arousal, then it is likely that in an individual suffering from both depression and anxiety these patterns will essentially cancel each other out (Heller et al., 1995). If anxiety is not controlled for in a study of parietal activity in depression, the presence of comorbid anxiety is likely to lead to noisy results. Heller et al. (1995) found evidence supporting this theory in a study investigating hemi-spatial bias for perceiving chimeric faces. Participants with high trait anxiety showed a large left-hemispatial (RH bias) while those with depression showed only a minor left-hemispatial bias indicating a loss of activity in the right parietal region. Additionally, patients with comorbid anxiety and depression show an opposing pattern of parietal asymmetry compared with participants with depression only (Bruder et al., 1997). Depression only was found to be associated with a relative reduction in right parietal activity while those with comorbid anxiety showed increased right posterior activity (Bruder et al., 1997). Bruder et al. (1999) found further evidence to support this theory with anxious-depressed participants showing a clear RH bias in a series of perceptual asymmetry tasks while the depressed only participants showed a LH bias. These findings may shed some light on the continuing debate regarding the separability of anxiety and depression (refer to Chapter 1) as opposing patterns of both physiological and behavioural measures suggest that, although frequently comorbid, anxiety and depression are independent entities.

It is theorised that some of the cognitive deficits in depression may be a result of reduced right parietal activity and associated reductions in arousal (Bruder et al., 1997;

Shenal et al., 2003). Resting asymmetry in parietal regions seems to predict performance in both verbal and non-verbal tasks (e.g., Davidson, Taylor, & Saron, 1979; Glass & Butler, 1977).

Persistence of asymmetrical brain activity in depression. In order to determine what asymmetries in brain activity tell us about depression, it is important to consider whether the activity is a state or trait characteristic of depression. Research predominantly indicates that reduced left frontal activity persists following recovery from depression (e.g., Allen et al., 2004; Gotlib et al., 1998; Henriques & Davidson, 1990). For example, Henriques and Davidson (1990) compared never depressed and previously depressed (currently asymptomatic) participants' frontal asymmetry and observed left-hypofrontality in the previously depressed group. Similarly, Gotlib et al. (1998) found both currently and previously depressed participants had relatively reduced left frontal activity relative to controls. It has been suggested that low-level residual symptoms of depression may be responsible for this observation.

Gotlib et al. (1998) found that the never depressed and previously depressed participants could not be differentiated by mood testing indicating that the differences in EEG asymmetry could not be a result of residual symptoms. Additionally, Stewart et al. (2010) found that both currently and previously depressed participants were both characterised by a relative reduction in left frontal brain activity compared with never depressed participants. Using a Current Source Density (CSD) reference scheme, a method that derives extracellular sources of activity to estimate current source, controlling for current symptom severity did not moderate the presence of relatively reduced left frontal activity in previously depressed participants indicating that the presence of residual symptoms was not responsible for the asymmetry. On the other hand, for both linked mastoids and CZ reference schemes, the relationship *was* moderated by severity of current symptoms.

The persistence of relative left hypoactivation after recovery from depression, might be a result of enduring biological changes due to having a depressive episode rather than conveying vulnerability towards developing depression (Nusslock et al., 2011). This is sometimes termed the ‘Scar Hypothesis’ in which brain activity becomes sensitised after the experience of a depressive episode which may predispose an individual to future episodes (Rohde, Lewinsohn, & Seeley, 1990). Evidence for the scar hypothesis largely comes from longitudinal research finding that those who became depressed during the study period did not show abnormal cognitions prior to their first episode of depression (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). However, the cognitive functions tested were very limited, for example irrational beliefs, and may not be cognitive factors linked to abnormal brain activity. The scar hypothesis also does not explain why reduced left frontal activity predicts the onset of the first episode of depression in longitudinal research (e.g., Nusslock et al., 2011). Similar patterns of reduced left frontal asymmetry are also observed in those at risk for developing depression such as infants of depressed mothers (Dawson et al., 1997; Field et al., 1995), although these findings might be a result of the mother’s depressive episode leaving a ‘scar’ on the infant’s brain activity.

Similar to the scar hypothesis, another explanation for the persistence of asymmetric brain activity in depression is the long-term effect of antidepressants. Chronic use of antidepressants has been linked long-term changes in brain structure and function such as neurogenesis in the hippocampus (David et al., 2009; Samuels & Hen, 2011). Although Thibodeau et al. (2006) did not find any evidence that current medication use moderated frontal asymmetry, longer term effects of antidepressant therapy on asymmetry have yet to be investigated. Therefore, it is possible that antidepressant treatment may lead to the apparent persistence of frontal asymmetry beyond remission from depression, and further study is needed comparing the persistence of frontal asymmetry in those who were medicated and

those who were un-medicated during the depressive episode(s). The observation that frontal asymmetry is predictive of the onset of the first episode of depression (Nusslock et al., 2011) suggests that long-term medication effects might not be the sole cause of the persistence of asymmetry in previously depressed individuals.

Due to the persistence of frontal asymmetry and the ability to distinguish remitted and current depressives from never depressed, frontal asymmetry has been proposed as a trait marker or endophenotype indicating a predisposition to developing depression (Schmidt et al., 2011; Stewart et al., 2010). Endophenotypes are “Measurable endogenous characteristics of an individual that are related to underlying mechanisms, conferring risk” (Stewart et al., 2010, p. 1).

To function as a useful endophenotype, frontal asymmetry would need to be related to other possible risk factors for depression such as certain genotypes (Stewart et al., 2010). Support for the association between genetics and asymmetric activity comes from heritability research indicating that frontal asymmetry may have a genetic basis (e.g., Anokhin, Heath, & Myers, 2006; Gao, Tuvblad, Raine, Lozano, & Baker, 2009; Smit et al., 2007). Smit et al. (2007) found that in young, female adults, frontal asymmetry was 37% heritable. This indicates that, although frontal asymmetry is influenced by environmental factors, there is a substantial genetic component. Hagemann, Naumann, Thayer, and Bartussek (2002) used structural equation modelling and estimated that approximately 60% of the variance seen in frontal asymmetry scores was a result of trait variance. Although the risk for depression is likely to be conveyed via multiple genetic differences, some genes have been found to relate to frontal asymmetry. For example, frontal asymmetry and depression risk have been linked with genes coding for serotonin receptors, specifically the HTR1A gene (e.g., Bismark et al., 2011).

Further support for the predictive ability of frontal asymmetry comes from longitudinal research conducted by Nusslock et al. (2011). Frontal asymmetry was found to predict the development of an individual's first episode of depression over a 3-year follow up period from the initial recording session.

Not all studies support the persistence of reduced left frontal activity in depression. For example, Baxter et al. (1989) noted that left hypometabolism did not appear to persist beyond remission from depression. Additionally, Debener et al. (2000) found evidence against using frontal EEG asymmetry as a trait marker for depression due to low test-retest reliability in the depressed participant group. Debener et al. suggested that high variability of frontal EEG asymmetry may be characteristic of depressed individuals.

What does asymmetry represent? One question that has rarely been addressed is the origin of asymmetrical brain activity. Asymmetry in the binding of dopamine to D2 and D3 receptors in the medial temporal cortex has been observed with less dopamine binding in the left hemisphere in the depressed group compared with the control group (Lehto et al., 2009). Interestingly, asymmetry in dopamine function has been linked to changes in novelty seeking and approach/avoidance behaviour in patients with Parkinson's disease (Tomer & Aharon-Peretz, 2004) which could indicate a link between dopamine asymmetry and the motivational model of frontal activity. Abnormalities in serotonin (5HT) receptors is another possible source of asymmetrical brain activity with indications of reduced 5HT₂ receptors in the left infero-frontal area in depressed participants compared with a control group (D'haenen et al., 1992). However, there have been no studies addressing a possible connection between asymmetrical function of neurotransmitter systems and EEG asymmetry in people with depression. Addressing this gap would help to determine the source of frontal asymmetry in depression which could assist in improving treatment and could also help to determine why the EEG asymmetry literature is so variable.

Subcortical Abnormalities in Depression

Subcortical structures that are theorised to be involved in the circuitry for emotion include the amygdala, hippocampus, and the basal ganglia (Davidson, 2004). Strong connections are present between these regions and the prefrontal cortex (PFC) highlighting the possibility that the PFC may modulate activity in the amygdala and other subcortical structures involved in emotion (Davidson, 2004). Abnormalities in these regions, and their connections to the PFC, have been implicated in the experience of depression.

Subcortical abnormalities in depression can be grouped into two classes, structural changes, such as loss of volume, and functional changes, such as reduced activity. Functional abnormalities such as asymmetrical brain activity seem to be more prominent than structural changes (Liotti & Mayberg, 2001). In a meta-analysis of changes in brain activity during depression, Fitzgerald, Laird, Maller, and Daskalakis (2008) found increased activity in the basal ganglia, amygdala, and thalamus in depression compared with controls. Since the amygdala is involved in fear and threat detection, increased activity here makes intuitive sense in depressed individuals. However, Fitzgerald et al. noted that there was substantial variability amongst studies using different methods to detect subcortical activity making it difficult to clearly outline a profile of subcortical activity in depression.

Structural changes have included reduced hippocampal volume in depressed participants compared with controls (e.g., Bell-McGinty et al., 2002; Frodl et al., 2002; MacQueen et al., 2003) and reduced volume in the basal ganglia (e.g., Steffens & Krishnan, 1998). A review of these results highlighted substantial inconsistency (Sheline, 2003). A possible link to asymmetrical cortical activity has also been found with increased right amygdala volume observed in some research and loss of normal asymmetry in both the amygdala and basal ganglia (e.g., Lacerda et al., 2003; Sheline, 2003).

When viewed in conjunction with cortical asymmetry in depression, abnormalities within subcortical regions implicated in emotion have led to the development of a model for depression characterised by dysfunction within the limbic-cortical network (Mayberg, 2003). Differences in the nature of the dysfunction within this network have been proposed to account for the heterogeneity in symptom profiles observed in depression (Mayberg, 2003). Cortical regions, particularly the PFC, have been found to modulate activity within the limbic system with increased blood flow in PFC regions associated with reduced activity in the amygdala during tasks requiring emotional processing (Hariri et al., 2000). Since EEG is relatively cost- and time-effective compared with other imaging methods, larger sample sizes are possible increasing statistical power and reducing statistical noise causing Type 1 error. Therefore, further investigation regarding the cause of inconsistencies in the neurological correlates of depression would be best approached by further study of cortical activity using EEG. This will allow some possible causes of inconsistencies, such as subtypes of depression, to be eliminated before more detailed study of dysfunction in the limbic-cortical circuit is conducted.

Usefulness of Asymmetry Metrics in Treating Depression

Depression is a highly heterogeneous condition which can impair both diagnosis and treatment. For example, while some people with depression might show flat affect and loss of motivation, others might exhibit tearfulness and distress. Although both presentations might lead to a diagnosis of depression, it is possible they have different underlying patterns of brain activity (Shenal et al., 2003). Treating both groups in the same way might limit effectiveness of the treatment. Using the circumplex model of emotion, Shenal et al. (2003) proposed that different underlying patterns of brain activity could account for different presentations of depression. Reduced left frontal activity could lead to depression with diminished positive affect and less approach motivated behaviour. In contrast, right frontal

dysfunction could lead to depression associated with an increased experience of negative affect and withdrawal behaviours. Alternatively, reduced right frontal activity could lead to depression characterised by learned helplessness due to a failure to avoid aversive situations. Finally, right posterior dysfunction could lead to depression with reduced arousal and failure to identify/engage with emotional material. There is a relative lack of research regarding the role that left posterior regions might play in emotion. Since patterns of asymmetrical brain activity have been found to predict the onset of the first episode of depression (e.g., Nusslock et al., 2011) and seem to persist beyond recovery from depression (e.g., Henriques & Davidson, 1990), different underlying patterns of brain activity may account for the different presentations of depression, rather than asymmetric patterns of brain activity arising a result of different presentations of depression.

Using Shenal et al.'s (2003) model it would be possible to classify depression more precisely and offer treatment options targeted towards each group, such as biofeedback or engaging in activities designed to increase activity in the desired region. An improved understanding of the varying brain activity underlying depression will also help to clarify the inconsistencies regarding cognitive symptoms in depression (see Chapter 3 for a review).

Preliminary research regarding the effectiveness of neurofeedback in reducing frontal asymmetry has shown promising results. For example, Peeters, Ronner, Bodar, van Os, and Lousberg (2014) found that, out of nine participants, four participants went into remission during neurofeedback treatment while one also showed a significant improvement in symptomology. Improved symptomology was associated with a reduction in frontal asymmetry scores. Similarly, transcranial magnetic stimulation (TMS) directed towards increasing left frontal activity has also been observed to have a type of antidepressant effect (George et al., 2000). Using brain asymmetry as an endophenotype to identify those at risk for developing depression will allow for early detection and intervention. Treatment plans

can be targeted towards different subtypes of depression characterised by unique patterns of brain activity.

Frontal asymmetry may also help to indicate which individuals will respond well to antidepressant medication (Bruder et al., 2001). Non-responders to a commonly used SSRI (Fluoxetine) tended to show the characteristic pattern of reduced left frontal activity while responders did not show this pattern. Similarly, Walsh, McDowall, and Grimshaw (2010) found that SSRI non-responders showed the absence of the typical LH advantage for the processing of emotional words while SSRI responders showed results consistent with never depressed individuals. Iosifescu et al. (2008) also found the frontal EEG activity was able to predict responsiveness to SSRI's. Using frontal asymmetry to predict responsiveness to treatment will assist with reducing unnecessary medication use by those unlikely to respond and will prevent exposure to negative side-effects of medication use. Despite the promise of frontal asymmetry as a biomarker to assist in the diagnosis and treatment of depression, the inconsistencies in the research findings need to be resolved before this potential is fulfilled.

Since the dorsolateral PFC is implicated in cognitive control processes (Davidson, 2004; Miller & Cohen, 2001) it is likely that asymmetry scores will be related to cognitive function and may be predictive of some of the functional deficits observed in depression. Cognitive impairment in depression will be reviewed in Chapter 3.

Chapter Three

Cognitive Impairment in Depression

Self-Reported Impairment

Despite being a predominantly affective disorder, sufferers of depression frequently report cognitive symptoms (Harvey et al., 2004; Rose & Ebmeier, 2006; Srisurapanont et al., 2015). Typical complaints include memory difficulties, reduced concentration, impaired problem solving, and poor decision making (Harvey et al., 2004; Taylor-Tavares et al., 2007; Srisurapanont et al., 2015). It is unclear whether self-reports of cognitive deficits in depression are reliable.

Hueng et al. (2011) examined the relationship between subjective reports of cognitive difficulties, measured using the cognitive subcomponents of the Taiwanese Depression Questionnaire (TDQ; Lee, Yang, Lai, Chiu, & Chau, 2000), and cognitive tests including the Wechsler Memory Scale (WMS; Wechsler, 1987) and the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1993). Although subjective reports of cognitive impairment in depression were related to impaired performance, there was a substantial amount of unexplained variance indicating that subjective reports may not give an accurate picture of cognitive function though it is also possible that tests of cognitive function are not reliable measures either. One domain of self-reported cognitive function that does not appear to relate to deficits is psycho-motor speed (Hueng et al. 2011; Naismith, Longley, Scott, & Hickie, 2007).

Perceived deficits are more severe than is revealed during cognitive testing (Lahr, Beblo, & Hartje, 2007). This may be a result of a negative cognitive bias in depressed individuals resulting in a tendency to exaggerate perceived shortcomings (Lahr et al., 2007;

Sweeney, Anderson, & Bailey, 1986). The inconsistency may also result from the artificiality of cognitive testing in a laboratory or lack of reliable and valid cognitive measures which may not accurately capture cognitive dysfunction in everyday life (Lahr et al., 2007).

Objective Measurement of Cognitive Impairment

Impairments have been observed in a wide variety of cognitive domains including processing speed (e.g., Gualtieri et al., 2006), memory (e.g., Landro, Stiles, & Sletvold, 2001; Porter et al., 2003), decision making (e.g., Taylor-Tavares et al., 2007), attention (e.g., Taylor-Tavares et al., 2007; Ravnkilde et al., 2002), problem solving (e.g., Naismith et al., 2003) and working memory (e.g., Christopher & MacDonald, 2005; Rose & Ebmeier, 2006). However, the findings have been highly variable (Rose & Ebmeier, 2006; Taylor-Tavares et al., 2007; Weiland-Fiedler et al., 2004). While the majority of studies have found evidence of widespread cognitive deficits in depression (e.g., Harvey et al., 2004; Lockwood, Alexopoulos, & van Gorp, 2002; Porter et al., 2003), a small number of studies have found that individuals with depression did not suffer from generalised cognitive impairment (e.g., Grant, Thase, & Sweeney, 2001; Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Wang et al., 2006). Variability in the specific domains affected has led to the inability to create a clear profile of cognitive impairment in depression.

Theories of Cognitive Profiles in Depression

Four main theories have been proposed to explain the pattern of cognitive deficits in depression (Den Hartog, Derix, Van Bommel, Kremer, & Jolles, 2003; Hammar & Ardal, 2009). The first of these is known as the global-diffuse hypothesis. This hypothesis suggests that individuals with depression show general cognitive impairment that is not domain specific (Hammar & Ardal, 2009; Veiel, 1997). Support for the global-diffuse hypothesis has been found by numerous studies (e.g., Gualtieri et al., 2006; Ravnkilde et al., 2002;

Reppermund, Ising, Lucae, & Zihl, 2008; Veiel, 1997). In contrast, a second hypothesis proposes domain-specific cognitive impairment (Hammar & Ardal, 2009). For example, Grant et al. (2001) found no evidence of widespread cognitive impairment in un-medicated, depressed individuals. Specific deficits were found in the WCST, a test of task-switching capability, and executive function (EF). This finding highlights the possibility that depressed individuals may only have deficits in specific domains of cognitive functioning. Further support for the specific impairment hypothesis comes from Sweeney, Kmiec, and Kupfer (2000), who identified an isolated impairment in episodic memory, and Purcell, Maruff, Kyrios, and Pantelis (1997) who found specific impairments in motor slowing and set-shifting but no evidence of general cognitive decline.

A third hypothesis suggests that individuals with depression show cognitive deficits only when the task is effortful compared with more automatic tasks (Gualtieri et al., 2006; Hammar & Ardal, 2009). Gualtieri et al. (2006) found that participants with depression had impaired performance on effortful tasks such as symbol-digit-coding but intact performance on more automatic tasks such as simple visual memory. This could account for Grant et al.'s (2001) finding of specific impairments in a test of EF since tests of EF are usually considered to involve a high level of cognitive effort. Den Hartog et al. (2003) found evidence disputing this hypothesis and instead proposed a fourth possibility. Den Hartog et al. found that individuals with depression suffered from reduced cognitive speed across all domains which may have been misinterpreted as global-diffuse deficits in other studies. In contrast to Gualtieri et al.'s finding, impairments were only observed in automatic components of the task and not more effortful components. Den Hartog et al. theorised that reduced cognitive speed may lead to impairments in some more effortful tasks, such as those used in Gualtieri et al., as reduced speed may lead to information decay.

These theories of cognitive deficits in depression may not be mutually exclusive. While depressed individuals may show a non-specific decline in cognitive performance, they may also show disproportionate dysfunction in specific domains. For example, Gualtieri et al. (2006) found that patients with depression showed widespread cognitive impairment but with exaggerated impairment in domains of cognitive flexibility, complex attention, and vigilance. The conflicting evidence regarding these hypotheses may be a result of methodological inconsistencies, heterogeneity in depression, and inadequate theories that do not fully explain the underlying profile of cognitive deficits in depression. Factors contributing to inconsistent findings will be discussed later in this chapter.

Specificity of Cognitive Impairment

Although cognitive deficits have the potential to be useful as diagnostic markers for depression, it is important to identify if cognitive deficits in depression are unique to unipolar depression or whether they are a more general impairment common to all psychiatric illness (Burt, Zembar, & Niederehe, 1995). Unsurprisingly, given the varied and inconsistent research regarding the presence and severity of cognitive deficits in depression, research regarding the specificity of cognitive impairment is also inconsistent.

For example, Fossati et al. (1999) found that while schizophrenic patients showed impaired memory function, patients with unipolar depression did not. In a review of memory function in depression, Burt et al. (1995) concluded that memory impairment was observed in a number of psychiatric conditions and may therefore not be specific to depression. Similar results were found by Egeland et al. (2003) who found that depressed participants showed impaired performance in working memory (WM) and recall but that these deficits were also present and more salient in schizophrenic participants. However, Merriam, Thase, Haas, Keshavan, and Sweeney (1999) found that depressed participants showed a more severe

impairment on the WCST than participants with schizophrenia. Taylor-Tavares et al. (2007) found that impaired spatial WM and attentional shifting was specific to depression as those with Bipolar-2 did not suffer from impaired WM and attentional shifting while those with unipolar depression were impaired. These differences could not be attributed to mood or anxiety levels as these were found to be comparable in the two groups, or to medication as both groups were non-medicated. Other aspects of cognitive performance, for example free recall, did not differ between unipolar and bipolar depression groups (Fossati et al., 2004). Sweeney et al. (2000) found that those with unipolar depression suffered a specific impairment in episodic memory while those tested during the manic phase of bipolar disorder showed more severe and pervasive impairment impacting on a variety of cognitive domains. Christopher and MacDonald (2005) obtained mixed results, finding that certain aspects of WM performance were unique to depression while other aspects were shared with anxiety disorders. Although this could suggest that depression might be associated with a distinct profile of cognitive deficits, no information is given regarding how comorbid anxiety and depression were controlled for. Given how highly comorbid anxiety and depression are (Fava et al., 2000); it is unclear how reliable the distinction between the depression and anxiety group was.

Apart from the few studies described above, the majority of studies compare cognitive performance in depressed participants with healthy control participants making it difficult to ascertain whether deficits are specific to depression or are more generally linked to psychiatric illness or other health conditions. In order to more clearly understand, identify, and treat cognitive impairment in depression, further studies comparing depressed patients with other psychiatric groups and matched controls are required to determine if cognitive deficits in depression are specific or a more general outcome of mental illness.

Domains of Cognitive Impairment

Executive function. One of the most common and robust findings is impaired EF in individuals with depression. EF is defined as “complex cognitive processing requiring the coordination of several sub-processes to achieve a particular goal” (Elliott, 2003, p. 50). Therefore, EF is a broad domain encompassing a number of more specific functions such as set-shifting ability, cognitive flexibility, and inhibition of inappropriate responses.

Deficits in EF are commonly found in later-life depression (e.g., Lockwood et al., 2002; Sheline et al., 2006). However, deficits in EF are also observed in younger individuals with depression (e.g., Castaneda et al., 2008; Fossati et al., 1999) indicating that EF impairment in depression is distinct from cognitive decline as a result of aging. In fact, Thomas et al. (2008) found comparable levels of impaired EF in both younger and older patients with depression.

Deficits have been demonstrated in set-shifting (e.g., Merriam et al., 1999; Taylor-Tavares et al., 2007), sustained attention (e.g., Porter et al., 2003), inhibition (e.g., Den Hartog et al., 2003), problem solving (e.g., Naismith et al., 2003) and cognitive flexibility (e.g., Fossati et al., 1999). The extent of impaired EF is still unclear. While Harvey et al. (2004) and Rogers et al. (2004) suggest widespread EF impairment in depression, Grant et al. (2001) and Purcell et al. (1997) found specific deficits in set-shifting ability while other functions remained intact. Furthermore, other studies find no evidence of impaired EF (e.g., Landro et al., 2001; Ravnkilde et al., 2002). The presence and severity of impaired EF in depression may be moderated by intelligence and the number of depressive episodes experienced (Stordal et al., 2005). Purcell et al. found that only half of their depressed participants showed impaired set-shifting ability suggesting that only a subgroup of individuals with depression show impaired EF. Further research is needed to identify the

characteristics of these subgroups and to establish whether subgroups characterised by this impairment represent a distinct subtype of depression.

Memory impairment. Another domain that is commonly impaired in depressed individuals is memory. Despite some inconsistencies, a meta-analysis by Burt et al. (1995) found that, in general, people with depression have impaired memory. The nature of memory impairment was found to be moderated by age (increased impairment in younger samples), medication status, and subtype. Inconsistencies become apparent when focussing on specific types of memory.

For example, Fossati, Coyette, Ergis, and Allilaire (2002) and Thomas et al. (2008) found impaired verbal memory in both younger and older depressed participants although the level of impairment was more severe in older age groups (Thomas et al., 2008). In contrast, Porter et al. (2003), Smith, Muir, and Blackwood (2006), and Wang et al. (2006) all found intact verbal memory in depression. Wang et al. speculated that their non-significant findings were a result of their use of non-medicated participants who had less severe depression than participants in other research. Their claim is supported by Schmitt, Kruizinga, and Riedel's (2001) finding that verbal memory may be influenced by medication for depression, so not controlling for medication status in participants may have led to some of the inconsistencies. Fossati et al. (2004) also found that patients suffering from their first depressive episode showed intact verbal memory. However, patients with recurrent depression showed impaired free recall of verbal information while cued recall and recognition remained intact (Fossati et al., 2004). This suggests that those with recurrent depression might be less motivated to remember when there are no cues present or it may reflect the effort hypothesis of cognitive deficits in depression with higher effort tasks, such as free recall, being more likely to be impaired than lower effort tasks such as cued recall. Similar inconsistencies are seen in other domains including short-term memory which has been found to be impaired in some research

(e.g., Ravnkilde et al., 2002) but is intact in other studies (e.g., Purcell et al., 1997). The clear inconsistencies observed here warrant a more systematic review of possible moderating factors.

Working memory. Working memory (WM) can be defined as the ability to store and actively manipulate incoming information (Baddeley & Hitch, 1974). WM consists of both executive processes and a memory component (Elliott, 2003). Both of these aspects of WM have been shown to be impaired in depressed individuals; therefore, one would expect to find impaired WM accompanying depression. In Baddeley's model of WM there are three key components: the central executive (CE), the visuo-spatial sketch pad and the phonological loop (Baddeley, 2000). The central executive is theorised to control and allocate the resources to control the remaining two components, the so-called 'slave systems' of WM (Baddeley, 2000). These systems handle the maintenance and rehearsal of domain-specific material. The phonological loop handles incoming information that is presented verbally while the visuo-spatial sketch pad briefly stores and manipulates spatial or visually presented information (Baddeley, 2000).

Due to the different processes involved in each of these components of WM, it is important to assess them separately in depressed individuals. However, the majority of studies have only assessed one aspect of WM and have used the results to represent WM as a whole (e.g., Rose & Ebmeier, 2006). To review how WM is affected by depression, multiple studies must be assessed. Due to variations in methodology and participant recruitment, direct comparisons are difficult. While some studies find WM deficits (e.g., Beats, Sahakian, & Levyl, 1996; Channon, Baker, & Robertson, 1993; Harvey et al., 2004; Landro et al., 2001; Nebes et al., 2000; Porter et al., 2003; Reppermund et al., 2008) others do not (e.g., Barch, Sheline, Csernansky, & Snyder, 2003; Grant et al., 2001; Purcell et al., 1997; Zakzanis, Leach, & Kaplan, 1998).

In an in-depth investigation of WM function in depression, Channon et al. (1993) found a specific deficit in CE function while slave system function was intact. From a large battery of tests designed to assess the function of each of the three main components, only one test of CE function, Backward Digit Span, showed impairment in the depressed participant group. Other CE tasks such as the trail making task showed no evidence of impairment. These tasks were an unusual choice of measures of CE function as random number generation and multitasking tests are more typical measures (Baddeley, 1996, 1998). Task-choice is an ongoing problem in WM research, especially regarding CE function since the CE has come to be understood as a homunculus, or attention controller, with a very broad range of capabilities and roles (Baddeley, 1996, 1998). Given the poor correlations between different cognitive measures, a lack of a clear definition of the CE's key functions is an ongoing problem in this field. Channon et al. also compared medicated and non-medicated participants and did not find any differences suggesting that the deficit in the backward digit span task was not a side-effect of antidepressants. Channon et al. theorised that more effortful tasks employing the CE revealed impairment, while more automatic tasks engaging the slave systems were intact. This theory was supported by Hartlage, Alloy, Vázquez, and Dykman (1993) who found impaired effortful processing in depression while more automatic processing was relatively spared. However, Channon et al. used inpatients as the depressed sample while the control group was from the community. As a result, the findings may be confounded by patient status. A control group consisting of inpatients with another psychiatric disorder would have been beneficial.

If individuals with depression experience impaired CE function, Rose and Ebmeier (2006) hypothesised that more difficult levels of the N-back task would be expected to show disproportionate impairment compared with healthy controls due to the increasing attentional demands. In an N-back task participants are asked to identify if the current

stimulus is the same as the one shown a certain number of stimuli ago (designated N). This hypothesis was not supported. One limitation with this research was that a visuo-spatial variant of the N-back task was employed without the use of a matched verbal task. As verbal and spatial stimuli have been found to be associated with activity in different regions of the brain (D'Esposito et al., 1998; Smith, Jonides, & Koeppe, 1996), it is possible that these tasks might be differentially affected. When Harvey et al. (2004) conducted similar research using a verbal N-back task, despite an overall impairment in performance, there was no evidence of disproportionate impairment as task difficulty increased compared with control participants. No impairment was observed in the 0-back level measuring attention suggesting the impairment in the 1-, 2-, and 3-back levels was due to a deficit in the updating component of WM. Harvey et al. also found evidence of global CE dysfunction with deficits in multiple tasks such as the trail making test.

In contrast to the aforementioned research suggesting a specific impairment in CE function, other research has found evidence of more widespread WM impairment in depression influencing all components of Baddeley's model. For example, Christopher and MacDonald (2005) conducted a battery of WM tests, including Backward Letter Span, Verbal Reasoning, Grid Recognition, and Word Length Effect, with multiple tests to measure each component of WM. Impaired performance was found in all tasks, not just those theorised to measure CE function. Although the tasks designed to assess slave system function were selected to minimise the influence of CE function, it is possible impaired CE function may still have resulted in the slave system impairment. Similarly, tasks designed to assess CE function are also likely to draw on slave system resources. In fact, one of the biggest difficulties facing this field of research is the inability to disentangle different domains of cognitive functioning and it is acknowledged that most, if not all, tasks will require multiple cognitive functions in order to be performed successfully.

In an effort to measure WM function in a more general sense, a number of researchers have focussed on comparing spatial and verbal WM function without trying to attribute performance to CE or slave system functioning. Due to the lateralisation of spatial and verbal processing (D'Esposito et al., 1998; Smith et al., 1996), this endeavour may help to elucidate specific areas of impaired brain activity which will inform a more targeted investigation of cognitive impairment in depression. Spatial WM deficits are commonly observed (e.g., Porter et al., 2003; Rose & Ebmeier, 2006; Taylor-Tavares et al., 2007; Thomas et al., 2009; Weiland-Fiedler et al., 2004) but not by all (e.g., Grant et al., 2001; Lahr et al., 2007; Purcell et al., 1997; Sweeney et al., 2000). Similarly mixed findings have been found in verbal WM research. While the bulk of studies have found impaired verbal WM (e.g., Christopher & MacDonald, 2005; Harvey et al., 2004; Nebes et al., 2000; Pelosi, Slade, Blumhardt, & Sharma, 2000; Ravnkilde et al., 2002; Reppermund et al., 2008), unimpaired verbal WM has also been noted (e.g., Barch et al., 2003; Lahr et al., 2007). These inconsistencies may have arisen due to the use of different measures to assess verbal WM. For instance, while Harvey et al. (2004) and Nebes et al. (2000) both used verbal N-back tasks, Lahr et al. (2007) utilised a digit suppression test (a modified version of a digit span task) while Reppermund et al. (2008) used a backward digit span task. There is considerable debate regarding the most appropriate measure of WM and there are only weak correlations between different measures highlighting the use of different tests as a strong candidate to at least partially explain these inconsistencies (Jaeggi, Buschkuhl, Perrig, & Meier, 2010; Kane, Conway, Miura, & Colflesh, 2007).

Origin of Impairment

Cognitive impairment seems to be present in a large proportion of those with depression so the question becomes, what is the cause of the impairments? There are two key approaches to explaining the source of cognitive impairment in depression.

The first approach explains cognitive impairment as a downstream effect of the affective component of depression with a number of proposed specific causes. The first of these is reduced motivation in depression leading people with depression to be less motivated to perform well in tasks of cognitive performance (Burt et al., 1995; Channon, 1996; Channon & Green, 1999; Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Porter et al., 2007). Decreased motivation may lead to reduced inclination to use more effortful strategies in tasks with a high cognitive load (Burt et al., 1995) and may leave individuals more vulnerable to perceived failure (Channon, 1996; Elliott et al., 1997). If reduced motivation is responsible for the cognitive impairments observed, it would be expected that participants with depression might be more likely to fail to respond, or guess, during an N-back task. However, Rose and Ebmeier (2006) found that this was not the case; participants with depression were more likely to provide an incorrect response than to not respond. Additionally, participants were performing above chance level indicating that they were not just guessing all the time; they were genuinely trying to complete the task to the best of their abilities. The motivation theory also does not explain why some automatic tasks are also impaired such as the automatic subcomponents of the Stroop Task where participants are asked to name colour words written in black ink (e.g., Den Hartog et al., 2003; Porter et al., 2003).

Individuals with depression may also experience more negative responses to perceived failure than healthy controls (Porter et al., 2007). The effect of this may be compounded as research suggests that depressed individuals commonly set unrealistic goals for themselves, particularly when performing multiple cognitive tasks (Kuhl & Helle, 1986). Evidence of this has been found in a Tower of London task where, once depressed participants made a single error, subsequent performance declined (Beats et al., 1996).

Similar findings have not been replicated in other studies (e.g., Shah, O'Carroll, Rogers, Moffoot, & Ebmeier, 1999).

Alternatively, observed deficits may not truly represent cognitive impairments and may simply be an artefact of reduced psychomotor speed. Ravnkilde et al. (2002) used an ANCOVA to attempt to control for psychomotor slowing but cognitive impairment remained significant suggesting that psychomotor retardation does not fully account for differences between controls and depressed patients. However, this conclusion should be treated with suspicion as a key requirement of ANCOVA is random assignment to participant groups (Miller & Chapman, 2001). Since Ravnkilde et al. were not able to randomly assign participants to the control and depressed groups; they attempted to match the control group as closely as possible to the depression group. Using this method, any remaining differences between the control and depression groups can interact with the covariate of interest, in this case psychomotor retardation, making it impossible to account for the covariance reliably (Miller & Chapman, 2001).

A final way in which the affective symptoms of depression may explain cognitive impairment is that a significant proportion of processing resources may be used up maintaining depressogenic conditions (Christopher & MacDonald, 2005; Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010). For example, ruminating about negative outcomes is likely to use up a significant portion of resources leaving less available for the performance of cognitive tasks. Similar explanations are given concerning the link between increased anxiety and impaired cognitive function (Eysenck, Derakshan, Santos, & Calvo, 2007). This theory does not account for why cognitive impairment continues even after remission (Reppermund et al., 2008; Weiland-Fiedler et al., 2004). It is possible that, despite the appearance of remission from the affective component of depression, recovered patients may

still maintain depressogenic cognitive styles leading to the persistence of impaired cognitive function.

The second main approach to explain cognitive impairment in depression is that it results from underlying abnormalities in neurobiological function (see Chapter 2 for a review.) The cognitive deficits observed in past research have led to many proposing frontal lobe dysfunction as a possible cause (e.g., Fossati et al., 1999; Lockwood et al., 2002; Reppermund et al., 2008). More specifically, neuroimaging studies suggest abnormalities in regions of the brain associated with WM, such as the dorsolateral prefrontal cortex (DLPFC) (Rose & Ebmeier, 2006). Other structural changes such as hippocampal atrophy may be associated with memory impairment (Porter et al., 2007). Neurobiological factors such as abnormalities in the Hypothalamic-Pituitary-Adrenal axis (HPA) are also implicated (Porter et al., 2007).

Taken together, it is clear that the cause of cognitive impairment in depression is far from certain. Given the range of impairments, it is likely that multiple factors may have to coincide in one patient in order to observe cognitive impairment (Neu et al., 2005). In fact, Reppermund et al. (2008) proposed that different underlying etiology may be related to depression subtypes and that this observation might help to explain some of the inconsistencies in depression research, although further control of experimental sources of variability, such as the use of different research techniques and measures, is required before this proposition can be tested.

Persistence of Impairment Beyond Recovery

A key question to answer in order to help determine the cause of cognitive impairment in depression is whether it represents a state or a trait characteristic of depression. In other words, is the cognitive impairment a result of being depressed or is it a more stable

trait that may predispose an individual to becoming depressed or suffer from future episodes of depression? To answer this, researchers have investigated whether cognitive impairment in depression remains following remission from the affective symptoms of depression (Hammar & Ardal, 2009; Reppermund et al., 2008; Weiland-Fiedler et al., 2004). Persistent deficits have been found to remain following remission in a number of studies (e.g., Butters et al., 2000; Hammar, Lund, & Hugdahl, 2003; Hasselbalch, Knorr, & Kessing, 2011; Nebes et al., 2000; Reppermund et al., 2008; Weiland-Fiedler et al., 2004). For example, Butters et al. (2000) found memory and EF deficits in elderly depressed patients who were in remission. Similarly, Nebes et al. (2000) found persistent deficits in WM and processing speed. Persistent cognitive deficits following remission from depression suggests that cognitive impairment in depression is not an epiphenomenon of depression; instead it is a trait characteristic common to currently and previously depressed individuals (Nebes et al., 2000; Reppermund et al., 2008). It is unclear whether the persistent cognitive deficits are a result of having depression in the past or whether individuals who are vulnerable to depression might be born with a characteristic pattern of cognitive function. Longitudinal research is needed investigate these possibilities.

Other research finds that only some of the deficits observed in depression seem to persist beyond remission. For example, Purcell et al. (1997) found that while deficits in set-shifting remained, planning abilities were intact in remitted depressives. Neu et al. (2005) found that while specific deficits in verbal memory and verbal fluency remained following remission, widespread cognitive impairment seemed to dissipate when patients had recovered. Gualtieri et al. (2006) found successfully treated, remitted depressives showed cognitive flexibility and complex attention scores comparative to the control group and significantly better than the currently depressed group. However, Gualtieri et al. also found that impaired processing speed and vigilance remained following successful treatment. These

results suggest that while some cognitive deficits may represent stable, trait-like factors suggesting vulnerability to depression, other cognitive deficits may be a symptom of current depression.

In an effort to ensure that remaining cognitive deficits in recovered individuals were not a result of remaining low-level depressive symptomology, Weiland-Fiedler et al. (2004) assessed whether cognitive impairment remained after controlling for residual symptoms. While some aspects of cognitive functioning were no longer found to be impaired (e.g., memory), sustained attention remained significantly impaired. Weiland-Fiedler et al. speculated that this pattern of results suggests abnormalities in the DLPFC and fronto-parietal cortex.

In contrast, some studies have found no evidence of remaining deficits after remission from depression (e.g., Biringer et al., 2005; Lahr et al., 2007). Impairment in remission may be mediated by other factors such as the number of prior episodes (Kessing, 1998; Porter et al., 2007). Not controlling for such factors may help to explain some of the inconsistencies. Persistent cognitive impairment in depression might only occur for a sub-group of depressed individuals such as those with more severe or recurrent depression or those with underlying changes in brain activity such as left hypofrontality (Hammar & Ardal, 2009).

Causes of Inconsistencies

When reviewing evidence of cognitive impairment in depression, inconsistencies are readily apparent. There are a number of potential causes of such inconsistencies including variation in symptom severity, subtype variation, medication status of participants, age of participants, and different methods of assessing cognitive performance (Baune et al., 2009; Castaneda et al., 2008; Hammar & Ardal, 2009; Porter et al., 2007; Rose & Ebmeier, 2006; Taylor-Tavares et al., 2007).

Symptom severity and the use of different samples are likely contributors to the observed inconsistencies. A review of the relationship between symptom severity and cognitive impairment found that the results were highly variable and identified the need for further research to help identify potential moderating factors (McClintock, Husain, Greer, & Cullum, 2010). Increased depression severity has been linked with an increased likelihood of associated cognitive impairment (Burt et al., 1995; Sweeney et al., 2000). However, Ravnkilde et al. (2002) found no correlation between severity and cognitive function but the participants were all hospitalized with moderate to severe depression which may have limited the potential to observe a relationship for less severe depression. Additionally, a number of studies only recruited inpatients for their depressed participant group (e.g., Fossati et al., 1999; Harvey et al., 2004; Ravnkilde et al., 2002). Inpatient samples are likely to consist of more severely depressed participants with more severely impaired functionality than community-based depressed samples and results from such studies may not generalise to the depressed population as a whole. Two of the studies that did not find evidence of widespread cognitive impairment both used outpatient samples (Grant et al., 2001; Wang et al., 2006). This could indicate that inpatients may suffer from more severe cognitive impairment than outpatient samples but a formal analysis of this possibility is required.

Similarly, inconsistencies have been found when addressing whether age differences of participants might help to explain variation in the presence of cognitive deficits. For example, while Ravnkilde et al. (2002) found no age-related pattern of impairment, Thomas et al. (2008) found that later-life depression was associated with more severe impairments in verbal learning, verbal memory, and motor speed than depression in young adults, and this was not due to normal aging processes.

Another potential cause of inconsistencies is failure to consider the medication status of participants. A review of the effect of antidepressants on cognitive function suggests that

older style tricyclic antidepressants may be more disruptive of cognitive function than more modern alternatives such as SSRI's and MAOI's (Amado-Boccaro, Gougoulis, Poirier Littré, Galinowski, & Lôo, 1995). When comparing medicated and non-medicated participants, Ravnkilde et al. (2002) did not find any difference in cognitive impairment. Amado-Boccaro et al. (1995) concluded that most antidepressants do not influence cognitive function or may actually lead to some improvements. However, benzodiazepines and antidepressants with anti-cholinergic properties may impair cognitive function (Porter et al., 2007).

Unfortunately, it is difficult to obtain participants with depression who are medication-free or to recruit sufficient participant numbers so as to control for the potential cognitive effect of each antidepressant. Additionally, it is likely that any study recruiting only drug-free participants would not be representative and may only include those with less severe depression who do not require medication. One study of drug-free depressed individuals found impairments in EF, attention, visuospatial memory while other domains including verbal declarative memory and motor speed were unimpaired (Porter et al., 2003). Similarly, Gualtieri et al. (2006) found evidence of global cognitive impairment in non-medicated depressed participants. This demonstrates that not all cognitive impairments in depression are due to medication use.

Another factor that has rarely been controlled for is comorbid illness. Baune et al. (2009) found that the presence of comorbid psychiatric conditions led to worse cognitive performance, although, medical comorbidity did not appear to be related to cognitive performance unless psychiatric comorbidities were also present. Anxiety has been shown to affect cognitive performance (Eysenck et al., 2007) and, given the high comorbidity of anxiety and depressive disorders (Fava et al., 2000), it is likely that not controlling for such conditions will cause a substantial amount of variability in the results (Porter et al., 2007).

Methodological inconsistencies may also play a role. There is little agreement regarding the best measures for assessing different domains of cognitive function and given the low correlations observed between some measures (Jaeggi et al., 2010; Kane et al., 2007), this may have contributed to the disagreement between different studies. For example, verbal memory is commonly assessed using either the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Thompkins, 1987) or a free and cued recall task described by Fossati et al. (2004). Wang et al. (2006) used the CVLT and found that verbal memory was intact in depression while Fossati et al.'s method found significant impairment in verbal memory. This demonstrates that the use of different tasks to assess the same construct can lead to conflicting results. Additionally, the type of stimuli used is likely to influence results. For example, in a standard N-back task, the use of verbal or spatial stimuli could lead to different findings due to the lateralisation of verbal and spatial WM (D'Esposito et al., 1998; Smith et al., 1996). Burt et al. (1995) found that positively valenced stimuli were less likely to be remembered than negatively valenced stimuli. Future research should aim to be consistent with past studies and consider the modality of the stimuli used.

As discussed in Chapter 1, depression may not be a homogenous construct and instead consist of subtypes. Treating depression as a unitary construct may have led to some of the inconsistencies. Brown, Scott, Bench, and Dolan (1994) identified three subgroups of depression characterised by different patterns of cognitive function but similar levels of depression severity as indicated by equivalent depression inventory scores. Brown et al. theorised that cognitive impairment in depression might vary due to underlying heterogeneity in neurobiology. One possible neurobiological source of variation could be different patterns of underlying brain activity (Lahr et al., 2007; Shenal et al., 2003). Specifically, depression is commonly associated with left hypofrontality (e.g., Diego et al., 2001). However, Shenal et al. (2003) hypothesised the existence of four subtypes of depression each characterised by a

different pattern of frontal or parietal asymmetry. A relative reduction in brain activity is likely to be associated with reduced capability to perform tasks that utilise that region. Therefore, depression characterised by different patterns of brain activity would be associated with unique profiles of cognitive impairment. Little research has been conducted investigating the relationship between neural activity and cognitive dysfunction in depression (Rogers et al., 2004).

A final possibility is that variability in the cognitive symptoms of depression may not be systematic and may simply reflect the inherent heterogeneity of depression. Despite the inconsistent findings, it seems likely that cognitive impairment is a part of everyday life for those suffering from depression. Cognitive deficits can significantly impair individuals' ability to function in their everyday lives and failure to address the cognitive symptoms of depression may lead to a prolonged period of illness (Christopher & MacDonald, 2005). A clearer understanding of the cognitive deficits in depression will assist in designing treatments that address both the affective and cognitive components of depression. Additionally, developing a specific profile of the cognitive deficits in depression will enable cognitive function to be used as a diagnostic marker to help distinguish depression from commonly confused conditions such as dementia and chronic fatigue syndrome. A primary goal for future research should be investigating the potential moderating factors for the presence of cognitive impairment in depression. Given the variability observed in brain activity in depression (see Chapter 2), it is possible abnormal patterns of brain activity and impaired cognitive function are linked. Furthermore, variations in the presence and severity of abnormal brain activity could account for differences in the presence and severity of cognitive deficits in depression. Chapter 4 briefly reviews evidence for the link between abnormal brain activity and cognitive impairment in depression before outlining research designed to further assess this link.

Chapter 4

The Missing Link: Abnormal Brain Activity in Depression as an Explanation for Cognitive Dysfunction

The Relationship between Abnormal Brain Activity and Cognitive Impairment

Relatively few studies have investigated how abnormal brain activity in depression and cognitive impairment in depression are related. However, given the substantial research on abnormal patterns of brain activity in depression, it is hard to ignore the possible implications this might have for cognitive function in depression (Austin et al., 2001; Harvey et al., 2005; Levin et al., 2007). Increased brain activity positively correlates with performance in tasks that utilise that region (Davidson, Chapman, Chapman, & Henriques, 1990; Heller & Nitschke, 1997). Therefore, it is likely the abnormal patterns of brain activity will result in associated changes in cognitive performance.

A common method for analysing the relationship between task performance and abnormal brain activity utilises functional imaging methods such as fMRI or regional Cerebral Blood Flow (rCBF) during task performance. Abnormal activity, compared with healthy controls, has been observed in multiple tasks including WM tasks such as N-back (e.g., Fitzgerald et al., 2008; Harvey et al., 2005; Matsuo et al., 2007; Rose, Simonotto, & Ebmeier, 2006; Walsh et al., 2007), spatial tasks such as dot localisation (e.g., Henriques & Davidson, 1997), EF and planning tasks such as the Tower of London task (e.g., Elliott et al., 1997; Fitzgerald et al., 2008) and verbal memory tasks (e.g., Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004). However, participants with depression sometimes

show increased brain activity to achieve similar task performance to the control group (Harvey et al., 2005). For example, Ravnkilde et al. (2003) found that rCBF correlated well with task performance in the control groups but that this relationship was absent in the depressed group. Similarly, Fitzgerald et al. (2008) found substantially increased right PFC activity in the depressed group, compared with the controls, during performance of a verbal 2-back task and the Tower of London Test. Fitzgerald et al. noted that intact performance in the N-back task may have been a result of the recruitment of extra cognitive resources to achieve intact performance, as indicated by increased levels of activity. Finally, during a verbal N-back task, depressed participants have been found to achieve intact performance but showed substantially increased bilateral activity in the lateral PFC, anterior cingulate, and parietal cortex (Rose et al., 2006). Taken together, these results may be indicative of compensatory brain activity in depression to achieve normal performance.

In contrast, in an fMRI study Okada, Okamoto, Morinobu, Yamawaki, and Yokota (2003) found that control participants showed increased activity, compared with the resting state, in the left PFC and anterior cingulate during a verbal fluency task while depressed participants showed only a marginal increase in left PFC activity and no increased activation of the anterior cingulate. Similar findings were observed in a comparison of spatial (dot localisation) and verbal (word finding) tasks where depressed participants showed intact verbal but impaired spatial performance compared with controls (Henriques & Davidson, 1997). EEG recordings taken during the tasks showed that depressed participants failed to show increased right posterior function found in control participants during the spatial task. Possible causes for inconsistencies in the evidence for compensatory brain activity lie in the tasks being used. It seems that compensatory activity may be more likely in tasks that draw on executive functions and frontal cortical activity, such as the WM tasks utilised by Rose et al. (2006) and Fitzgerald et al. (2008).

When assessing how abnormal patterns of brain activity, cognitive function, and depression are related, the relationship can potentially be obscured by the presence of compensatory activity. Does an increase in activity during a task indicate that this region is overcompensating for a lack of activity in other regions or does it represent inefficiency in the region where the high activity is observed? The possibility of compensatory activity complicates the interpretation of any functional imaging study. Therefore, it is important to combine results from functional imaging with studies of how resting patterns of brain activity might be associated with cognitive impairment in depression. This will help to minimise the impact of compensatory activity and will also help to assess the utility of resting asymmetry metrics in the diagnosis and treatment of depression. The need to further investigate the link between brain abnormalities and cognitive function to better utilise treatments such as TMS, deep brain stimulation and neurofeedback has been emphasised by Clark, Chamberlain, and Sahakian (2009). If the findings reveal that reduced left frontal resting activity in depression is associated with cognitive impairment, then targeting treatment towards increasing activity in this region may help to reduce some of the functional impairments associated with depression and improve quality of life for sufferers.

Despite few studies directly investigating how resting brain activity and cognitive performance are related, there is some indirect evidence. For example, the RH, particularly posterior regions, seems to be important for heuristic-based information processing while the left-hemisphere seems to be involved in more detailed-oriented information processing (Heller, 1994). Given the research showing relatively reduced right posterior activity in depression, it is not surprising that depressed participants would adopt a cognitive style linked to increased left posterior activity. Depressed patients have been found to show more detail-oriented, systematic information processing styles compared with control participants who tended to utilise more intuitive, heuristic-based processing methods (Clore, Schwarz, &

Conway, 1994). While global differences in cognitive processing may be associated with posterior asymmetry, cognitive function may also be influenced by abnormalities in frontal brain activity. For example, the valence model of emotion posits that right frontal regions are involved in negatively valenced emotion compared with left frontal regions involvement in positively valenced emotion (Tucker, 1981). This could explain the bias for negatively valenced information commonly apparent in depression (Gotlib & Cane, 1987). One of the most common findings regarding cognitive function in depression is poor problem solving and reduced ability to effectively utilise strategy and planning to improve performance (e.g., Castaneda et al., 2008; Fossati et al., 1999), all tasks of executive function. Given that frontal regions seem to be important in EF (Heller & Nitschke, 1997) and abnormalities are commonly observed in frontal cortical function in imaging research, a potential link is apparent. To investigate the role that frontal asymmetry might play, research utilising lateralised EF tasks is required.

Aims of the Current Study

Further investigation of the link between abnormal resting state activity and cognitive deficits in depression is clearly required. However, given the substantial variability in previous findings regarding both cognitive deficits and brain activity in depression, the current study investigated how abnormal brain activity in depression and cognitive performance are related while taking a number of measures to minimise possible causes of variability.

Firstly, some variation has been thought to result from different methods for classifying depression. Therefore, the current study will classify depression using multiple methods: diagnosis by medical professionals and based on two separate self-report depression inventories (BDI-II, and Hamilton Depression Inventory-Short Form, HDI-SF). This will

help to account for potential different diagnosis methods and different inventories. These inventories were selected due to their common use in previous studies and clinical settings enabling comparison of present findings to previous work.

Secondly, considerable variation is thought to arise due to the confounding effect of anxiety (Heller & Nitschke, 1997; Levin et al., 2007). Therefore, all participants will be asked to complete an anxiety inventory to help account for the possible influence of anxiety. Since previous research has noted a difference in the way different types of anxiety influence cognitive performance and brain activity (e.g., Nitschke et al., 1999), the State-Trait Anxiety Inventory (STAI) was selected so the differential influence of current anxiety levels (state anxiety) and long-term anxiety (trait anxiety) could be examined.

Some of the inconsistencies in previous findings of cognitive performance have been attributed to task choice. The current study will assess a single aspect of cognitive function, WM, using multiple tasks. While a majority of previous studies of functional imaging during WM task performance in depression have utilised the N-back task, there is strong debate regarding its validity and conflicting evidence regarding the most appropriate method to measure WM (Jaeggi et al., 2010; Kane et al., 2007). Both the N-back and the Complex Span Task (CST) will be utilised. This will enable further investigation of the differences between the two tasks and also help account for possible differences between them. While WM dysfunction in depression has received less research attention than other cognitive domains, the involvement of the PFC in WM (Heller & Nitschke, 1997; Smith & Jonides, 1997) makes WM an ideal candidate to investigate how frontal asymmetry in depression may be related to cognitive performance.

Another source of variability in studies of cognitive deficits in depression is the use of tasks without consideration for the modality of the stimuli utilised. For instance, Kane et al.

(2007) compared Operation Span (a numerical and language-based CST) with a letter-based N-back task. This comparison may have been confounded by individuals' performance in the non-shared numerical component of the CST. Therefore, the current study will use both a spatial and verbal version of each task. Since verbal WM is linked to left frontal activity, while spatial WM is linked to right frontal activity (D'Esposito et al., 1998; Smith et al., 1996), the use of both types of stimuli will allow an investigation of how frontal asymmetry influences cognitive performance.

There is some indication that there may be differences in medial and lateral frontal activity in depression (Thibodeau et al., 2006) so recordings will be taken at both sites. Due to the role of the parietal lobe in depression and anxiety (Stewart et al., 2011), recordings will also be taken from medial parietal sites.

Hypotheses of the Current Study

There are four key hypotheses in the current study. Firstly, it is hypothesised that depressed participants will show reduced left frontal brain activity as has been demonstrated in a number of previous studies (e.g., Bruder et al., 1997; Davidson, 1992; Diego et al., 2001; Henriques & Davidson, 1991; Kemp et al., 2010; Miller et al., 2002; Thibodeau et al., 2006). Secondly, it is hypothesised that depressed participants, without comorbid anxiety, will show reduced right parietal activity while those with high anxiety will show increased right parietal activity. This hypothesis is based on past findings that show that anxiety and depression may be related to right parietal activity in opposite directions (Bruder et al., 1997; Stewart et al., 2011). This has been theorised to account for some of the inconsistencies observed in previous studies of parietal activity in depression, so the current study will investigate if accounting for the presence of anxiety will reveal a clearer pattern of right parietal activity in depression.

In reference to cognitive function, the third hypothesis is that depressed participants will show an overall impairment in WM function with disproportionate impairment in verbal WM tasks due to the reduced activity in the left frontal regions, known to be involved in verbal WM (D'Esposito et al., 1998; Smith et al., 1996). Spatial WM will be relatively spared since higher levels of activity are observed in right frontal regions associated with spatial WM function. This hypothesis is supported by previous findings indicating that induced approach- or withdrawal-motivated mood states were linked to WM performance (Gray, 2001). While verbal WM was enhanced by approach-motivated affective states (associated with left frontal activity) and impaired by withdrawal-motivated mood (associated with right frontal activity), the opposite pattern was found for spatial WM tasks. Since depressed individuals are typically characterised by increased withdrawal-motivated affect, the findings of Gray (2001) are expected to be replicated in the current study. An overall impairment is expected for multiple reasons including the possibility that the frontal asymmetry in depression seems to be superimposed on a bilateral decrease in frontal activity (Heller & Nitschke, 1997), reduced parietal activity and associated decreases in arousal (Stewart et al., 2011), and reduced motivation experienced during depression (Beck & Alford, 2009).

Finally, as discussed in the introductory chapters, depression is highly heterogeneous and it has been theorised that depression may not be a unitary construct and may instead consist of subtypes. Therefore, the possibility of different patterns of cognitive impairment in different subtypes of depression needs to be addressed (Rogers et al., 2004). Although little research has been conducted to investigate this possibility, Austin et al. (1999) found differences in the pattern of cognitive deficits in melancholic and non-melancholic depression supporting further investigation of the possible role of subtypes of depression. One subtype system, as described by Shenal et al. (2003), involves four subtypes each characterised by

dysfunction in one of the quadrants of the brain. It is thought that each of these subtypes may be associated with different patterns of cognitive impairment specific to the region of abnormal functioning. The current study will attempt to account for this by categorising participants into left and right frontal dominant groups to see if there is any evidence for this theory. It is hypothesised that depressed participants with reduced left frontal activity will demonstrate impaired verbal WM while those with relatively reduced right frontal activity will show impaired spatial WM. If this hypothesis is supported, it will further indicate the usefulness of subtypes of depression and may help to account for some of the inconsistencies regarding the presence of cognitive impairment in past research.

Chapter 5

Method

Participants

A total of 78 participants were recruited from the general student population at Massey University of Palmerston North. Participants were recruited using advertising around the Turitea campus. Interested participants were asked to make contact via email for further details about the research and to book a time to participate.

There were five key criteria for participation. Firstly, all participants needed to be females as heritability of frontal brain asymmetry is stronger in females and thought to be more closely linked with vulnerability for depression (Kendler et al., 2006). Secondly, only right-handed participants were recruited as left-handed and ambidextrous individuals show less task-dependent hemispheric asymmetry (Galín, Ornstein, Heron, & Johnstone, 1982). As a result, in left-handed individuals, task performance is less likely to be influenced by hemispheric asymmetry. Thirdly, all participants were aged between 18-40 years. This was done because older adults have reduced lateralisation of spatial and verbal WM which has been theorised to reflect a compensatory mechanism for age-related cognitive impairment (Reuter-Lorenz et al., 2000). Therefore, including older participants in the sample might have reduced the observable relationship between hemispheric asymmetry in depression and WM impairment. Finally, all participants had to be fluent in English, due to the language component of the cognitive tasks, and free of significant traumatic brain injury that may have altered patterns of brain activity.

The participants were assigned to three separate groups: Currently depressed, previously depressed, and never depressed. If participants scored 14 or more on the BDI-II and/or 10 or more on the HDI-SF they were classified as currently depressed ($N=36$, $M_{age}=23.28$, $SD=4.53$). These thresholds were used as they are provided in the inventory manuals as the threshold for mild depression (Beck, Steer, & Brown, 1996; Reynolds & Kobak, 1995). This helped to maintain consistency with thresholds used in past research. Two inventories were chosen to ensure a maximum chance of picking up all depressed participants in the sample. Of the participants, 23 were classified as depressed based on both inventories, 12 based on the BDI-II only, and one participant based on the HDI-SF only. Although most participants who were only classified as depressed based on one inventory were mildly depressed, four were classified as moderately depressed (using the standardised cut-off points). The variation is assumed to have arisen from the slightly different content of the items and the different response scales used.

If participants had indicated in their history that they had received a diagnosis of depression but were below the inventory cut-off points they were classified as previously depressed ($N=11$, $M_{age}=24.64$, $SD=3.70$). This was done to account for the persistent nature of cognitive deficits in depression (Hammar & Ardal, 2009; Rogers et al., 2004; Sweeney et al., 2000). Participants were instructed that a diagnosis of depression could include a diagnosis from their GP, psychologist, or psychiatrist. Those who scored below the cut-off points and had never received a diagnosis of depression were classified as never depressed ($N=31$, $M_{age}=22.81$, $SD_{age}=4.30$). There were no significant age differences between the groups ($F(2,75)=0.72$, $p=.49$). See Table B-8 for descriptive statistics of the depression and anxiety scores for each group.

Materials and Procedure

Participation was carried out individually due to the EEG component of the research and to maintain privacy. Participants were informed about the nature of the research via email before agreeing to participate. All participants were given a further verbal briefing, time to read through the information sheet, and ask any questions they had before signing the consent form. At this time it was emphasised that participants were free to withdraw from the study at any point.

Participation was divided into two phases: The data collection phase and the EEG phase. A separate information and consent form was provided for each study phase so participants could be given a detailed description of the EEG procedure before agreeing to participate. Participants were given the opportunity to take a break between phases.

During the data collection phase participants were asked to complete a short survey regarding their history of depression, three mood questionnaires and four WM tests. All tasks were completed in a counter-balanced order using a balanced Latin-Squares method. There were a total of eight tasks and each task was randomly assigned a number between one and eight. For the first participant, the following formula was applied: 1, 2, n, 3, n-1, 4, n-2, 5, where n is the number of tasks. For each subsequent participant, one was added to each task, returning to one after n. For example, participant two followed the order 2,3,1,4,8,5,7,6. The participant numbers were assigned when participants signed up to complete the experiment. This method ensured that every test followed every other test at least once to help minimise the impact of any carryover effects. Participants were given as long as they required to complete the tasks although most participants took approximately one hour. All participants were provided with movie vouchers as compensation.

The depression history survey was an 8-item paper form assessing whether participants had been diagnosed with depression by a medical professional, whether they were currently taking medication, and whether they had any comorbid anxiety diagnoses. This took approximately two minutes for participants to complete. See Appendix A for a full copy.

Mood questionnaires. Symptoms of depression were assessed using two standardised depression inventories: BDI-II and HDI-SF. These two depression inventories were chosen to enable comparison with past research and to ensure that all students showing symptoms of depression were identified. It should be noted that these inventories only identify symptoms of depression but do not necessarily reflect the presence of clinical depression. Symptoms of anxiety were assessed using Spielberger's State-Trait Anxiety Inventory for Adults (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Anxiety was recorded as it has been shown to be related to both cognitive performance and parietal brain asymmetry (Eysenck et al., 2007; Kentgen et al., 2000). For each of the mood questionnaires, participants were given a short verbal briefing. For example, for the BDI-II the participants were told "*This task is designed to assess your mood state over the previous two weeks. Please circle the option that applies most to you. You can choose to skip any questions that you do not feel comfortable answering*". These are all paper-based tasks that each took approximately five minutes to complete.

BDI-II. The BDI-II is a 21-item self-report survey with a minimum score of 0 and a maximum score of 63 (Beck et al., 1996). The questions asked participants about their mood and functioning over the previous two weeks. All questions have a scale of 0-3 with increased scores indicating increased symptom severity. For example, one question about sadness asked participants to circle the option that best described them. 0 was associated with the statement "I do not feel sad" while 3 was associated with the statement "I am so sad

or unhappy that I can't stand it". Scores of 14 and above indicate the presence of mild depression, 20-28 moderate depression and higher scores indicating severe depression (Beck et al., 1996). This measure has been demonstrated to show high internal consistency ($\alpha=0.91$ to 0.93) (Beck et al., 1996; Dozois, Dobson, & Ahnberg, 1998) and good convergent validity with the original BDI (Dozois et al., 1998).

HDI-SF. The HDI-SF is a 9-item self-report survey with a minimum score of 0 and a maximum score of 33 (Reynolds & Kobak, 1995). All items relate to how the participants had felt during the previous two weeks. Questions were answered using a variable scale and included questions such as "Do you feel helpless or incapable of getting everyday tasks done?" Higher scores represented increased severity of symptoms. For example, using the aforementioned question, an answer of zero was associated with the answer "Not at all" while a score of three was associated with the answer "Almost constantly". Final scores of 10 or more indicate mild depression, 13-16.5 moderate depression, 17-20.5 moderate-severe depression and higher scores indicating severe depression. The HDI-SF has demonstrated high internal consistency ($\alpha=.93$) and high re-test reliability ($r=.95$) (Reynolds & Kobak, 1995).

STAI. Spielberger's STAI consists of two 20-item subscales; one for state and one for trait anxiety. State anxiety refers to the current level of anxious mood the participant is experiencing while trait anxiety refers to a more long term measure of how anxious that individual is in general. All items had a 4-point Likert scale ranging from 1 (*Not at all*) to 4 (*Very much so*). An example statement is "I feel nervous and restless". Possible scores for each subscale range from 20-80 with higher scores indicative of increased anxiety. The trait subscale has been found to have good test-retest reliability ($r=.97$) (Metzger, 1976). The state subscale shows lower test-retest reliability ($r=.45$) but this is acceptable given that state anxiety reflects a variable mood state and is therefore likely to differ across different testing

occasions. A review found that, in most contexts, the STAI demonstrates good internal consistency ($\alpha_{\text{state}}=.91$, $\alpha_{\text{trait}}=.89$) (Barnes, Harp, & Jung, 2002).

WM measures. In order to assess WM performance in each of the domains of interest (verbal and spatial), two different tasks were used for each domain: N-back and complex span. This was done because there is considerable debate regarding the most appropriate measure of WM (Kane et al., 2007; Redick & Lindsey, 2013). Using both task types helped to improve comparability with past research and meant that the results would still be relevant if/when the task debate is resolved. In the N-back task the participants were asked to identify if the current stimulus matched the one displayed a set number of stimuli ago (designated N). This is thought to measure WM as participants have to consciously store a number of stimuli (storage component) and continually update what is stored in their memory set each time a new stimulus is displayed (processing component). CST's ask participants to complete two separate (sometime unrelated) tasks. One part of the task involved short term storage of a set of stimuli and the second component involved a processing task such as completing a maths equation. Although both N-back and CST's possess face and content validity, there is low convergent validity suggesting that the tasks may be measuring different aspects of cognitive function (Kane et al., 2007; Redick & Lindsey, 2013). Using both tasks ensured that all aspects of WM were adequately represented in the data. All four tasks were tested using a pilot study ($N = 20$) and were found to discriminate between individuals well.

N-back tasks. As seen in Figure 1, during the N-back tasks, participants were asked to decide if the current stimulus on the screen matched the one displayed two (2-back condition) or three (3-back condition) screens ago. For 500 ms, at the beginning of each block of trials, a central fixation cross was displayed. Each stimulus was then displayed for up to 3000 ms. Failure to respond within 3000 ms resulted in a response being recorded as

incorrect and the subsequent stimulus being displayed. Participants used their mouse to answer ‘yes’ or ‘no’ in response to the question: “Is this (stimulus) the same as the one displayed N-back ago?” Although many traditional cognitive psychology tasks ask participants to indicate their responses using the keyboard, mouse response was chosen for this study as it more closely replicates how people are used to interacting with computers so possesses more ecological validity (see Mcpherson & Burns, 2005). This also removes an unrelated memory component from the task as participants no longer need to remember which button corresponds with which response.

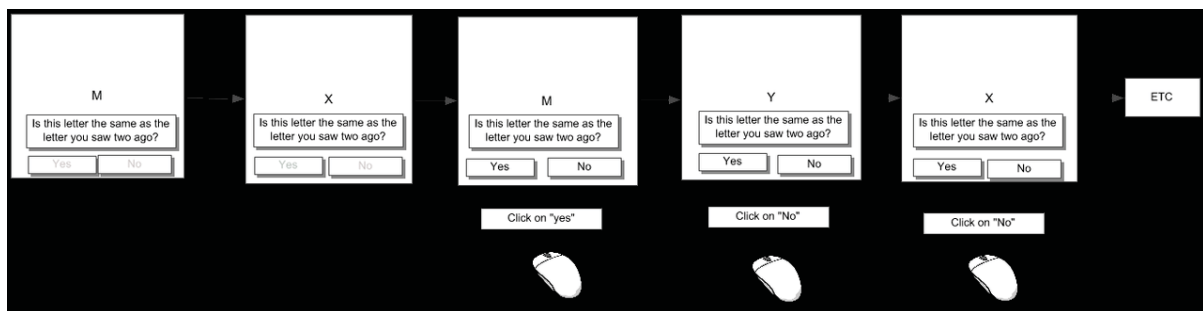


Figure 1. In the verbal N-back task, the participant is shown a continuous string of letters. For every letter displayed the participant must click to indicate whether the letter displayed matches the one displayed a set number of items ago. This figure displays a 2-back version of the task.

The maximum time given to respond in this task was determined with the marginally longer time taken to respond by mouse compared with keys in mind. No answers were accepted after 3000 ms as longer response times are likely to involve considerable rehearsal and the use of alternative strategies which would introduce extra variance. After the response was given, or the time limit had lapsed, the inter-stimulus interval was 500 ms during which the fixation cross was displayed. Both N-back tasks consisted of four blocks, two for each of the 2-back and 3-back conditions. Each block contained 40 continuous stimulus presentations consisting of eight unique stimuli displayed in a counterbalanced order. The

verbal stimuli were eight phonologically distinct letters: M, H, K, Q, X, R, F, and B. These letters were displayed in the centre of the screen in place of the fixation cross and were 3 cm tall by 2.8 cm wide. The spatial stimuli were squares located around a circle, equidistant from the fixation cross (at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°, with 0° representing the top of the circle, directly above the fixation cross). Before beginning both of the N-back tasks, the participants were given a brief verbal description of the task, a set of detailed written instructions, including diagrams, and two brief, 18-stimuli practice trials (one for the 2-back and one for the 3-back condition). During the practice trials the participants were given immediate auditory feedback to let them know if they had answered correctly (a brief tone) or incorrectly (a distinctly different tone). This helped to ensure that they had understood the instructions. Answers were coded as hits, misses, false alarms, and correct rejections. A percentage accuracy score was calculated using the number of hits and correct rejections as well as d' (sensitivity) and c (bias). Each N-back task took participants 5-10 minutes.

Verbal span task. For the complex verbal span task the Automated Reading Span Task was employed (Unsworth, Heitz, Schrock, & Engle, 2005). Participants were asked to verify whether a sentence made sense or not (50% did) and were then shown a letter to remember. Sentences that did not make sense included a single word inappropriate to the context. After between two and five sentence-letter pairs, participants were asked to recall all of the letters they had seen, in the correct order. Each trial length was repeated three times during the experiment resulting in 12 blocks of trials. Prior to starting the task, participants were provided with a detailed set of written instructions and practice trials for each task component, both separately and together. The Automated Reading Span Task has been found to show high convergent validity with non-automated CST's and shows good test re-test reliability ($r_{absolute}=.76$, $r_{total}=.82$). (See CST scoring subsection for a comparison of absolute

and total scoring methods.) High internal consistency has also been observed ($\alpha_{\text{absolute}}=.78$ to $.83$, $\alpha_{\text{total}}=.86$ to $.88$) (Redick et al., 2012). This task took participants approximately 10 minutes.

Spatial span task. The complex spatial span task was adapted from Shah and Miyake (1996). For this task, participants were asked to decide if a series of rotated letters were reflected (like they would be in a mirror) or normally presented. Participants indicated their decision by clicking on either “reflected” or “normal” buttons at the bottom of the screen . After between one and six reflection decisions (trial size), participants were asked to recall the correct orientation for each letter seen, in the correct order. To indicate orientation, participants clicked on an arrow to indicate the direction that the top of the letter was pointing. (see Figure 2). The stimuli were three phonologically distinct letters: F, P, and R. Letters were rotated to one of seven orientations: 45° , 90° , 135° , 180° , 225° , 270° , and 315° with 0° representing an upright letter. Given that letters could either be reflected or normal,

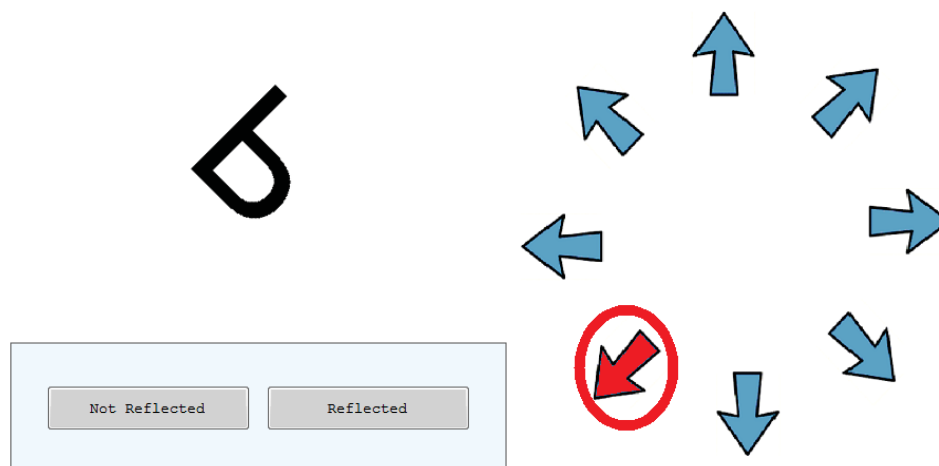


Figure 2. During the Spatial Span task, participants were asked to indicate if a series of rotated letters were ‘normal’ or ‘reflected’ by clicking on their selection. After a series of these decisions, participants then needed to indicate the orientation of each of the letters shown, in the order they were seen, by clicking on an arrow to indicate the direction that the top of each letter was pointing.

this resulted in 42 unique stimuli and each stimulus was presented once. Each trial size was repeated twice resulting in 12 trials. This task took approximately five minutes to complete.

CST scoring. For the CST's the storage component of the tasks assesses WM capacity and the processing component of the result is not assessed. Participants were given prompts during the instructions to ensure that they focussed on both tasks and WM was engaged. Two scoring methods are used for CST's: total and absolute. The total scoring method gives participants a point for each correctly remembered stimulus, regardless of whether the rest of the block was recalled correctly while the absolute scoring method is more stringent and participants are only given a point for each stimulus if all items within the block were recalled in the correct order. For example, in a block of five stimuli, if a participant made a single mistake then none of the stimuli within that block would count towards the absolute score. This can help to reduce the influence of guessing. However, total span scores may be more reliable and provide a better indicator of individual differences (Conway et al., 2005; Friedman & Miyake, 2005; Redick et al., 2012).

EEG phase. Due to equipment failure, two different EEG recording systems were used. The first system, Neuroscan, used the SynAmpModel 5083 EEG amplifier and data acquisition system, used a 500 Hz sampling rate. The second system, ADI, included the 8 speed PowerLab unit, model ML785, and an Octal BioAmp model ML138, using a 400 Hz sampling rate. For a comparison of data recorded using both systems, see Appendix D. For both systems a 50 Hz notch filter was applied to remove noise from electrical equipment and both high-pass (1 Hz) and low-pass (100 Hz) filters were applied.

EEG recording. Participants were guided to a comfortable chair in the EEG recording room and given a detailed description of the EEG procedure before signing the consent form for this phase. Participants were shown the equipment in the recording room during the

briefing to reduce situational anxiety that could influence EEG activity. Participants were given a chance to ask any questions they had before set-up commenced.

Set-up was aided by a research assistant to ensure that the process did not take too long for the participants. The first step was preparing the sites for the reference and facial free electrodes. These sites were cleaned with rubbing alcohol to remove any substance (e.g., make-up) that could impair electrode attachment and readings. The facial electrode sites were the left supra and infra-orbital sites to measure electrical activity produced by vertical eye movements and the right and left outer canthi to measure horizontal eye movements. Measurements of electrical activity at these sites enables artefacts created by eye movements to be removed before waveform analysis. The right and left mastoid electrodes were used to create a linked mastoids averaged reference site.

The optimal reference site is still being debated in EEG literature (Allen et al., 2004; Thibodeau et al., 2006). The most commonly employed reference montages include the linked ear mastoid reference, CZ, and an averaged referenced scheme. The CZ is typically considered a poor reference for asymmetry research as it is an electrically active site making it difficult to assess activity at the target site and also appears to produce data that are inconsistent with other reference schemes (Davidson, 1998; Thibodeau et al., 2006). The averaged reference scheme is less widely used but is useful if a large array of electrodes is being used and, as such, is not suitable for use in asymmetry research where only six scalp electrodes are being used. The linked mastoid reference is often favoured in asymmetry research as it is thought to act as a neutral base-line with minimal electrical activity passing from the brain. Despite some criticisms of this explanation (e.g., Pivik et al., 1993) it appears that linked mastoid references are the most reliable reference scheme to use in frontal asymmetry research (Hagemann, 2004). Additionally, this reference scheme has been popular in past research so its use in the current study will facilitate comparisons.

The alcohol wipe was followed by the use of Nu-Prep, a gel that was rubbed vigorously onto the sites using cotton pads. This was done to lightly abrade the surface of the skin to remove dead skin cells ensuring a low impedance connection.

The EEG cap was then put on by the experimenter and the assistant in order to evenly stretch the cap over the participant's head. Correct fit was determined by making sure that the CZ electrode was at the midpoint between the ears and midway between the front and back of the head. Foam padding was applied to the unused electrodes at the front of the cap to minimise discomfort.

The facial and reference electrodes were then filled with ten20 conductive paste for signal conduction. To ensure a strong attachment, the electrodes were secured with strips of paper medical tape.

The cap was then plugged into the amplifier and ECI brand Electro-gel was inserted into the ground electrode on the cap. The gel was inserted using blunt tip syringes that had been filled prior to the participant's arrival and warmed in a water bath. The impedance of the facial electrodes was then checked. The first EEG system, Neuroscan, contained an inbuilt impedance checker. With the ADI system, Checktrode model 1089mkIII, was used to determine impedance. Impedance of less than 10K ohms was required for each facial electrode location before set-up could proceed. Additionally, homologous sites (e.g., left and right outer canthi) needed to be within 1K ohm of each other. If impedances did not meet these criteria the electrodes were reapplied.

Once complete, the electrodes of interest on the cap were prepared. These were: F3, F4, F7, F8, CZ, P3, and P4 (using the 10-20 electrode placement system). To reduce the impedance of all electrodes to the required 5K ohms or less, the tip of the needle was used to move hair and lightly abrade the surface of the scalp and the gel was inserted. Homologous

sites (e.g., F3 and F4) were checked to ensure they were within 1K ohm of each other. The EEG activity recording was also visually checked to ensure no anomalies were present.

When this process was completed the participants were given instructions on the computer monitor in front of them. The instructions asked participants to rest in one-minute blocks during which their EEG activity was to be recorded. Although it was once believed that a minimum of eight minutes recording time was required, recent research suggests that recordings can be reliable in as few as three minutes (Davidson, 1998; Hagemann, 2004; Thibodeau et al., 2006; Towers & Allen, 2009). Four, one-minute recording blocks were used.

During two of the blocks, participants were instructed to close their eyes, and to leave their eyes open in the remaining two blocks. The start and finish of each block was signalled to participants using a beep and the order of these conditions was counterbalanced. Participants were asked to remain as still as possible during the recording periods and were given time to move around between blocks. Participants were able to control the length of the interval between blocks to enable them time to move or get comfortable before the next block. This was done to help minimise the influence of electrical activity from muscular sources on the recorded data. During each block a fixation cross was shown on the screen to help minimise eye movements.

Once recording was completed, the electrode cap was removed and participants were given the option of a shower to remove the electrode gel, or a towel was provided to remove excess gel. The EEG phase of the research took approximately one hour per participant.

Debriefing. During data collection, the inventories were scored to screen for symptoms of depression and anxiety. If evidence of moderate to severe depression was identified, participants were informed and were given contact details for a series of free and

confidential counselling services. All participants who were found to experience moderate to high levels of anxiety and depression were already aware of this and were already being treated by their doctor or were seeing a counsellor. The participants were shown a section of their EEG recording and were given a chance to ask questions about what the recording showed. A brief description of the background and aims for the experiment was also given. A screenshot of their brain activity and a photo wearing the EEG cap was provided for participants who desired it, and all participants were given movie vouchers for DownTown Cinemas in Palmerston North to thank them for participating. The consent form contained a box for participants to tick if they wished to receive a summary of the findings once the research was completed.

EEG data analysis. The data were analysed in MATLAB using a custom script that utilised .NET version 2 Epoch Viewer. For each one-minute block, the data were segmented into 59 two-second epochs with a 50% overlap to ensure equal representation of data after windowing during the Discrete Fourier Transform (DFT). A baseline correction was applied.

The epochs were then screened for artefacts. Any epochs containing voltages exceeding $75 \mu\text{v}$ were removed as this voltage is outside of the range that can be produced by the brain and must therefore represent an artefact. Although there is some variation between studies, this is the most commonly used threshold in previous research. Each remaining epoch was also visually screened for remaining artefacts and removed if required. For example, epochs showing sudden spikes indicative of eye blinks that were slightly below the rejection threshold were the most commonly removed artefact. Epochs showing evidence of amplifier saturation were also rejected. There were no group differences in the percentage of epochs retained for analysis and no relationship between the number of epochs retained and the calculated asymmetry scores (refer to Appendix E). To extract alpha power (activity in the 8-13 Hz range) a DFT with a Hanning window was applied. Since alpha power is

inversely related to cortical activity, low activity is represented by high alpha power. The alpha power figures for each electrode were then log-transformed as raw values are usually positively skewed (Allen et al., 2004).

To calculate an alpha asymmetry score, a difference score metric was utilised.

Index of Alpha Asymmetry= \ln (right electrode site) – \ln (left electrode site)

This metric minimises differences between individuals' scores that are due to confounding variables such as skull thickness (Allen et al., 2004). The asymmetry statistic provides a relative measure of activity in the left and right hemispheres and cannot tell you which hemisphere is functioning abnormally, only that one hemisphere has relatively greater or lesser activation than the other (Tomarken et al., 1992). The metric was calculated for the F3-F4, F7-F8, and P3-P4 homologous electrode pairs. Negative scores indicate relatively greater right than left EEG activity while positive scores indicate greater left hemisphere activity (Diego et al., 2001). Resting frontal alpha asymmetry is a reliable measure with high internal consistency (Tomarken et al., 1992), and high test-retest reliability (Allen et al., 2004; Tomarken et al., 1992).

Storage of data. All electronic data (computer test scores and EEG data) were stored on a password-protected hard-drive within the School of Psychology at Massey University in Palmerston North. All paper-based data were stored in a locked filing cabinet in the researcher's office. The data will be kept for 10 years before being destroyed.

Ethics. Ethical approval for this research was obtained by the Health and Disability Ethics Committee (HDEC, Reference: CEN/11/EXP/002).

Chapter 6

Results and Discussion

The results will be presented in four main sections, each covering one of the four hypotheses of the current research. Supplementary statistics and results will be included in appendices and referred to here. Note that for all statistical tests, assumptions have been checked and, unless otherwise stated, have been satisfied.

Hypothesis 1: Participants with depression will show relatively reduced left frontal activity compared with control participants

The first hypothesis for this study was that participants with depression would show relatively reduced left frontal activity compared with controls. This hypothesis was based on past research that used EEG to determine relative hemispheric activity and found that, compared with controls, participants with depression show a relative reduction in left frontal activity (e.g., Bruder et al., 1997; Davidson, 1992; Diego et al., 2001; Henriques & Davidson, 1991; Kemp et al., 2010; Miller et al., 2002; Thibodeau et al., 2006). This pattern of asymmetry has been explained in reference to the circumplex model of emotion where increased right frontal activity is associated with increased experience of negatively valenced and withdrawal-motivated emotions (Coan & Allen, 2003).

The first approach to assessing whether the data support Hypothesis 1 is a one-way analysis of variance (ANOVA) comparing currently depressed, previously depressed, and never depressed participants' frontal asymmetry scores for both medial (F3/F4) and lateral (F7/F8) sites (see Figures 3 & 4 for results). Never depressed and previously depressed participants were separated due to past research indicating that reduced left frontal activity

may persist beyond recovery from depression (Gotlib et al., 1998; Henriques & Davidson, 1990). Although this method of grouping participants has reduced power, if reduced left frontal asymmetry did persist beyond recovery from depression, grouping never depressed and previously depressed participants together could mask any observable effects. While lateral frontal asymmetry scores revealed little evidence of group differences ($F(2,74)=0.61$, $p=.54$, $f=0.13$), group comparisons of medial frontal asymmetry ($F(2,74)= 3.09$, $p=.05$, $f=0.29$) yielded a moderate effect size (see Table B-1 for descriptive statistics).

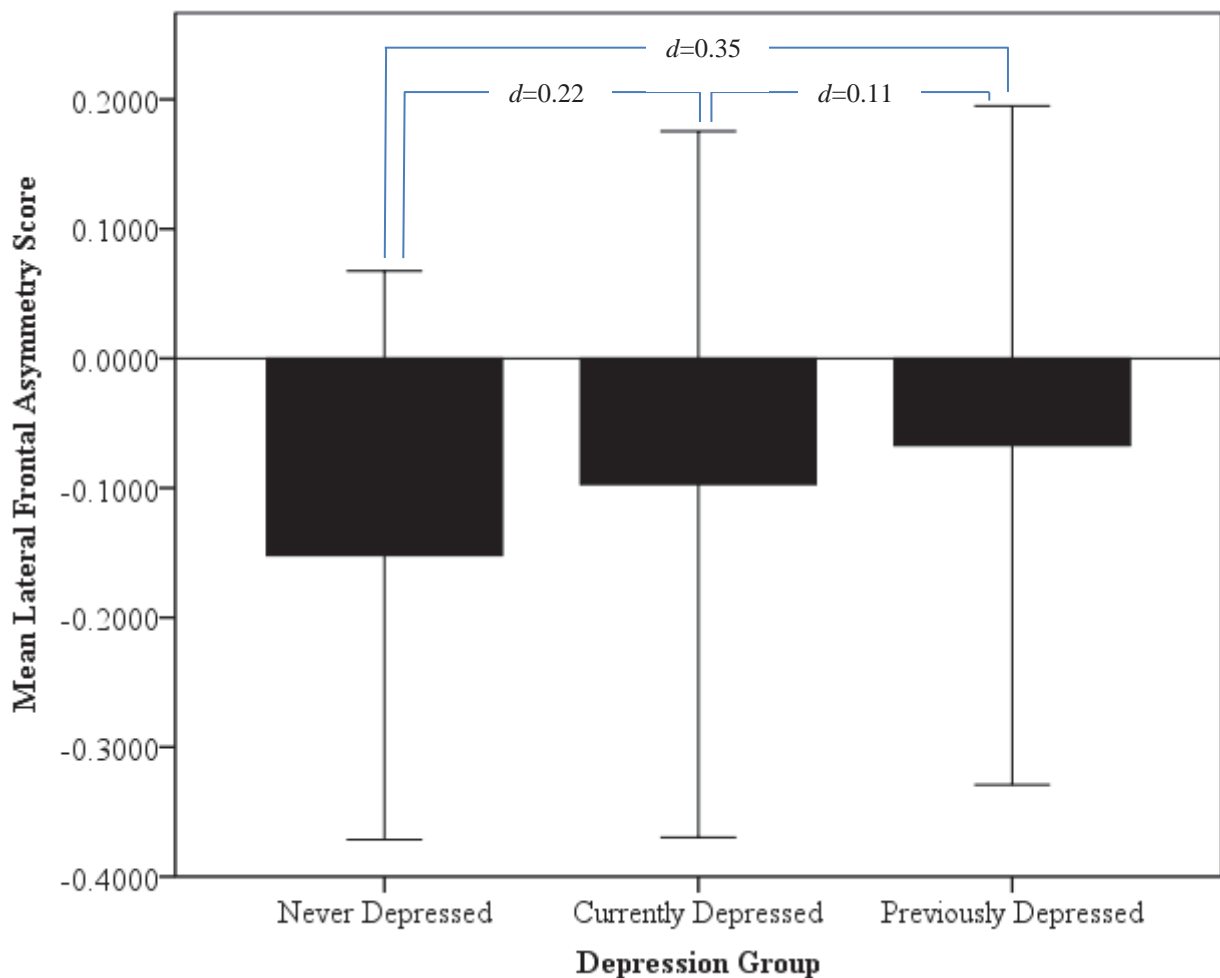


Figure 3. Differences in Mean Lateral Frontal Asymmetry Scores for Never, Currently, and Previously Depressed Groups with Cohen's d Effect Sizes from Tukey Test Comparisons Indicated. Error Bars Indicate ± 1 SD.

Analysis of Tukey test results indicated that previously depressed participants' medial asymmetry scores differed significantly from never depressed participants ($p=.04$, $d=.71$). Never depressed participants ($N=30$) showed a relative balance between left and right medial activity ($M=0.005$, $SD=0.22$) while previously depressed participants ($N=11$) showed more positive asymmetry scores indicating left dominance ($M=0.24$, $SD=0.42$).

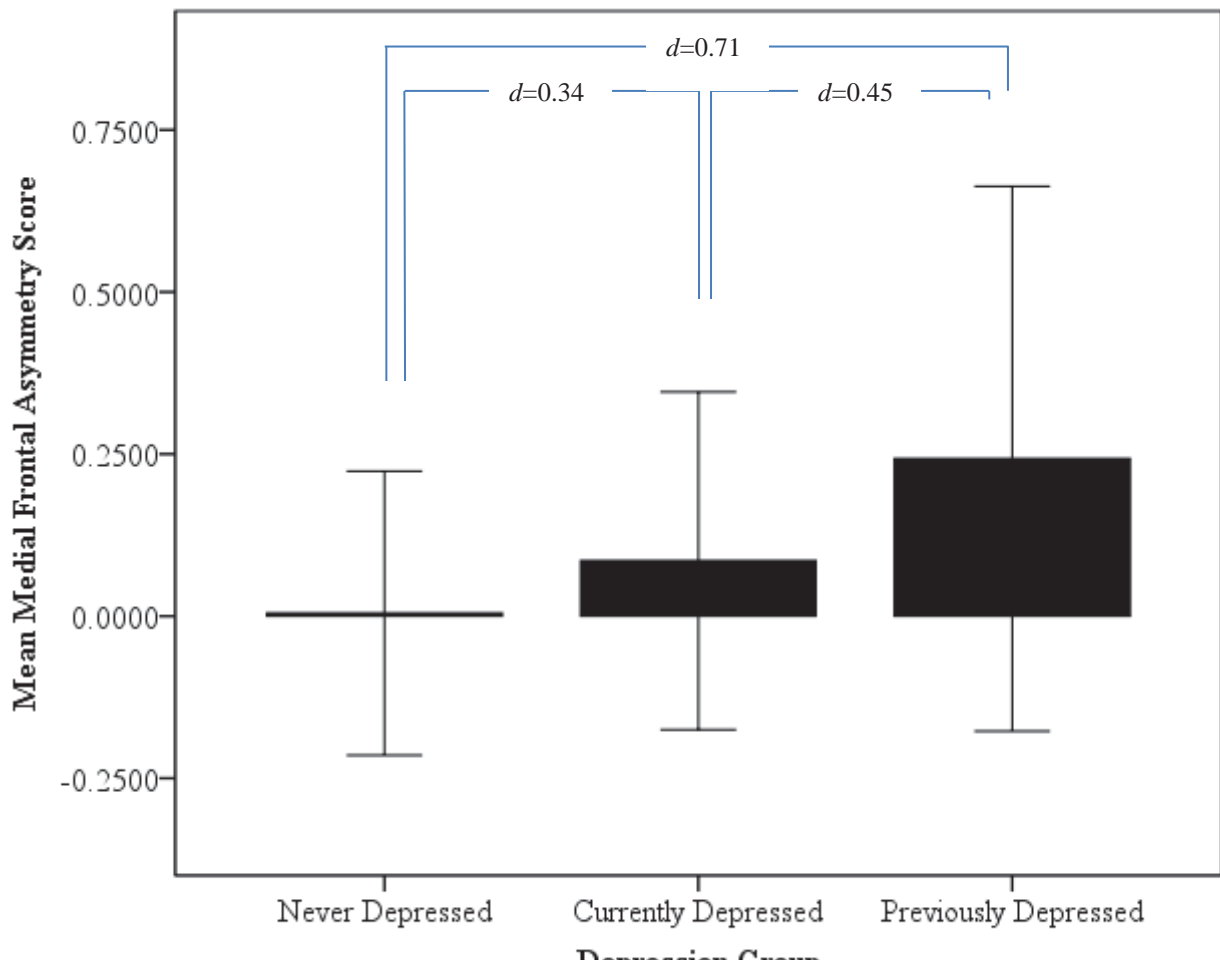


Figure 4. Differences in Mean Medial Frontal Asymmetry Scores for Never, Currently, and Previously Depressed Groups with Cohen's d Effect Sizes from Tukey Test Comparisons Indicated. Error Bars Indicate ± 1 SD.

However, large SD's were observed in both groups suggesting substantial variability. In a small sample, the presence of this much variation is a concern because the means can be distorted by outlying values or chance effects making it difficult to interpret the results.

Furthermore, increased left frontal activity in previously depressed participants is contrary to past results, thereby reducing confidence in the findings. Increased left frontal activity in previously depressed participants could indicate that successful treatment has resulted in a relative dominance of positively valenced emotions and approach motivation. There is no indication that currently depressed or previously depressed participants experience reduced left frontal activity as was hypothesised (see Figure C-1 and C2 for distributions of frontal asymmetry scores).

Analysis of the two EEG systems used revealed a significant difference in recorded asymmetry scores at both lateral frontal ($t(75) = -2.43, p = .02, d = 0.58$) and medial frontal ($t(75) = -2.95, p = .004, d = 0.70$) recording sites with moderately strong effect sizes. For both the lateral ($N = 28, M = -0.20, SD = 0.24$) and medial ($N = 28, M = -0.04, SD = 0.23$) sites, the average Neuroscan asymmetry score was more negative (right dominant) than the average ADI asymmetry scores for both lateral ($N = 49, M = -0.06, SD = 0.24$) and medial ($N = 49, M = 0.14, SD = 0.29$) sites. The differences between the EEG systems are explored further in Appendix D.

To investigate whether discrepancies between the EEG systems may have masked depression group differences in frontal asymmetry scores, the analysis was re-run with EEG system as a factor. The results from a 2 (System) x 3 (Recording site) ANOVA found that the main effect of EEG system was significant, $F(1,71) = 6.26, p = .02, f = 0.30$, showing that the mean lateral frontal asymmetry score on the Neuroscan system was significantly more negative (more right dominant) than the mean lateral frontal asymmetry scores recorded on the ADI system with a moderate effect size. However, the main effect for depression group (never depressed, previously depressed, and currently depressed) was not significant ($F(2,71) = 0.13, p = .88, f = 0.06$). There was no significant interaction between EEG system and depression group ($F(2,71) = 0.73, p = .49, f = 0.14$).

Similar results were observed for medial frontal asymmetry scores as the main effect of EEG system was significant ($F(1,71)=4.67, p=.03, f=0.26$) showing that mean medial frontal asymmetry score on the Neuroscan system was significantly more negative (more right dominant) than the mean medial frontal asymmetry scores recording on the ADI system with a moderate effect size. The main effect for depression group (never depressed, previously depressed, and currently depressed) showed a moderate effect size, $F(2,71)=2.88, p=.06, f=0.28$. Tukey tests revealed the main difference was between the previously depressed and never depressed group ($p=.03, d=0.84$) with the previously depressed group showing more positive asymmetry values ($M=0.24, SD=0.42$) indicating increased left frontal activity compared with the never depressed group who showed more balanced activity ($M=0.005, SD=0.22$). There was no significant interaction between EEG system and depression group ($F(2,71)=0.28, p=.76, f=0.10$). Even when considering System as a factor, these results do not provide any support for the hypothesis that depressed participants show reduced left frontal activity. However, Levene's Test for Equality of Variance was violated for both medial ($F(5,71)=3.76, p=.004$) and lateral ($F(5,71)=2.65, p=.03$) sites so these results should be interpreted with caution (variances are included in Table B-2). It is likely that this violation was a result of the small sample size of the previously depressed group ($N_{ADI}=7, N_{Neuroscan}=4$) as supported by the much higher variance of the previously depressed group (See Table B-2).

Adding System as a factor may not be an optimal method to control for the EEG system differences. As described in Appendix D, participants recorded on the ADI system had significantly higher, BDI-II, HDI-SF, and Trait Anxiety scale scores. This indicates that there was a systematic difference between the participants recorded on the ADI and Neuroscan systems. Although recruitment was conducted in a non-systematic order, it appears that the participants whose data were collected on the second recording system (ADI)

were more symptomatic than those recorded on the Neuroscan system. Despite the results including EEG System as a factor supporting those when assessing group differences only, this is confounded with the differences in symptom severity which makes interpretation of the results problematic. Adding EEG system as a factor to investigate these differences also reduces statistical power. For example, when adding System as a factor, only four participants are in the previously depressed Neuroscan condition, and only eight in the currently depressed Neuroscan condition. This will have made it more difficult to observe any statistically significant differences and also raises the likelihood that chance effects will have influenced the means for the smaller sample conditions.

Although this first approach, using ANOVA to compare the frontal asymmetry scores for currently, previously, and never depressed groups, found no evidence to support the hypothesis, it is possible this is partially due to the sample used. The sample consisted of students, and recruitment was conducted on campus. Therefore, it is likely that the sample consisted of relatively high functioning students with depression and a number of the participants who were identified as having mild depression may have been showing symptoms due to situational factors such as high workload or being away from home for the first time rather than having clinical depression. To make a comparison between more severely depressed participants, those less likely to be symptomatic due to situational factors, and control participants, two new groups were created. These groups were the high BDI group who scored in the top 25% on the BDI-II and the low BDI group who scored in the bottom 25% on the BDI-II. The high BDI group is more likely to contain only true cases of clinical depression compared to the depressed group created using depression inventory cut-off points. A moderate effect size was found for lateral asymmetry group with the low depression group ($N=22$, $M=-0.16$, $SD=0.24$) showing a more negative asymmetry score (right dominant) than the high depression group ($N=20$, $M=-0.08$, $SD=0.25$) ($t(40)=-1.06$,

$p=.30, d=0.33$). Medial recordings for the high depression group showed relatively greater left frontal activity ($M=0.07, SD=0.18$) compared to the low depression group ($M=0.03, SD=0.28$) ($t(40)=-0.59, p=.56, d=0.18$). This difference showed a weak effect size. This pattern of results is in the opposite direction to that expected and to past research findings which found relatively reduced left frontal activity (right dominance) in depressed participants (e.g., Bruder et al., 1997; Henriques & Davidson, 1991; Thibodeau et al., 2006). Although the high depression group had a negative lateral asymmetry score average, which does support the hypothesis, right lateral dominance was exaggerated in the low depression group which does not support the hypothesis. Increased right frontal activity is associated with negatively valenced/withdrawal-motivated emotion. Therefore, it is possible that situational factors, such as a participant being uncomfortable in the testing environment, have contributed to this right hemisphere dominance in the low depression group. Perhaps those who already have increased right hemispheric activity or are already in a depressed mood state are less responsive to such situational factors. However, past research suggests that frontal activity is a relatively stable trait-like factor that may not be easily influenced by situation factors, although there is still considerable debate regarding this conclusion (Allen et al., 2004; Tomarken et al., 1992). Every effort was made to ensure participants were comfortable but it is still possible the testing environment may have contributed to the increased right hemisphere dominance observed in the control group.

To further complicate interpretation of this test, medial asymmetry scores were positive/left dominant for both groups. Although effect sizes were small, it was expected that lateral frontal and medial frontal sites would vary together. Past research suggests that people without depression or with very low level symptoms typically show relative left dominance (e.g., Debener et al., 2000). Although the relative left dominance of the low depression group is consistent with Debener et al. (2000), left dominance was exaggerated in

the high depression group. With only 22 participants in the low depression group and 20 participants in the high depression group, it is likely that this test was underpowered and could be influenced by outliers. There appears to be a number of outliers in the low depression group's medial asymmetry scores as displayed in Figure C-5. Since these scores were in the tail-end of the distribution expected for asymmetry scores, they were not removed from the analysis but may still have influenced the findings. No such outliers were apparent for lateral frontal asymmetry (see Figure C-4).

The opposing findings for the lateral and medial frontal asymmetry sites are an unusual finding. However, Thibodeau et al. (2006) noted that a relative lack of findings regarding the lateral site make interpretation of any differences difficult. In their meta-analysis, Thibodeau et al. noted that medial frontal asymmetry findings showed larger effect sizes than frontal asymmetry findings but that this may have been an artefact of fewer studies reporting results from both locations. Since group differences at both lateral and medial frontal sites in the current study yielded small effect sizes, and since results conflict with previous findings, replication is needed before conclusions can be made.

Another consideration in the extant literature is that there is no clear indication of whether the reduced left frontal activity commonly seen in depression is a result of an all-or-nothing difference between depressed and non-depressed individuals or whether reduced left frontal activity becomes more evident the more severe the depressive symptoms are (Thibodeau et al., 2006). To investigate the relationship between symptom severity and asymmetric brain activity, frontal asymmetry scores for both lateral and medial sites were correlated with both HDI-SF and BDI-II scores. Table 1 shows that there were no significant correlations between depression inventory scores and frontal asymmetry scores. All correlations were very weak indicating a lack of any discernible relationship between

depression and frontal asymmetry, which does not support the hypothesis. As seen in Appendix F, despite having three groups of participants, scores on the depression and anxiety inventories were roughly continuous suggesting that the lack of significant correlations was not a result of distinct groups obscuring the relationship. This finding conflicts with previous research conducted by Diego et al. (2001) who found that reduced left frontal activity was correlated with higher scores on the CES-D. This could be a result of the different test used. While CES-D was originally designed for use in adult community samples, BDI was targeted towards identifying severity of depression in clinical settings (Santor, Zuroff, Ramsay, Cervantes, & Palacios, 1995). Further, Santor et al. (1995) found that CES-D may lack specificity and may therefore be more likely to detect individuals with other mood disorders or some personality characteristics as being depressed. The correlation between asymmetry and CES-D might be a result of the correlation between mood and personality characteristics rather than depression. Similar to the current study, Blackhart, Minnix, and Kline (2006) found that frontal EEG asymmetry did not predict future BDI scores. Their findings support those from the current ANOVA which did not find reduced left frontal activity in those with current symptoms of depression.

Table 1.

Pearson's Correlation Coefficients and Significance Levels for Correlations Between Depression Inventories and Medial and Lateral Frontal Asymmetry Scores

| | Lateral Frontal | | Medial Frontal | |
|--------|-----------------|----------|----------------|----------|
| | <i>R</i> | <i>p</i> | <i>R</i> | <i>P</i> |
| BDI-II | .08 | .49 | .06 | .63 |
| HDI-SF | .02 | .88 | .04 | .74 |

Note. $N=78$

None of the three approaches used here have found clear support for the hypothesis of reduced left frontal activity in currently and previously depressed participants. Despite some moderate effect sizes, these have been in the opposite direction to that predicted based on theoretical models of the approach-withdrawal system and previous findings.

The present results conflict with a large number of previous results that have found reduced left frontal activity in depressed samples (e.g., Davidson, 1992; Diego et al, 2001; Kemp et al., 2010; Thibodeau et al., 2006). A meta-analysis based on 31 articles found a moderate effect size ($d=0.54$) (Thibodeau et al., 2006) and this pattern has been observed in patient (e.g., Debener et al., 2000) and community samples (e.g., Schaffer et al., 1983). However, a smaller portion of published studies have found no evidence of reduced left frontal activity in depression (e.g., Minnix et al., 2004; Nitschke et al., 1999; Reid et al., 1998; Segrave et al., 2011). It is probable that a substantial number of other studies have also found non-significant results but have not been published. The causes of such inconsistencies are unclear but likely include methodological differences, sampling differences, and difficulty in accurately defining and measuring the construct of interest - depression. It is of note that, as in the current study, Minnix et al. (2004), Nitschke et al. (1999), and Reid et al. (1998) all used student samples for both their depressed and control groups and found no significant findings. This could indicate that, although showing symptoms of depression, students who continue to study throughout their depression may constitute a different group, or have different symptom clusters, to people who do not continue to study and may therefore show atypical patterns of asymmetrical brain activity. Students who continue to study while affected by depression are more motivated than depressed individuals who do not study or are unable to continue with everyday activities. Although other symptoms may still be severe, relatively increased motivation may be observed as increased activity in the approach-motivated, left hemisphere system. A number

of studies yielding significant findings were conducted using non-student samples including inpatients and community samples which supports this possibility (e.g., Debener et al., 2000; Diego et al., 2001). On the other hand, a student sample was utilised by Gotlib et al. (1998) who did find significant left frontal hypoactivation in depression, so although it is possible that using a student sample may make it more difficult to detect significant differences, it is likely that a number of other factors also contributed to the inconsistent findings.

One methodological limitation with electrophysiological research is low power. Collecting EEG data is a time consuming process; so obtaining large samples is difficult and must occur over a long period of time which can introduce extra variation. For example, cortisol levels are known to correlate with EEG asymmetry and cortisol levels vary according to season and time of day (Peterson & Harmon-Jones 2009).

However, in the current research, even when focussing on effect sizes rather than statistical significance, there is little evidence of any clear relationship between depression status and frontal brain activity. In fact, some of the results are in the direction opposite to what is predicted based on past research, even though a larger sample was used than many past studies (e.g., Baehr, Rosenfeld, Baehr, & Earnest, 1998; Henriques & Davidson, 1991). Even using smaller samples than the current study, these studies found moderate to strong effect sizes so it is unclear whether a larger sample in the current study would have changed the results.

Another issue with EEG research is reference electrode choice (see page 31). Given that all EEG recordings are made in relation to recordings at a reference electrode, it is concerning that there is no clear agreement regarding the most suitable reference scheme for asymmetry research. There is poor convergent validity when data is recorded using different reference schemes ($r = -0.33$ to 0.86 , Reid et al., 1998) and effect size appears to be

moderated by reference choice (Thibodeau et al., 2006). Given the choices, linked-mastoids was selected for the current study but there is a clear need to find a consensus regarding the most appropriate reference scheme to use in asymmetry research because it seems that research conducted using different reference schemes cannot be directly compared.

Although past research has observed reduced left frontal activity in a range of samples including community and student samples, differences in the recruitment method may also contribute to the inconsistent results. In the current sample, participants volunteered after seeing advertisements for the study placed around campus. This method may have resulted in a fundamentally different set of depressed participants being recruited than studies recruiting participants in a more direct manner. Although the depression inventory scores showed a wide spread with participants who were mildly, moderately, and severely depressed, it is possible that the sample in the current study had a different symptom cluster compared to those in other studies. Despite their depressive symptomology these participants were still attending university and were motivated enough to contact the researcher to participate. This may indicate depression with higher levels of approach behaviour than past studies which could account for the unusual findings in the current study. Shenal et al.(2003) described a subtype of depression characterised by right frontal dysfunction that could lead to an increase in approach behaviour and depression associated with learned helplessness. It is also possible that high-functioning depressed individuals may employ compensatory techniques to achieve 'normal' functioning, which could be observed as increased activity in the left hemisphere relative to controls. The small effect sizes and inconsistent findings in the current study may be a result of a heterogeneous sample of depression participants, some characterised by depression with right frontal dysfunction described by Shenal et al. (2003) and others by left hypofrontality as found in a number of previous studies (e.g., Gotlib et al., 1998; Henriques & Davidson,1990).

The non-significant findings of the current study, and inconsistencies in past research findings, exemplify a key problem with research on depression. Depression research is 'hit or miss' and, as described in the introductory chapters, there are a lot of conflicting results and theories. This suggests that there is an underlying problem that is not being addressed. This may be a problem with how researchers are conceptualising and measuring depression. Current definitions and diagnostic criteria may be too broad and may also capture depressed mood resulting from external factors rather than 'true' depression. It is also possible that depression is not a unitary construct and may consist of subtypes each with their own pattern of symptoms and biological indicators. Failing to consider the heterogeneity of depression may account for some of the inconsistencies in depression research. Shenal et al. (2003) proposed four subtypes of depression, each characterised by different patterns of brain activity. If each of these four subtypes exists, then treating all depressed participants as a single group could account for the non-significant findings in the current study, as well as some past research findings. Therefore, when investigating how WM is effected in depression, the current study will attempt to categorise participants as left or right dominant and see if different patterns of memory functioning are revealed (see the results for Hypothesis 4).

The current findings only add to the inconsistencies in the research regarding frontal asymmetry in depression. With such variability in the presence of strength of the effect, the question becomes, are the differences in frontal activity in depression substantial and consistent enough to have any practical consequences for the treatment and understanding of depression? If there is only a minimal difference in observed activity, would targeting this aspect with treatment such as TMS provide improved treatment for depression beyond the outcomes which can be achieved with traditional psychotherapy or SSRI's?

Hypothesis 2: Depressed participants, without comorbid anxiety, will show reduced right parietal activity

Based on past research that found a relationship between parietal activity and anxiety levels in depressed participants (e.g., Bruder, 2003; Heller & Nitschke, 1997) it was hypothesised that depressed participants with low levels of anxiety would show reduced right parietal activity compared with depressed participants with high anxiety and non-depressed participants. High levels of anxiety have been found to be related to high levels of parietal activity (Bruder et al., 1997; Heller et al., 1995) which has been explained by the probable role of right parietal regions in arousal. Since anxiety is associated with high arousal, it follows that high anxiety levels will be associated with high levels of activity in this region. However, in depression, many sufferers experience low levels of general arousal, and lack of interest in normal activities, thought to be associated with reduced right parietal activity (Heller, 1993; Liotti & Tucker, 1992). Since depression and anxiety are highly comorbid, and associated with opposing patterns of parietal activity, past findings regarding parietal activity in depression have been highly variable (Stewart et al., 2010). The current study aimed to investigate parietal activity in relation to anxiety and depression status. Both the State and Trait anxiety subscale of the STAI were analysed separately. In order to be useful as an endophenotype or marker of depression, a relationship between trait anxiety (independent of current state) and parietal activity would be necessary. However, past research suggests that parietal activity in depression may be influenced by current anxiety levels (Stewart et al., 2010).

As seen in Table 2, correlations between the two depression and two anxiety measures (state and trait) and parietal asymmetry scores did not reveal any relationship. Based on past findings, this result is not surprising as, despite the high correlation between depression and anxiety scales ($r = .70$ to $.90$, see Supplementary Results 1), depression and anxiety are

thought to relate to parietal asymmetry in opposite directions. Therefore, it is likely that any potential relationship is essentially being cancelled out using this analysis (Heller & Nitschke, 1998). Similar findings were seen by Bruder et al. (1997) who did not find any relationship between parietal activity and STAI scores even with finding group differences in parietal asymmetry scores between anxious-depressed, depression only, and control groups.

Table 2.
Pearson's Correlations Between Parietal Asymmetry Score and Depression/Anxiety Inventory Scores

| | <i>r</i> | <i>P</i> |
|---------------|----------|----------|
| BDI-II | -.04 | .72 |
| HDI-SF | -.06 | .63 |
| State Anxiety | .04 | .76 |
| Trait Anxiety | .05 | .68 |

Note. $N=76$

One method used to assess the hypothesis that low parietal activity would be present in depressed participants with relatively low levels of anxiety was a partial correlation, controlling for anxiety. This test was repeated three times while controlling for both state and trait anxiety together and then controlling for each individually. When controlling for both state and trait anxiety, both the correlation between BDI-II and parietal asymmetry score ($r(72)=-.18, p=.13$) and between HDI-SF and parietal asymmetry score ($r(72)=-.22, p=.06$) revealed a weak relationship between parietal asymmetry score and depression. The direction of the correlation indicated that as depression increased, the parietal asymmetry score became more negative, indicating increased right parietal activity. This is in the opposite direction to what has been hypothesised. Similar findings were found when controlling for state and trait anxiety separately as displayed in Table 3.

Table 3.
Partial Correlation between Depression Inventory Scores (BDI-II, HDI-SF) and Parietal Asymmetry Score

| Controlling For | BDI-II | | HDI-SF | |
|-----------------|-----------|----------|-----------|----------|
| | <i>pr</i> | <i>p</i> | <i>Pr</i> | <i>P</i> |
| State Anxiety | -.09 | .43 | -.12 | .31 |
| Trait Anxiety | -.18 | .13 | -.22 | .06 |

Note. $df=73$

As well as the results showing the opposite trend to what was hypothesised, all correlations are weak and non-significant. Furthermore, as seen in Table 4, scores on the depression inventories (BDI-II and HDI-SF) showed strong, positive correlations with scores on both the State and Trait subscales of the STAI. Therefore, it is highly likely that attempting to control for anxiety levels using a partial correlation analysis is also removing some of the variance associated with depression scores.

Table 4.
Pearson's Correlations between Depression Measures (BDI-II, HDI-SF) and Trait/State Anxiety Subscales of STAI

| | BDI-II | HDI-SF |
|---------------|--------|--------|
| State Anxiety | .70** | .72** |
| Trait Anxiety | .88** | .90** |

Note. ** $p<0.001$. $N=78$

All participants who were currently depressed, based on their inventory scores, were also anxious as indicated by their STAI scores. In fact, all but one of the individuals in the currently depressed group had higher levels of trait anxiety than the mean of the control

group. As a result of this comorbidity, this hypothesis could not be tested by directly comparing parietal activity of anxious depressed, non-anxious depressed, and control participants and also suggests that the results of the partial correlation may not be valid.

In an attempt to circumvent some of these issues, a second approach was devised involving creating a highly anxious depressed group and a less anxious depressed group. This was achieved by ranking the depressed participants in terms of anxiety levels and putting the top 25% into the high anxiety depressed group and the bottom 25% into the low anxiety depressed group. The parietal asymmetry scores for these groups were then compared with the non-depressed participants. This was repeated for both state and trait anxiety subscales (see Figures 5 & 6 for results).

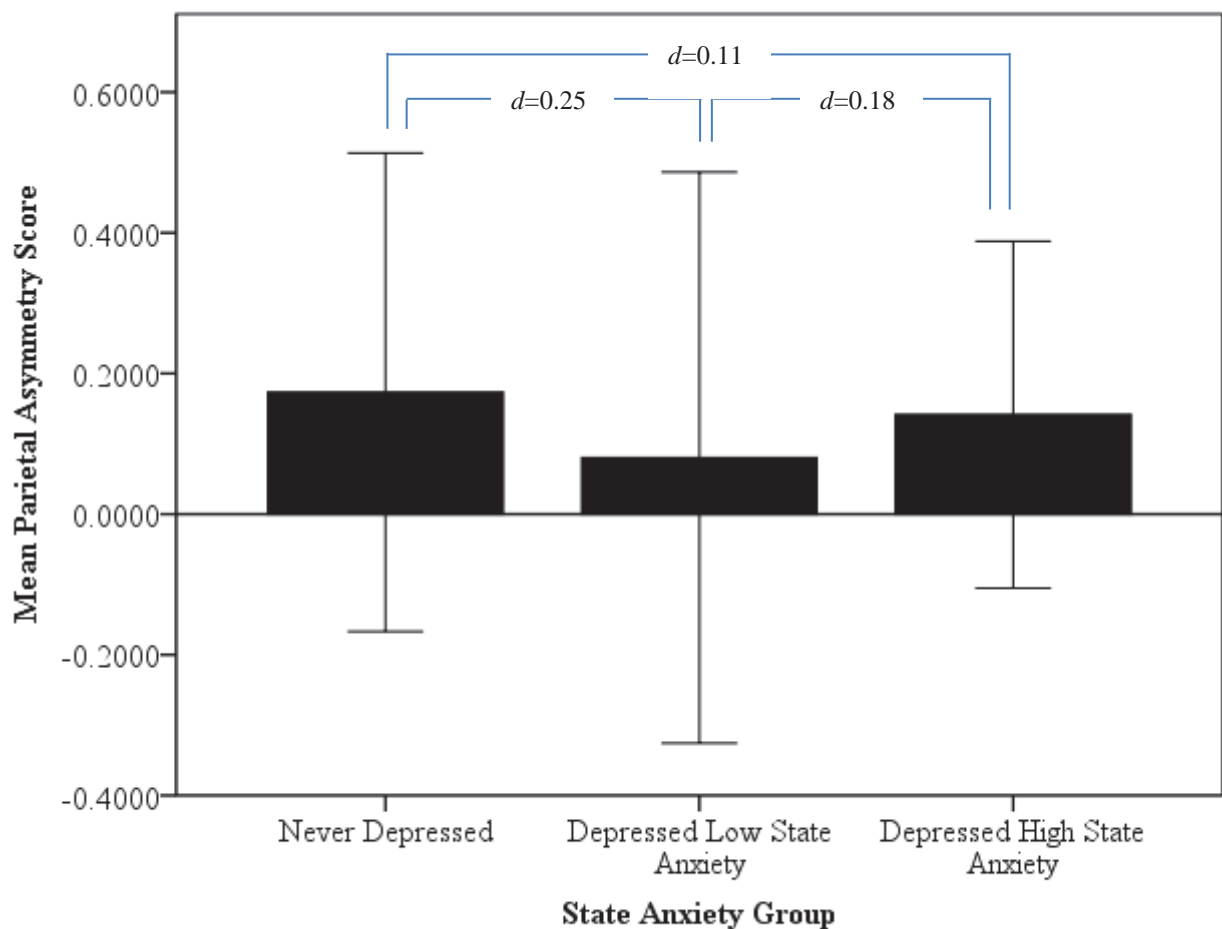


Figure 5. Differences in Mean Parietal Asymmetry Scores for High State Anxiety, Low State Anxiety, and Never Depressed Groups with Cohen's d Effect Sizes from Tukey Test Comparisons Indicated. Error Bars Indicate ± 1 SD.

For the state anxiety analysis, no significant differences in parietal activity were found between the three groups, $F(2,57)=0.29$, $p=.75$, $f=0.10$. Similar results were observed when comparing groups based on trait anxiety score, $F(2,56)=0.43$, $p=.65$, $f=0.12$. Despite the disparate sample sizes, the assumption of homogeneity of variance was satisfied (refer to Table B-3). These results do not support the hypothesis that depressed individuals with low/no anxiety would experience reduced right parietal activity (see Table B-3 for descriptive statistics and Figure C-3 for parietal asymmetry score distributions).

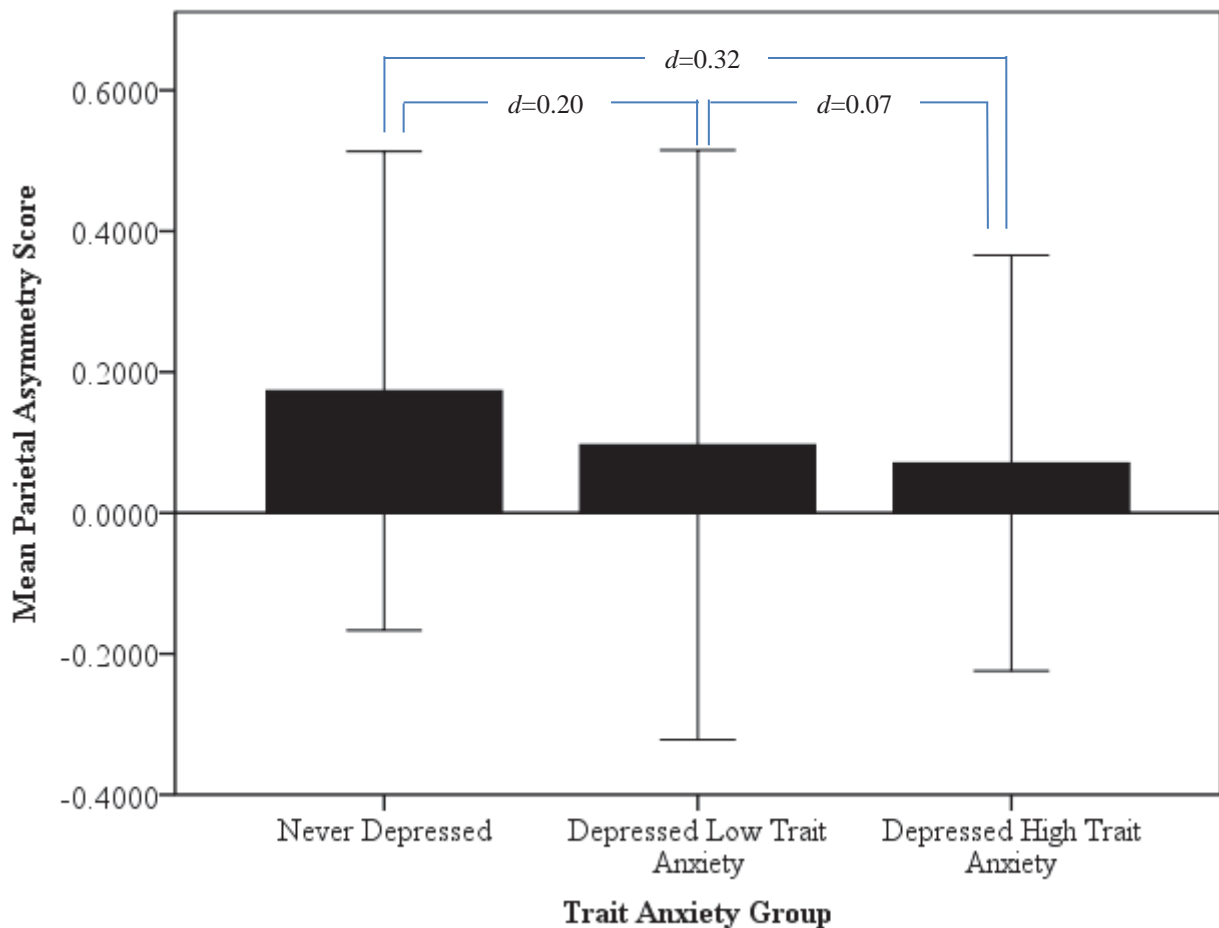


Figure 6. Differences in Mean Parietal Asymmetry Scores for High Trait Anxiety, Low Trait Anxiety, and Never Depressed Groups with Cohen's d Effect Sizes from Tukey Test Comparisons Indicated. Error Bars Indicate ± 1 SD.

Similar to the findings for frontal asymmetry, differences in recordings obtained from the different EEG systems may have influenced these results. Parietal asymmetry scores

calculated from recordings on the ADI system ($N= 48$, $M=0.20$, $SD=0.32$) were more positive (left dominant) than those calculated from the Neuroscan system ($N= 28$, $M=0.07$, $SD=0.33$).

A moderate effect size warranted further investigation ($t(74)=-1.74$, $p=.09$, $d=0.41$).

Therefore, the analyses were re-run adding System as a factor (further comparison of EEG machines is made in Appendix D).

The main effect of EEG system on parietal asymmetry ($F(1,54)=3.04$, $p=.09$, $f=0.24$) showed a moderate effect size while the main effect of state anxiety group ($F(2,54)=0.71$, $p=.50$, $f=0.16$) on parietal asymmetry score was weak and non-significant with a non-significant interaction between them ($F(2,54)=0.17$, $p=.84$, $f=0.08$). The main effects of EEG system ($F(1,53)=0.11$, $p=.75$, $f=0.04$) and trait anxiety group ($F(2,53)=0.50$, $p=.61$, $f=0.14$) on parietal asymmetry score were non-significant and the interaction between the two factors yielded a weak effect size ($F(2,53)=1.10$, $p=.34$, $f=0.20$). Although underpowered, adding EEG system as a factor has not given any indication that the results for this test would have been any different if the same machine had been used throughout.

These findings seem to conflict with past research indicating that highly anxious depressed individuals would show right dominant parietal activity while less anxious depressed individuals would show reduced right parietal activity (e.g., Bruder et al., 1997; Kentgen et al., 2000). However, compared with frontal asymmetry, past research on parietal asymmetry in depression has been even more inconsistent and has been found to be influenced by state factors including current anxiety level, caffeine intake, and general arousal levels (Stewart et al., 2010). While studies finding a relationship between depression and parietal activity have found a moderate effect size (e.g., Bruder et al., 1997), non-significant findings have also been found (Debener et al., 2000; Henriques & Davidson, 1991). One study of an at-risk group, adolescent children of depressed mothers, even found an effect in the opposite direction, increased right parietal activity (Tomarken, Dichter,

Garber, & Simien, 2004). Although past research has suggested that right parietal hypoactivity could represent an endophenotype for depression (e.g., Allen, Coan, & Nazarian, 2004), mixed results in past studies and the current findings do not support this proposition.

Further complicating the relationship between depression, anxiety, and parietal brain activity is evidence that different subtypes of anxiety may be associated with opposing patterns of parietal activity. For example, Heller et al. (1997) demonstrated that anxious apprehension was associated with increased left activity and anxious arousal was associated with increased right parietal activity. Therefore, not only does research investigating the role of anxiety in brain activity of depressed individuals, the specific type of anxiety also requires consideration.

Given how intertwined depression and anxiety appear to be, further study regarding parietal activity in depression needs to carefully assess possible ways to account for this. In the current study, a strong positive correlation was observed between depression and anxiety. The relationship between HDI-SF and trait anxiety indicated that 81% ($r=.90$) of the variance in trait anxiety could be explained by HDI-SF score. It is likely that creating a high and low anxiety depressed group, was analogous to creating a mild and severe depression group so it is difficult to clearly interpret the results. It is unclear how future studies could address this issue and the high correlations seen here would seem to suggest that current methods of measuring depression and anxiety are not specific to their goal. Therefore, further research is needed to determine if depression and anxiety can really be separated or whether they are better thought of as symptoms of the same condition. If the former is true, then improved screening methods are required.

Hypothesis 3: Depressed participants will perform worse on working memory tasks than control participants with disproportionate impairment in verbal working memory tasks due to reduced left frontal activity.

It was hypothesised that depressed participants would show an overall reduction in WM test performance as a result of a reduced level of arousal and a bilateral reduction in frontal activity (Heller & Nitschke, 1997). Furthermore, it was hypothesised that verbal WM tasks would be disproportionately impaired due to the reduction in left frontal activity commonly observed in EEG studies (Bruder et al., 1997; Davidson, 1992; Henriques & Davidson, 1991; Kemp et al., 2010; Thibodeau et al., 2006). Since verbal WM performance has been associated with left frontal activity, while spatial WM is associated with right frontal activity (D'Esposito et al., 1998; Reuter-Lorenz et al., 2000; Smith et al., 1996), verbal WM task performance may be disproportionately impaired in depressed participants. In order to test this hypothesis two main approaches were used, correlational and group differences.

Firstly, scores on the depression inventories (BDI-II and HDI-SF) were correlated with standardised scores (z -scores) on the WM tasks. Performance for the complex span tasks was assessed using two measures, absolute and total span score. Absolute span scores involve participants only getting points for correct recall if all stimuli within a set were recalled in the correct order whereas total span scores involve participants getting a point each time they remembered a stimulus correctly regardless of the accuracy of the rest of the set. Both measures were used here as there has been some debate regarding which measure is most useful. While absolute span score reduces chance effects and guessing, total span scores have been found to relate to performance using other measures more clearly (Conway et al., 2005; Friedman & Miyake, 2005; Redick et al., 2012). For the N-back task, performance in the 2-back and 3-back conditions was analysed separately as well as a mean

score of the two conditions. Since the 3-back condition is arguably more difficult, it is possible that performance in this condition might relate to depression differently.

There is no consistent relationship between WM performance and depression inventory scores as shown in Table 5. There is a mixture of positive and negative correlations and all correlations are weak. The only statistically significant correlation was between BDI-II score and absolute spatial span ($r(77)=.23, p=0.05$) indicating that increased BDI-II scores were associated with increased absolute scores in the spatial span task. A similar correlation was found for the total scoring method of spatial span ($r(77)=.21, p=.07$). Although weaker, a positive correlation was also observed between HDI-SF and both scoring methods of the spatial span task. In contrast, all correlations between the verbal span scores and depression inventories were negative indicating that as depression inventory scores increased, performance on the verbal span task decreased. Although the first part of the hypothesis, an overall reduction in performance, was not supported by the results, there is some evidence that verbal WM may be impaired with increased depression symptoms, as shown by the negative correlations between the verbal span task and depression inventory score. On the other hand, spatial WM performance seems to improve with increased symptoms, as shown by the positive correlations. Relatively increased activity in the right frontal regions, the typical pattern of asymmetric activity found in previous research (Thibodeau et al., 2006), may result in increased performance in spatial WM tasks and impaired performance in verbal WM tasks since verbal WM is associated with left frontal activity and spatial WM is associated with right frontal activity (Smith & Jonides, 1997).

Since this sample of depressed participants showed relatively high levels of anxiety, it is likely that the assumption of reduced arousal levels was violated which could explain why the first part of the hypothesis was not supported. There is some support for this possibility as significant positive correlations were observed between state anxiety scores and absolute

and total spatial span scores and verbal 3-back scores (see Table 5). Since these are arguably the most difficult tasks, this result could indicate that those with high state anxiety had higher levels of arousal and therefore were more attentive to the task. Forgas (2013) suggests that in some instances, negative mood states can actually heighten attention to surroundings and improve cognitive function. It is possible that the positive correlations in the spatial WM tasks may be related to this possibility. Similarly, Gable and Harmon-Jones (2008) found that high levels of approach motivation focussed attention while less strongly motivated approach-motivated emotion was associated with less focus and speculated that a similar pattern would occur with highly motivated withdrawal behaviours, with highly motivated withdrawal being associated with improved focus of attention which could result in improved performance in depressed participants. However, it is unclear why this might not extend to all tasks. This could be a result of heightened focus only in tasks perceived as more difficult or perhaps this adaptive mechanism is more effective in increasing focus to spatial stimuli/awareness of surroundings compared with verbal stimuli. A similar finding was documented by Gray (2001) who found that withdrawal-motivated affect, strongly associated with the experience of depression, has also been found to relate to improved spatial WM and impaired verbal WM. Interpretations of these findings should be made with caution as the effect size for these relationships is very small and the number of correlations conducted result in an inflated probability of Type 1 error,

Correlations with the other WM measure, N-back, show more mixed findings. While all correlations between depression inventory scores and spatial N-back were also positive, they were very weak. While negative, weak correlations were observed in the 2-back condition of the verbal version of the task, weak positive correlations were found in the 3-back condition. It is possible that increased difficulty resulting in increased participant focus

may have contributed to this positive correlation but the correlations are too weak to be interpreted reliably.

The second main approach used to test this hypothesis involved comparing currently, previously, and never depressed participant group scores on the WM tests to look for group differences (see Figure 7 for results). This analysis was conducted in addition to the correlational analysis in case memory differences in depression are an all-or-nothing type effect and not related to the severity of illness. As seen in Table 6, there were no significant group differences and effect sizes were small indicating that there are no clear group differences in memory performance (see Table B-4 for descriptive statistics).

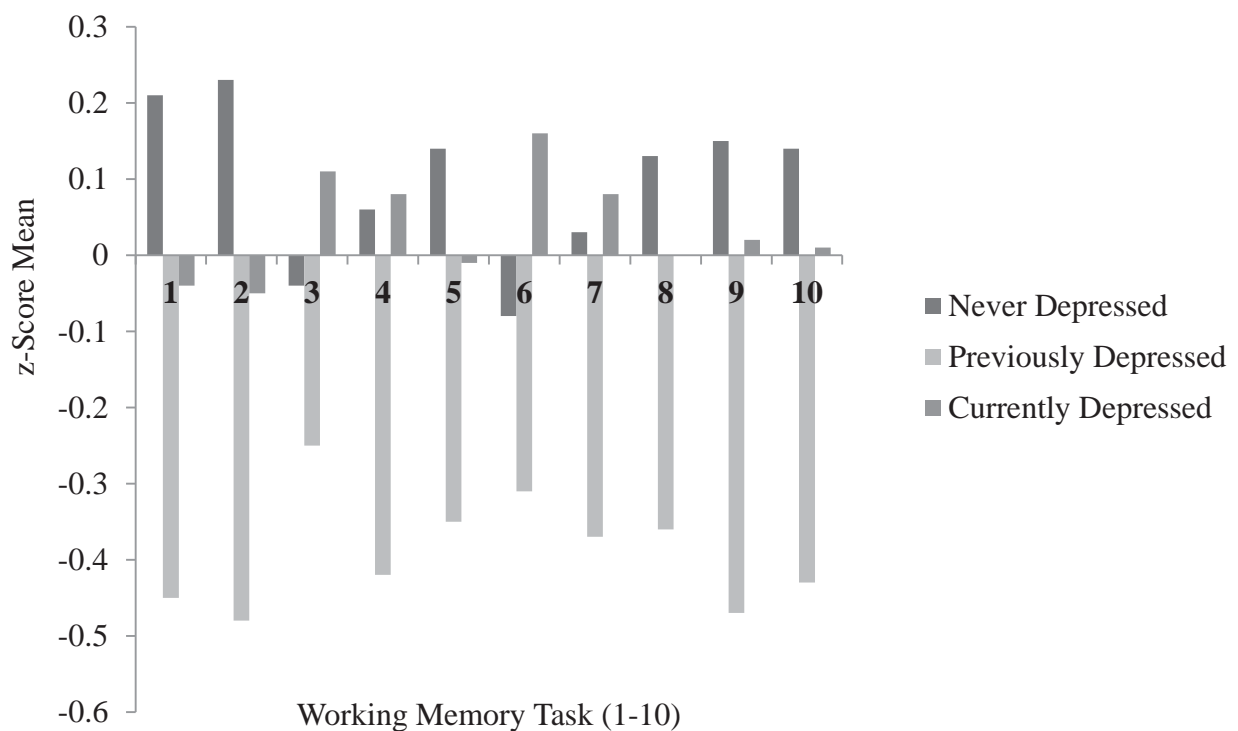


Figure 7. Mean z-Scores for Never, Previously, and Currently Depressed Groups on Working Memory Tasks (Labelled Task 1-10). Task 1-Verbal Span Absolute, Task 2- Verbal Span Total, Task 3-Spatial Span Absolute, Task 4- Spatial Span Total, Task 5-Verbal 2-Back, Task 6-Verbal 3-Back, Task 7-Verbal N-Back Mean, Task 8-Spatial 2-Back, Task 9- Spatial 3-Back Mean, Task 10- Spatial N-Back Mean.

In contrast to the correlational findings, the largest effect sizes were seen for the verbal span task, using both absolute and total scoring methods. Tukey test results were non-significant but indicated that the largest group differences were between the never depressed and previously depressed groups in both the absolute ($p=.14$) and total ($p=.11$) scoring methods. As seen in Table B-4 the never depressed group performed better in both the absolute ($M=0.21$) and total ($M=0.23$) scoring of the verbal span task compared with the previously depressed group who showed impaired performance in both the absolute ($M=-0.45$) and total ($M=-0.48$) scoring methods. However, this pattern of performance was not limited to verbal WM tasks. Previously depressed participants showed relatively impaired performance in all WM tasks (refer to Table B-4) while currently depressed and never depressed participants' results were less consistent.

It has been theorised that negatively-valenced mood may actually improve vigilance and attention since these mood states indicate that the surrounding environment may be threatening (Forgas, 2013). This information processing theory could account for the normal performance of the currently depressed group and may act like a compensatory mechanism preventing impaired cognitive function during depression.

Participants in the previously depressed group no longer suffer from high levels of negatively valenced mood so this mechanism may no longer exist. Other persistent factors associated with depression, such as reduced left frontal activity, may still be present leading to impaired performance. The conflict with correlational findings has likely occurred because both never depressed and previously depressed participants all show low depression inventory scores but, on verbal tasks at least, seem to have differences in performance which cannot be addressed by correlational analysis.

Table 5.
Pearson's Correlations Between z-Scores of Working Memory Tasks Performance and Depression and Anxiety Inventories

| | Verbal | Verbal | Spatial | Spatial | Verbal | Verbal | Verbal | Spatial | Spatial | Spatial | Spatial |
|---------------|--------|----------|---------|---------|--------|--------|--------|---------|---------|---------|---------|
| | Span | Span | Span | Span | 2-back | 3-back | 3-back | N-back | 2-back | 3-back | N-back |
| Absolute | Total | Absolute | Total | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean |
| BDI-II | -.03 | -.05 | .23* | .21 | -.11 | .08 | -.02 | .04 | .04 | .06 | .05 |
| HDI-SF | -.07 | -.12 | .16 | .15 | -.06 | .12 | .03 | .04 | .04 | .04 | .04 |
| State Anxiety | .06 | -.03 | .28* | .25* | -.05 | .24* | .10 | .03 | -.02 | -.02 | .01 |
| Trait Anxiety | -.03 | -.08 | .15 | .14 | -.05 | .13 | .04 | .01 | -.01 | -.01 | -.00 |

Note. * $p < 0.05$

Table 6.
ANOVA Results and Effect Sizes (f) for Comparison of Working Memory Test Scores between Currently, Never, and Previously Depressed Groups

| | <i>F</i> | <i>p</i> | <i>F</i> |
|-----------------------|----------|----------|----------|
| Verbal Span Absolute | 1.88 | .16 | 0.22 |
| Verbal Span Total | 2.18 | .12 | 0.24 |
| Spatial Span Absolute | 0.56 | .57 | 0.12 |
| Spatial Span Total | 1.16 | .32 | 0.18 |
| Verbal 2-back | 0.96 | .39 | 0.16 |
| Verbal 3-back | 1.09 | .34 | 0.17 |
| Verbal N-back Mean | 0.88 | .42 | 0.15 |
| Spatial 2-back | 0.95 | .39 | 0.16 |
| Spatial 3-back | 1.60 | .21 | 0.21 |
| Spatial N-back Mean | 1.37 | .26 | 0.19 |

An additional analysis was performed to look for evidence of different strategies or possible evidence of compensatory mechanisms in the depressed group. To do this, comparisons of d' (sensitivity) and c (bias) were made for the verbal N-back and the spatial N-back tasks. In the verbal N-back task, never depressed ($M=1.86$, $SD=0.40$, $N=31$) and currently depressed ($M=1.91$, $SD=0.50$, $N=36$) groups showed higher sensitivity than the previously depressed group ($M=1.68$, $SD=0.77$); however the effect size was small making it difficult to interpret these differences ($F(2,75)=0.79$, $p=.46$, $f=0.15$). A similar pattern was seen in the spatial N-back task with both never depressed ($M=2.04$, $SD=0.56$, $N=31$) and currently depressed ($M=2.10$, $SD=0.61$, $N=36$) showing higher sensitivity than the previously depressed participants ($M=1.67$, $SD=0.77$, $N=11$). A weak/moderate effect size was

observed for spatial N-back group differences ($F(2,75)= 2.11, p=.13, f=0.24$). This finding is consistent with the overall impairment seen in the previously depressed group (as seen in Table B-4).

For the verbal N-back task, never depressed participants showed a stronger bias (c) towards the no response ($M=.19, SD=.18, N=31$) than either the currently depressed ($M=.06, SD=.21, N=36$) or the previously depressed ($M=.05, SD=.43, N=11$) groups. This difference showed a moderate effect size indicating that never depressed participants show a clear bias to answering “no” compared to the currently and previously depressed groups who showed a relatively neutral bias value ($F(2,75)=2.89, p=.06, f=0.28$). This effect was not found in the spatial N-back task where never depressed participants showed a bias towards “yes” responses ($M=-.05, SD=.86, N=31$) while both currently depressed ($M=.16, SD=.35, N=36$) and previously depressed ($M=.06, SD=.35, N=11$) showed a bias towards “no” responses. This effect size was relatively weak ($F(2,75)=1.08, p=.35, f=0.17$) and the high SD’s suggest that the comparison of the means may not be accurate. It would appear that in spatial tasks, previously and currently depressed participants are risk averse while being risk-prone in the verbal tasks. This is the opposite pattern to the never depressed group which could be related to asymmetrical patterns of brain activity or differences in mood-related information processing effects for different types of stimuli.

Previous findings regarding sensitivity and bias in depression have been highly variable (Brebion, Smith, & Widlocher, 1997). For example, Watts, Morris, and MacLeod (1987) found that depressed participants produced fewer hits and that this was not just a result of more conservative response strategies due to a significantly reduced d' . Interestingly, Watts et al. also found that false alarm rates were dependant on the condition of testing, whether the response was to be vocalized or not, which could indicate that differences in stimulus modality influence false alarm rates and strategy in a different manner, supporting

the findings from the current study. However, Brebion et al. (1997) found that, despite overall memory impairment, there were no group differences in bias. Similar to other findings regarding cognitive function in depression, the study of signal detection in depression has produced conflicting results which may be a result of uncontrolled procedural differences but may again suggest a problem with how depression is conceptualised and measured in experimental research.

Overall, there was no clear support for the hypothesis that depressed participants would be disproportionately impaired in verbal WM tasks. The mixed findings with relatively small effect sizes do not seem to indicate any systematic differences between performance on spatial and verbal WM performance in depression. However, there is some indication that depressed and never depressed participants may employ different strategies depending on the type of task. This could be a result of motivational changes or a result of compensatory activity but further research would be needed to find support for these possibilities. It is of note that the poorest performance was observed in the previously depressed group. This may be a result of the absence of compensatory mechanisms employed during depression but may also be an artefact resulting from the small sample size of this group. Further research with previously depressed participants is needed to replicate this finding.

Impaired performance in verbal WM tasks in depression was hypothesised to be associated with the pattern of reduced left frontal activity commonly found in depression. In order to further investigate the relationship between WM performance, depression status, and brain activity, a further analysis is required comparing subgroups of depressed participants based on brain activity. As Shenal et al. (2003) theorised, depression could result from multiple different patterns of brain activity and it is likely that different patterns of abnormal brain activity would be associated with different profiles of cognitive deficits. This will be analysed in Hypothesis 4.

Hypothesis 4: Working memory performance will be related to specific patterns of asymmetric brain activity.

It was hypothesised that different patterns of asymmetric brain activity would be associated with different patterns of WM performance. Specifically, since verbal WM has been associated with left frontal activity (D'Esposito et al., 1998; Smith et al., 1996), those with relatively reduced left frontal activity may show impaired verbal WM performance. On the other hand, spatial WM has been associated with right frontal activity (D'Esposito et al., 1998; Smith et al., 1996) so reduced right frontal activity is hypothesised to be linked to impaired spatial WM performance. Finally, since right parietal regions are associated with arousal, it is hypothesised that reduced right parietal activity will result in an overall reduction in performance due to reduced arousal and therefore reduced focus on the task. Since different sub-types of depression may be characterised by different patterns of brain activity (Shenal et al., 2003) it follows that different subtypes of depression could be associated with different patterns of cognitive performance. The current hypothesis aims to test this theory by assessing whether depressed individuals with different patterns of brain activity show different patterns of cognitive performance.

Two main approaches were used to assess this hypothesis. Firstly, a correlational analysis was used to determine whether there is any relationship between asymmetry scores at all three locations (medial frontal, lateral frontal, and parietal) and standardised measures of WM test performance. A second analysis then compared depressed and non-depressed groups of right and left dominant participants to determine whether the relationship between WM test performance and asymmetry scores might differ in depressed compared with control participants. Since it is unclear if WM impairment in depression might be all-or-nothing, or dependent on symptom severity, it is important to combine both correlational and group analysis.

As outlined in Table 7, medial asymmetry scores showed a significant negative relationship with scores on all measures of performance on the verbal N-back task. As verbal N-back task performance improved, medial asymmetry score decreased (became more negative) indicating relatively greater right medial frontal activity. This is contrary to what was predicted as it was thought that relatively increased right frontal activity, and therefore a relative reduction in left frontal activity, would be associated with impairment in tasks thought to utilise left frontal regions, such as verbal WM tasks. This pattern of negative correlation was not unique to medial asymmetry and verbal N-back tasks and was actually observed in every task and scoring method with the exception of the absolute scoring method of the spatial span task, which showed a very weak positive correlation.

Table 7.
Pearson's Correlations between Lateral Frontal, Medial Frontal, and Parietal Asymmetry Scores and z-Scores of WM Task Performance

| | Lateral Frontal | Medial Frontal | Parietal |
|-----------------------|-----------------|----------------|----------|
| Verbal Span Absolute | -.12 | -.16 | -.11 |
| Verbal Span Total | -.11 | -.15 | -.11 |
| Spatial Span Absolute | .03 | -.02 | -.06 |
| Spatial Span Total | -.03 | -.07 | -.04 |
| Verbal 2-back | -.04 | -.27* | -.17 |
| Verbal 3-back | -.17 | -.26* | -.22 |
| Verbal N-back Mean | -.07 | -.30** | -.21 |
| Spatial 2-back | -.02 | -.13 | -.14 |
| Spatial 3-back | -.04 | -.10 | -.13 |
| Spatial N-back Mean | -.04 | -.12 | -.14 |

Note. * $p < .05$, ** $p < .01$

Lateral and Medial Frontal Asymmetry $N=77$, Parietal Asymmetry $N=76$

This could indicate that increased right activity results in a general improvement in WM performance. Based on the models of emotion discussed in Chapter 2, right frontal activity is associated with increased withdrawal-motivated and negatively valenced emotions.

Forgas (2013) demonstrated that negatively valenced emotions may lead to increased vigilance and attention to surroundings. This was theorised to be a result of negatively valenced emotions signalling possible danger in the environment. Increased task performance with more negative asymmetry scores (more right dominant) may be a result of activation with the withdrawal-motivated, negative valence system of the right frontal regions.

Negative correlations were also observed with parietal asymmetry scores. Since right parietal regions are associated with general arousal, it is not surprising that increased activity here, as demonstrated by negative asymmetry scores, is associated with improved task performance. Increased arousal is likely to result in increased attention to the task and therefore improved task performance. However, all correlations were weak and few were statistically significant so it is clear that many other factors are involved in WM performance.

Table 8.
Pearson's Correlations between Lateral Frontal, Medial Frontal, and Parietal Asymmetry Scores and Sensitivity (d') and Bias (c) for N-back Task Performance

| | Lateral Asymmetry | Medial Asymmetry | Parietal Asymmetry |
|---------------------|-------------------|------------------|--------------------|
| Spatial N-back d' | .01 | -.21 | -.22 |
| Verbal N-back d' | -.09 | -.34** | -.27* |
| Spatial N-back c | -.02 | .02 | .11 |
| Verbal N-back c | -.07 | -.05 | -.03 |

Note. * $p < .05$, ** $p < .01$

Lateral and Medial Frontal Asymmetry $N=77$, Parietal Asymmetry $N=76$

As seen in Table 8 there was also negative weak/moderate correlations between sensitivity (d') on the spatial and verbal N-back tasks and both medial frontal and parietal asymmetry scores. This indicates increased sensitivity in participants with high right parietal and medial activity, consistent with the results in Table 7. All correlations between bias (c) and asymmetry score were very weak indicating no relationship between asymmetric brain activity and response bias.

Although it was originally intended to use a MANOVA to look for group differences in WM performance, the lower than expected correlations between the different WM tests means that the assumption of correlated DV's is not met (see Supplementary Results 2). Therefore, multiple ANOVA's were required. Participants were split into four separate groups for each asymmetry score location (lateral frontal, medial frontal, and parietal, see Figures 8, 9, & 10 for results). The groups were depressed right dominant, depressed left dominant, control right dominant, and control left dominant. A one-way ANOVA was then used to compare these four groups performance on the WM tasks. Standardised scores (z -scores) of performance were used to enable easier comparison. The most apparent effects, as revealed in Table 9, were noted when comparing groups formed using medial asymmetry scores. Moderate effects were observed in both the total and absolute scoring methods of the verbal span task and in the 3-back condition of the verbal N-back task. Post-hoc Tukey tests revealed that the main source of these differences was between the control left dominant and control right dominant groups. For the absolute scoring of the verbal span task, Tukey tests revealed that the control right dominant group scored higher ($M=0.53$, $SD=0.87$, $N=19$) than the control left dominant group ($M=-0.40$, $SD=1.08$, $N=22$, $p=.02$).

Similarly, for the total scoring method of the verbal span task, the control right dominant scored higher ($M=0.57$, $SD=0.62$, $N=19$) than the control left dominant group ($M=-0.43$, $SD=1.13$, $N=22$, $p=.01$). As seen in Table B-5 similar, albeit smaller, effects were

present in the depression right and left dominant groups. Weak effects were seen when subtypes were formed using lateral frontal and parietal asymmetry scores as seen in Table 9 (Descriptive statistics in Tables B-6 and B-7).

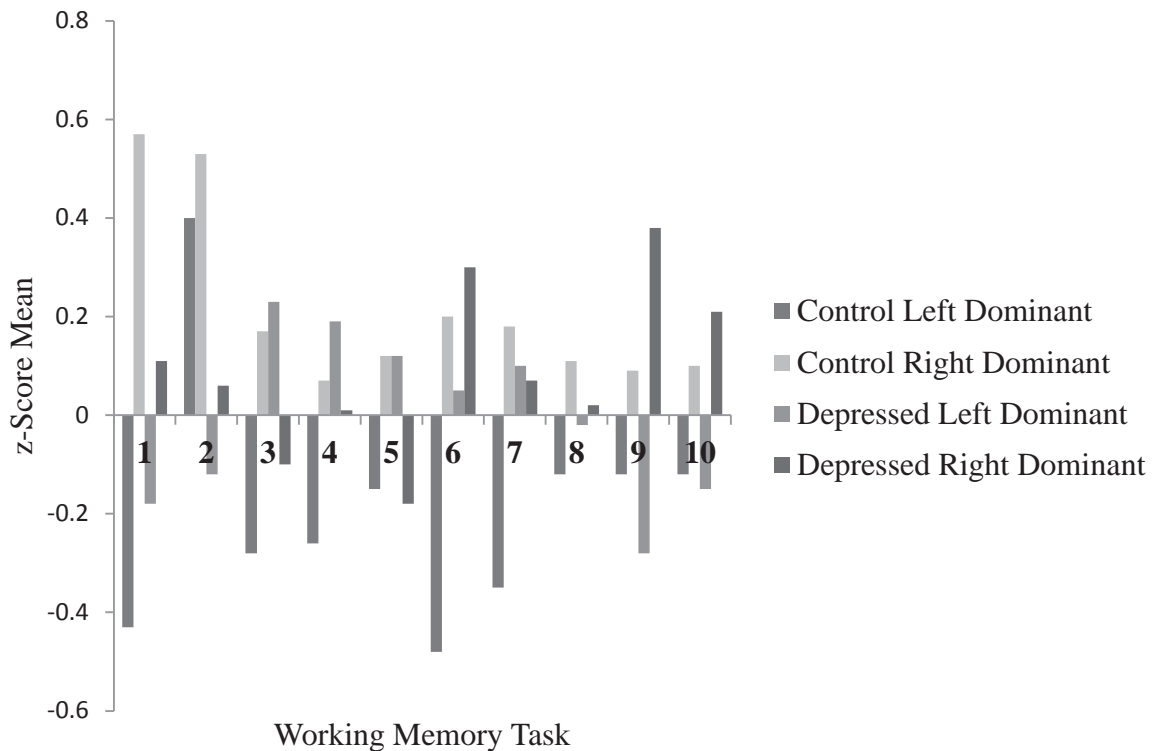


Figure 8. z-Score Mean z-Scores for Left and Right Dominant Subgroups Based on Medial Frontal Asymmetry Scores for Working Memory Tasks (Labelled Task 1-10). Task 1-Verbal Span Absolute, Task 2- Verbal Span Total, Task 3-Spatial Span Absolute, Task 4- Spatial Span Total, Task 5-Verbal 2-Back, Task 6-Verbal 3-Back, Task 7-Verbal N-Back Mean, Task 8-Spatial 2-Back, Task 9- Spatial 3-Back Mean, Task 10- Spatial N-Back Mean.

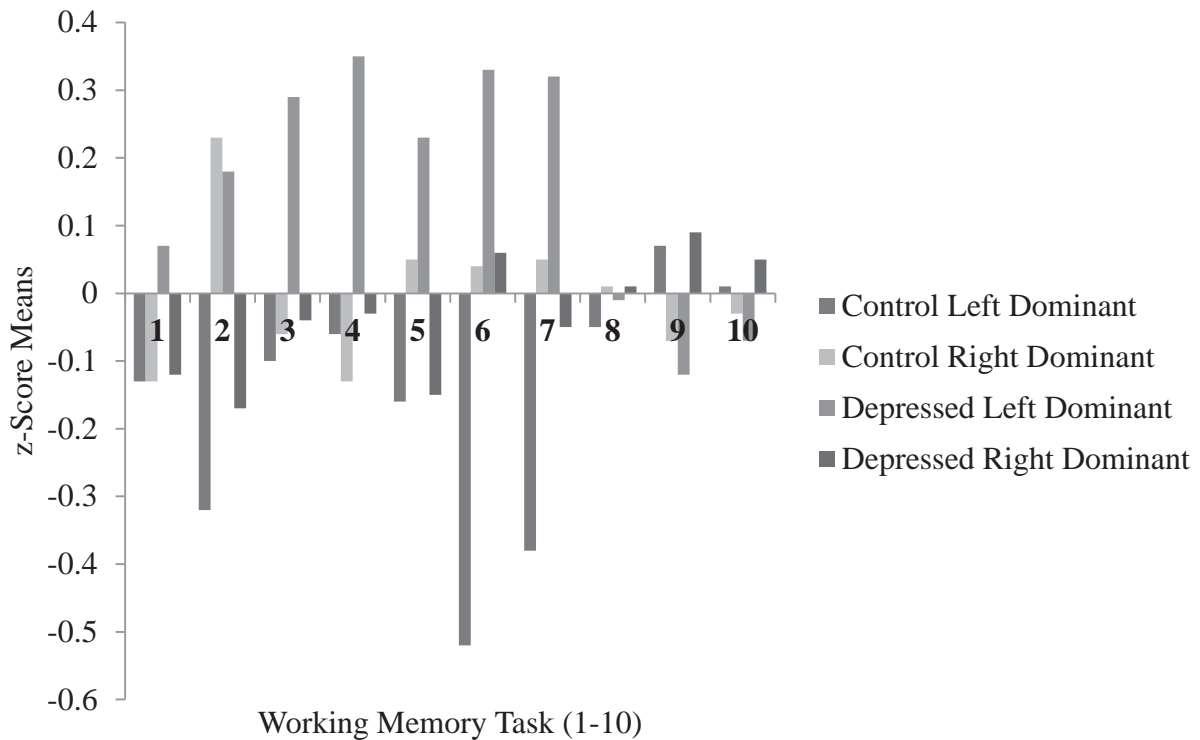


Figure 9. z-Score Mean z-Scores for Left and Right Dominant Subgroups Based on Lateral Frontal Asymmetry Scores for Working Memory Tasks (Labelled Task 1-10). Task 1-Verbal Span Absolute, Task 2- Verbal Span Total, Task 3-Spatial Span Absolute, Task 4- Spatial Span Total, Task 5-Verbal 2-Back, Task 6-Verbal 3-Back, Task 7-Verbal N-Back Mean, Task 8-Spatial 2-Back, Task 9- Spatial 3-Back Mean, Task 10- Spatial N-Back Mean.

Consistent with the results from the correlational analysis, this finding is in the opposite direction to that predicted. Since verbal WM tasks are thought to utilise left frontal regions (Smith & Jonides, 1997), it was hypothesised that right dominant individuals, whether depressed or not, would show relatively worse performance on these tasks compared with those who were left dominant.

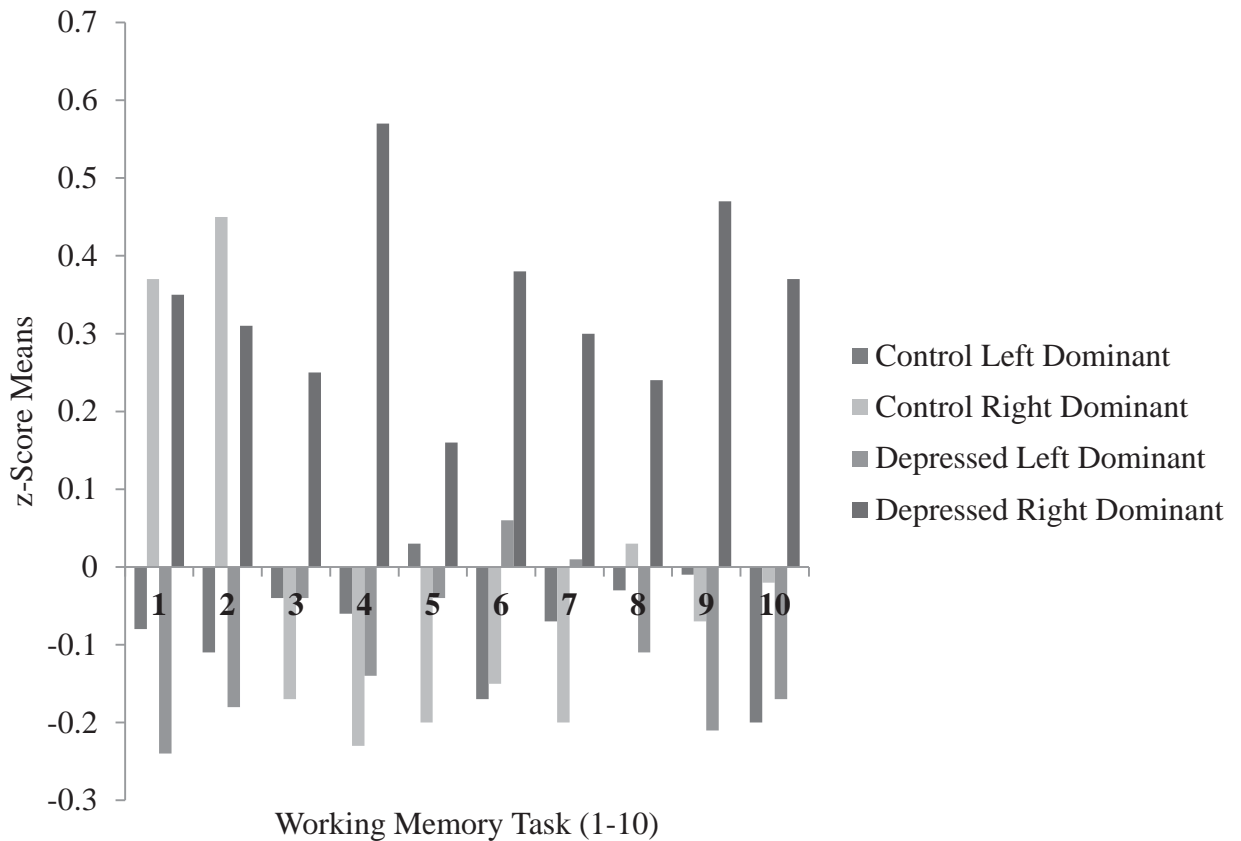


Figure 10. z-Score Mean z-Scores for Left and Right Dominant Subgroups Based on Parietal Asymmetry Scores for Working Memory Tasks (Labelled Task 1-10). Task 1- Verbal Span Absolute, Task 2- Verbal Span Total, Task 3-Spatial Span Absolute, Task 4- Spatial Span Total, Task 5-Verbal 2-Back, Task 6-Verbal 3-Back, Task 7-Verbal N-Back Mean, Task 8-Spatial 2-Back, Task 9- Spatial 3-Back Mean, Task 10- Spatial N-Back Mean.

Increased resting activity in left frontal regions may impair performance as higher baseline activation may leave fewer resources available to be activated to help complete the task. It is additionally possible that something about increased right activity improves performance on tasks thought to utilise left frontal regions, such as increased attention or arousal. As described by Forgas (2013), increased vigilance and attention to surroundings may result from activation of the negatively valenced, behaviour inhibition system, typically associated with increased right frontal activity.

Table 9.
One-Way ANOVA Results Comparing Depressed and Control Right- and Left-Dominant Groups' Mean z-Score Performance on Working Memory Measures

| | Medial Frontal | | | Lateral Frontal | | | Parietal Asymmetry | | |
|-----------------------|-----------------|----------|----------|-----------------|----------|----------|--------------------|----------|----------|
| | Asymmetry Group | | | Asymmetry Group | | | Group | | |
| | <i>F</i> | <i>P</i> | <i>f</i> | <i>F</i> | <i>p</i> | <i>f</i> | <i>F</i> | <i>p</i> | <i>f</i> |
| Verbal Span Total | 4.08 | .01 | 0.41 | 0.34 | .80 | 0.12 | 1.46 | .23 | 0.25 |
| Verbal Span Absolute | 3.32 | .02 | 0.37 | 1.31 | .28 | 0.23 | 1.44 | .24 | 0.25 |
| Spatial Span Total | 1.16 | .33 | 0.22 | 0.43 | .73 | 0.13 | 0.36 | .78 | 0.12 |
| Spatial Span Absolute | 0.73 | .54 | 0.17 | 0.67 | .57 | 0.17 | 1.70 | .18 | 0.27 |
| Verbal 2-back | 0.51 | .68 | 0.14 | 0.54 | .65 | 0.15 | 0.27 | .85 | 0.11 |
| Verbal 3-back | 2.54 | .06 | 0.32 | 1.94 | .13 | 0.28 | 0.95 | .42 | 0.20 |
| Verbal N-back Mean | 1.17 | .33 | 0.22 | 1.19 | .32 | 0.22 | 0.54 | .66 | 0.15 |
| Spatial 2-back | 0.17 | .92 | 0.08 | 0.01 | .99 | 0.02 | 0.32 | .81 | 0.11 |
| Spatial 3-back | 1.44 | .24 | 0.24 | 0.19 | .90 | 0.09 | 1.22 | .31 | 0.23 |
| Spatial N-back Mean | 0.55 | .65 | 0.15 | 0.05 | .99 | 0.04 | 0.74 | .53 | 0.18 |

Note. $df_{\text{Frontal}}=3,73$, $df_{\text{parietal}}=3,72$

However, if the latter hypothesis was true, this does not readily explain why right dominant individuals did not perform significantly better in all tasks (both spatial and verbal) or why medial frontal asymmetry scores seem to be most relevant to performance. While the findings regarding medial frontal asymmetry scores yielded weak/moderate effect sizes, only weak effects were observed for lateral frontal and parietal asymmetry scores. The stronger effects for medial asymmetry scores are consistent with the group differences approach of

Hypothesis 1 but conflict with the second approach for Hypothesis 1 where low and high depression groups were compared. The cause of this inconsistency is unclear.

As a result of differences in asymmetry scores recorded between the machines (described in Appendix D), categorisation of participants into groups based on their dominant hemisphere may be biased. Since depressed participants recorded on the ADI system demonstrated increased symptom severity and participants recorded using the ADI system had consistently more positive asymmetry scores, depressed participants are more likely to be categorised as left dominant. It is impossible to tell the extent to which this may have influenced the results but its possible impact should be considered. The finding of possible differences in asymmetry metric values between different EEG systems may help to explain some of the inconsistencies among past studies. Although asymmetry metrics should not theoretically be different on a different system, the current study suggests that differences may occur which may make comparisons between research using different systems challenging.

When interpreting these findings, it is important to keep in mind that the asymmetry metric used to assess brain activity in the current study only assesses relative differences in activity between the hemispheres. It is possible that performance is more dependent on absolute levels of activity rather than relative levels. However, when looking for group differences, absolute levels are of limited use as they can be easily influenced by extraneous variables such as skull thickness. Further, although resting asymmetry levels were useful because they avoid the confound of compensatory activity, baseline levels cannot predict how reactive a region will be during the performance of a task. For example, a region with high resting activity might have fewer resources available to recruit for task performance. Therefore, it is important to consider the relationship between resting activity and responsiveness to stimuli.

Supplementary Results Part 1: A Comparison of Depression and Anxiety Inventories.

Given that both BDI-II and HDI-SF were designed to measure symptom severity for the same construct, depression, high convergent validity was expected. As predicted, a very strong positive correlation was found between these measures (refer to Table 10 for descriptive statistics and Table 11 for correlations). This supports the validity of the measures. A small amount of variability is to be expected due to the slightly different composition of the scale questions and the scoring method used. Interestingly, despite the high correlation, there were 12 participants who were classified as depressed using the recommended cut-points on the BDI-II but not the HDI-SF and only one who was classified as depressed by the HDI-SF and not the BDI-II. This may indicate that while the scales correlate well, further consideration is needed regarding the placement of these cut-points.

A lower correlation was expected between the Trait and State subscales of the STAI since the State anxiety subscale is designed to assess current mood state, a less stable characteristic than Trait anxiety or the amount of anxiety an individual experiences on a regular basis. A strong positive correlation ($r=.77$) was observed between these subscales which fits with this theory and supports the utility of these measures in assessing different aspects of the same construct.

The correlations between the anxiety and depression measures were also strong and positive. The strength of these correlations ($r=.70$ to $.90$) were stronger than would be expected if the measures are assessing different constructs. The highest correlation was between the HDI and trait anxiety with 81% shared variance. While the high comorbidity of anxiety and depression is well-known (Bruder et al., 1997; Kessler et al., 2003), the strength of these correlations suggests that these measures may be assessing the same construct. However, Burns and Eidelson (1998) argued that the high correlations demonstrate strong convergent validity which is expected due to the overlapping symptoms.

The separation of depression and anxiety is an ongoing concern in clinical psychology. For instance, while some argue that the two are separate entities, each with their own unique features, others argue they are dimensions of the same condition (e.g., Burns & Eidelson, 1998; Feldman, 1993; Kocovski et al., 2004). The Tripartite model suggests that the high overlap between depression and anxiety is due to the shared component of negative affect but that depression can be distinguished due to low arousal and low positive affect whereas anxiety can be distinguished by high physiological arousal and the experience of positive affect (Clark & Watson, 1991). That said, there is conflicting evidence regarding the utility of this model in distinguishing between anxiety and depression (Anderson & Hope, 2008). One of the main challenges to addressing this debate is flaws in the methods used to measure anxiety and depression. Feldman (1993) suggests that it is not surprising that anxiety and depression are unlikely to be distinguishable when measured using inventories as many of the commonly used inventories could be better characterised as generalised tests of negative affect. The Tripartite model suggests that negative affect accounts for the high overlap so depression and anxiety inventories may be more effective at distinguishing between depression and anxiety if more items related to the distinctive characteristics of arousal and experience of positive affect. It remains unclear if anxiety and depression are truly distinguishable or whether the inventories utilised to measure them are not specific enough to separately diagnose anxiety and depression. Given that some depression inventories show poor convergent validity (e.g., Tanaka-Matsumi & Kameoka, 1986), it seems that further work is needed to create inventories showing strong convergent validity and high specificity for the construct of interest before this debate can be resolved.

Table 10.
Descriptive Statistics for Depression (BDI-II, HDI-SF) and Anxiety (State and Trait Subscales of STAI)

| | <i>M</i> | <i>SD</i> | Range |
|---------------|----------|-----------|-------------|
| BDI-II | 14.86 | 12.15 | 0.00-46.00 |
| HDI-SF | 7.69 | 5.96 | 0.00-23.50 |
| State Anxiety | 38.15 | 11.60 | 23.00-67.00 |
| Trait Anxiety | 46.09 | 14.24 | 22.00-75.00 |

Note. $N=78$, BDI scale=0-63. HDI scale=0-33. State Anxiety Scale=20-80 . Trait Anxiety Scale= 20-80.

Table 11.
Pearson's Correlations between Depression (BDI-II, HDI-SF) and Anxiety (State and Trait Subscales of STAI)

| | 2. | 3. | 4. |
|-----------------|-------|-------|-------|
| 1.BDI-II | .94** | .70** | .88** |
| 2.HDI-SF | - | .72** | .90** |
| 3.State Anxiety | | - | .77** |
| 4.Trait Anxiety | | | - |

Note. $N=78$, ** $p<0.01$ (2-tailed)

Supplementary Results 2: Relationship between Working Memory Tasks

There is an ongoing debate regarding the most appropriate method to measure WM (Jaeggi et al., 2010; Kane et al., 2007). WM is defined as including both a passive storage component and an active processing component (Baddeley & Hitch, 1974). Therefore, both CST's and N-back tasks possess good face validity. However, past research has found that correlations between these tasks are low suggesting they may not be measuring the same construct.

As seen in Table 12, similar findings were found in the current study. The Verbal Span task (both absolute and total scoring methods) showed weak positive correlations ($r=.09$ to $.32$) with the Verbal N-back task (2-back, 3-back, and Mean). Similar results were observed in the spatial tasks with weak correlations ($r=.26$ to $.38$) between the N-back and Complex Span tasks. These correlations are considerably lower than would be expected if both the N-back and Complex Span tasks both assessed performance on the same construct.

This could indicate that there is a fundamental difference between the two tasks types that cannot be accounted for by current models of WM. For example, Jaeggi et al. (2010) suggested that N-back tasks rely primarily on recognition memory, while CST's require recall memory. Recognition memory is a dual-process involving both recollection and familiarity, while recall tasks rely solely on recollection due to the absence of cues required to make familiarity judgements (Rugg & Yonelinas, 2003). In CST's the cues available are limited and participants must utilise recollection memory to answer accurately. However, in N-back tasks participants are provided with cues so may employ both recollection and familiarity processes. The use of different underlying processes may reduce the shared variance.

While the low correlations could indicate that one or both tasks possess poor validity, if the variation is a result of different strategies such as recall and recognition, it is of concern that current models of WM do not allow for the use of different processes. Models of long-term memory distinguish between implicit and explicit memory processes. Perhaps a similar model of WM with branches for different underlying processes is required.

Table 12.
Pearson's Correlations between Complex Span and N-back Measures

| | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. |
|----------------------------|-------|-------|-------|------|-------|-------|-------|-------|-------|
| 1.Verbal Span Absolute | .92** | .36** | .28* | .10 | .32* | .23* | .22 | .15 | .19 |
| 2.Verbal Span Total | - | .36** | .30** | .09 | .29* | .21 | .29** | .27* | .29** |
| 3.Spatial Span Absolute | | - | .91** | .28* | .38** | .37** | .26* | .34** | .32** |
| 4.Spatial Span Total | | | - | .23* | .36** | .32** | .28* | .38** | .35** |
| 5.Verbal 2-back | | | | - | .61** | .90** | .56** | .45** | .53** |
| 6.Verbal 3-back | | | | | - | .90** | .47** | .52** | .51** |
| 7.Verbal N-back Mean | | | | | | - | .57** | .54** | .58** |
| 8.Spatial 2-back | | | | | | | - | .82** | .96** |
| 9.Spatial 3-back | | | | | | | | - | .95** |
| 10.Spatial N-back Mean | | | | | | | | | - |

Note. * $p < .05$, ** $p < .01$
 $N = 78$

Chapter 7

General Discussion

Summary of Key Findings

The hypotheses for this research were not supported by the findings. It was hypothesised that participants with depression would have reduced left frontal activity. However, the depressed participants asymmetry scores for both medial and lateral frontal recording sites did not differ from the previously depressed or never depressed groups. It was also hypothesised that the previously depressed participants would show reduced left frontal activity but the findings revealed relative left dominant frontal activity in the previously depressed group compared with the never depressed group. This finding was only apparent at the medial frontal recording site. In contrast, when comparing depression groups based on the upper and lower quartile of the BDI-II scores, the largest effect sizes were observed for the lateral recording site. Contrary to the hypothesis, the low depression group showed stronger right hemisphere dominance than the high depression group. Furthermore, there was no relationship between frontal asymmetry scores and degree of depression, as measured by the BDI-II and HDI-SF. These results showed no clear indication of a consistent relationship between depression and frontal brain activity.

It was also hypothesised that depressed participants with low levels of anxiety would show reduced right parietal activity. However, due to the majority of depressed participants also being highly anxious, this hypothesis was difficult to test. A comparison of the most anxious depressed participants, least anxious depressed participants, and control participants did not find any group differences, and a partial correlation between depression and parietal asymmetry scores controlling for anxiety did not suggest any relationship between parietal asymmetry and depression. The relationship between depression, anxiety, and parietal

activity remains unclear and analysis of this is complicated by the high levels of comorbidity between anxiety and depression.

The third hypothesis was that depressed participants would suffer from impaired WM ability with disproportionate impairment in verbal WM tasks. There was no clear indication that depressed participants were impaired in any of the WM tasks compared with the control group. The previously depressed group did show some evidence of impairment with lower average scores in all WM tasks. The strongest effect was observed in the verbal CST. In contrast, for the correlational analysis, the strongest correlations were found between the spatial span score and current symptom severity (scores on BDI, HDI-SF, and STAI). Spatial span score increased as symptom severity increased. The findings seem to indicate that previously depressed participants may suffer from cognitive impairment, while increased severity of depression actually improves performance in some domains. This suggests an apparent reversal or change in symptoms at some point during the recovery process. At what point during recovery does this switch occur? If this change occurs before people are officially classed as 'recovered', then the inclusion of participants on the road to recovery could account for inconsistencies in the findings regarding the presence of cognitive deficits in past studies as it is likely that the proportion of participants at this stage of recovery will differ between studies. This could account for why spatial span improvements were not demonstrated in the current depression group during the group analysis. If the currently depressed group contained some people who were close to being recovered then they may have been experiencing cognitive impairment which could have cancelled out any group effects. However, small effect sizes and high variation limit the ability to form strong conclusions regarding this apparent conflict, and replication of this finding is required.

It was thought that the inconsistent and unexpected findings from the first three hypotheses may be a result of heterogeneity within the depressed group. If only a subset of

those with depression had reduced left frontal activity and associated deficits in tasks utilising left frontal regions, then treating depression as homogenous may have obscured important patterns in the data. Therefore, in the final analysis, participants were categorised into one of four groups based on their frontal asymmetry scores: control right dominant, control left dominant, depressed right dominant, and depressed left dominant. The largest effects were observed when comparing the control left and right dominant groups where right dominant (relatively reduced left frontal activity) participants performed better in the both the verbal span task and the verbal 3-back task. This finding was contrary to expectations since reduced left frontal activity was hypothesised to result in *poorer* performance on tasks utilising this region, the verbal WM tasks. Similarly, when correlating performance on the WM tasks with frontal asymmetry scores, increased right dominance was associated with improved performance in all tasks, with the largest effect in the verbal WM tasks.

While none of the original hypotheses were supported, these findings help to illustrate some of the key difficulties in this field of research and have also raised some further questions that should be addressed in future research. These findings were incongruent with substantial number of past studies and conflicts were even found when using different methods to assess the same hypothesis. These findings only add to the already inconsistent and varied literature on cognitive and neurological correlates of depression which raises several possibilities, including problems with conceptualising depression, and assessing it in a research setting.

Measurement of Depression

As outlined in Chapter 1, depression is primarily an affective disorder with associated cognitive and physiological symptoms (Beck & Alford, 2009). While this basic outline is agreed upon, there is a wide array of different approaches used to detect the presence of

depression and clinicians disagree about what should be classified as depression and what is better represented by other mental health diagnoses (Beck & Alford, 2009). Therefore, it is not surprising to learn that in research settings, where the researchers come from a wide range of different disciplines, there are a substantial number of approaches employed. Generally the approaches fall into two categories: diagnosis by a medical professional and use of self-report depression inventories. Studies using both methods have found mixed results (see introductory chapters) so there is no clearly superior method.

To see if the use of different methods to classify depression may play a role in the inconsistencies in past research, the current study used both methods. Participants were asked if they had ever received a diagnosis of depression from a medical professional and whether this diagnosis was current. Participants were then classified as currently, previously, or never depressed using depression inventory scores. Further, all participants completed two depression inventories (BDI-II and HDI-SF) to help account for potential differences between the inventories. There were some differences when categorisation of participants was done using different methods. For example, while 36 participants indicated they had a current diagnosis of depression from a medical professional, 35 participants were above the cut-off for mild depression using the BDI-II and only 24 were above the cut-off for mild-depression using the HDI-SF. This reveals considerable discrepancies. If anything, one would expect fewer participants to be diagnosed formally as having depression than would be picked up using the questionnaires (Byerly & Carlson, 1982). This could indicate a tendency for depression to be over-diagnosed in a general practice setting, where most of the participants indicated that their diagnosis has originated from. Further, despite a strong correlation between BDI-II and HDI-SF measures, substantially more participants would have been categorised as depressed using the BDI-II than the HDI-SF if recommended inventory cut-off points were utilised as has been done in some past research. This could indicate problems

with the standardised cut-off points so caution is needed when interpreting study results and making diagnoses based on cut-off points only.

Results analysed using depression severity (measured by BDI-II and HDI-SF) and using diagnosis by a medical professional did not always tell the same story. For instance, when comparing the depression groups based on diagnosis by a medical professional, the previous depression group was found to have impaired WM performance with the largest impairment in the *verbal* span task, even though BDI-II and HDI-SF scores were comparable to the control group (see Table B-8). In contrast, when depression inventory scores were correlated with WM test performance, increased depression severity was associated with improved performance on the *spatial* span task. This conflict provides some evidence that depression categorised using different methods may influence study results. The small effect sizes indicate a need to replicate this finding before drawing conclusions.

Despite common usage, use of inventories to classify depression may be imperfect. One potential issue that arose during the current study was that participants frequently commented that there seemed to be large gaps between options on the inventories. For example, on the BDI-II, question 1 asks about sadness and the options provided are “0-I do not feel sad”, “1- I feel sad much of the time”, “2-I am sad all the time”, and “3- I am so sad or unhappy that I can’t stand it”. There seems to be a substantial gap between the first and second option which participants reported to be a bit frustrating. They usually opted to choose “1-I feel sad much of the time” instead of indicating the absence of sadness altogether which seemed dishonest. Although such a forced-choice decision may help to improve the specificity and sensitivity of the measure, there were some instances where the participants did not perceive the options to be in a logical order. For example, in the HDI-SF, question 2 relates to suicidal ideation and asks “in the past 2 weeks, have you thought about suicide”, with the response options being “0- I have not had any thoughts about suicide”, “1-I feel like

life is not worth living”, “2-I think about killing myself but I have no plans”, “3-I think about killing myself and have a specific method or plan”, and “4-I tried to kill myself in a way I was sure would succeed”. In this question, many participants mentioned that they had briefly thought about suicide during the previous two weeks but would not consider acting on these thoughts as they considered life to still be worth living. This left many of these participants to select “2”, giving them a higher total than those who selected “1” despite them perceiving option “2” to be less severe. Participants reported that brief suicidal ideation did not necessarily mean they did not feel that life was worth living. These, and other similar questions may have artificially inflated the score on the depression inventories which could lead to more participants being classified as depressed and may obscure some correlational differences.

Further, there is always concern regarding the use of self-report measures and whether participants are likely to answer accurately. This was evidenced in the current study when one participant noted they did not know how to answer the question regarding suicidal ideation as they were already in treatment for depression and did not want to be considered a danger to themselves and be forced to undergo further evaluation and treatment. Similar concerns were raised by Byerly and Carlson(1982) who noted that the most severely depressed participants may not have been willing to complete the survey fully resulting in the finding that depressed inpatients did not seem to be more severely depressed than outpatients. Depression inventories may also be unable to distinguish between low mood due to situational factors and clinical depression which is why the use of diagnosis by medical professional is sometimes warranted.

Diagnosis by medical professionals is not infallible. The majority of participants indicated they had been diagnosed by their GP. Given the short time constraints that many GPs are allowed, it can be difficult to rule out personality disorders in which some of the

symptoms mirror depression (e.g., Borderline Personality Disorder), other mental health conditions with similar presentations (e.g., SAD, depressed phase of bipolar) and other health conditions such as chronic fatigue syndrome, thyroid dysfunction, and general fatigue and stress as a result of studying. Although DSM criteria for depression indicate that there should be no better explanation (e.g., grieving) or no indication of physical health conditions like thyroid dysfunction, when GPs are given limited time and resources, alternative explanations may not always be reliably excluded. Since depression is relatively common, affecting approximately 25% of people (Browne et al., 2006), doctors are likely to suggest the more common interpretation of the symptoms (Mitchell, Vaze, & Rao, 2009). A meta-analysis conducted by Mitchell et al. found that false-positives for depression diagnosed in a primary care setting were higher than missed cases and even higher than true cases in some settings. Although ratings from specialist professionals such as clinical psychologists, psychiatrists, or mental health practitioners may be more reliable, there are still some concerns about disagreement on what constitutes depression compared with other mental illness with overlapping symptomology (Beck & Alford, 2009). Employing direct screening by such professionals may not be feasible within the research setting.

A further complication is the high comorbidity of anxiety and depression. The current study found that a high proportion of variance was shared between the depression and anxiety inventories (refer to Supplementary Results 1) and all participants classified as currently depressed also showed symptoms of anxiety. This raises the question, are depression and anxiety separable or dimensional aspects of the same conditions? This question has received a great deal of research attention and still no clear answer is available. As outlined in Chapter 1, one of the most common models used to explain the overlap and help differentiate anxiety and depression is known as the Tripartite model (Clark & Watson, 1991). This model theorises that the high overlap is due to the shared symptoms of negative affect but that

anxiety can be further characterised by the experience of positive affect and high physiological arousal levels. On the other hand, those with depression frequently show anhedonia or lack of positive affect and low arousal levels. Despite its widespread support, this model cannot account for the high variability within anxiety disorders such as the experience of low positive arousal during social phobia (Anderson & Hope, 2008). Furthermore, high negative affect is highly correlated with generalised anxiety disorder (Anderson & Hope, 2008; Watson, Gamez, & Simms, 2005). Large sample research conducted by Burns et al. (1998) found no support for the Tripartite model and instead proposed that depression and anxiety could be distinguished by variations in the non-specific negative affect component.

Nitschke et al. (2001) supported the notion that depression and anxiety could be psychometrically differentiated if enough items and tests were used but this is not always feasible as part of a wider research setting involving collection of other data. Burns et al. (1998) argued that the high correlations between measures of depression and anxiety are not problematic and instead represent strong convergent validity. Burns et al. noted that, although depression and anxiety can be psychometrically distinguished, they do share an overlapping component of negative affect so relatively high correlations, around 0.7, should be expected. In the current study, the results for state anxiety seem on par with this theory, but the even higher correlation between depression and trait anxiety measures do pose a problem. Feldman (1993) argued that the high correlations observed suggest that depression and anxiety inventories do not measure distinct aspects of mood and supported this proposition using factor analysis. It is clear that, since anxiety and depression seem to be differently related to cognitive performance and parietal activity, further analysis of this question is required before the inconsistencies can be resolved. This emphasises the need for

studies to measure multiple aspects of depression and anxiety possible to account for differences between diagnoses and the effect this might have on the outcome measures.

In the current study, due to the pre-existing time components involved in the recording of spatial and verbal WM function and asymmetry of brain activity, it was decided that using several tests to characterise every type of anxiety was infeasible with depressed participants. Therefore, one aspect was chosen to investigate, the possible divergent impact of State and Trait anxiety, since this has been found to be related to parietal brain activity in past studies (e.g., Stewart et al., 2011). Although there was some indication that trait anxiety was more highly correlated with outcome measures than state anxiety, the depression and anxiety inventories used did not seem to provide enough specificity to truly distinguish anxiety from depression. Despite its widespread usage and general acceptance as a measure of anxiety, Watson et al. (1995) have criticised the content of the STAI suggesting it might be more characteristic of depression than anxiety. In future studies it is recommended that the impact of other types of anxiety be assessed or different dimensions of anxiety and depression, as characterised by the Tripartite model, be investigated. For example, using the Positive and Negative Affect Schedule (PANAS) might help to distinguish anxiety and depression if the Tripartite distinction between positive and negative affect holds.

A further issue to address is possible influence that subtypes of depression may have on cognitive and neurological correlates of depression. The existence of subtypes has long been posited but, as outlined in Chapter 1, no subtype system has ever received strong support. The wide variety of different symptoms and presentations of depression raises two possibilities. Firstly, depression may be better characterised by subtypes with different, possibly overlapping, symptoms and etiology and secondly that depression is a unitary condition with a high degree of heterogeneity. The current study attempted to address the matter of inconsistent results regarding WM performance in depression by addressing one

proposed subtype system where four subtypes of depression are characterised by dysfunction in each of the four quadrants of the brain. The current study did not find any support for a connection between different patterns of asymmetric brain activity in depression and WM performance. Given the concerns regarding measurement of depression and WM performance, further study is needed before this possibility can be discounted entirely. Future studies should attempt to replicate this finding and investigate if other possible subtype systems for depression could account for the inconsistencies in WM findings.

Depression may also be variable with respect to the functioning of its sufferers. Despite similar scores on depression inventories, some people with depression are relatively high-functioning compared to others and seem to be able to attend work, social activities, and even complete volunteer work though often reporting less enjoyment from these activities. Support for this possibility was found by Merikangas et al. (1994) who found that four proposed subtypes of depression differed in terms of the daily-life functioning of the members of that group. The current study, and many previous studies, relied on participants volunteering to participate by making direct contact after seeing an advertisement for the study. This means that the sample is more likely to be made up of high-functioning depressed individuals as they are more likely to see the advertisements and have the motivation to volunteer to participate. Increased motivation and approach behaviours are associated with increased left frontal activity, the opposite to the pattern of left hypofrontality predicted by the circumplex model of emotion. This could indicate that high-functioning depressed participants are a substantively different group from low-functioning depressed people who are less likely to volunteer to participate in research. Future studies are needed to investigate the impact of participant functionality using either a dual-recruitment method or by assessing the relative functionality of the participants.

A final concern with research on depression is the possible impact of medication use on the results. In the current study, 34 of the 36 currently depressed participants were taking antidepressants. The remaining two participants both showed relatively mild depression as indicated by the inventory scores. Therefore, no comparison could be made between a currently medicated and non-medicated group. Further a wide range of different medications were indicated including SSRI's, tricyclic antidepressants, and benzodiazepines making it nearly impossible to account for the possible influence that each type of medication may have had. Some past studies have attempted to address this concern by only recruiting non-medicated participants but it is unlikely that these participants represented depressed patients as a whole since they were likely to have less severe depression that did not require medication. Thibodeau et al. (2006) and Henriques and Davidson (1991) did not find any evidence that medication was related to effect size for frontal asymmetry in depressed adults. Ravnkilde et al. (2002) and Amado-Boccaro et al. (1995) found that most antidepressants do not influence cognitive function or may actually lead to some improvements. However, Porter et al. (2007) disputed this noting that benzodiazepines and antidepressants with anti-cholinergic properties may impair cognitive function. While it may be impossible to completely account for the influence of medication in studies of depression, medication use should be addressed as a possible source of variance, although in the current study this was not possible due to the high proportion of medicated participants.

Measuring working memory

Previous debate regarding the optimal method for measuring WM informed the use of multiple methods in the current study- the N-back task and the CST. Both tasks show good face validity as they both involve a storage and manipulation component fitting with the definition of WM. In the current study, these tasks were found to correlate only moderately, lower than would be expected if both tasks are measuring the same construct. In general a

correlation classed as 'strong' should be observed if two tasks measure the same construct (Miller, McIntire, & Lovler, 2011). Despite some subjectivity and different thresholds for what is considered to be a strong relationship, the results of the current study cannot be considered to show a strong correlation between N-back and CST using any accepted definition.

Verbal reports from participants indicated a possible cause of this finding. Many participants noted that during the N-back tasks, they would begin each trial by actively rehearsing and recalling all stimuli and attempting to update the memory string with each new stimulus. These reports seem to fit with the definition of WM as participants are storing stimuli and actively updating the contents of the memory string. However, participants also reported that during the trials they would frequently lose track of where they were and would have to switch to using a process of simple familiarity or recognition. Since recognition is not able to be employed during CST, as all stimuli are present during the memory test phase, this switch in strategy could account for the lower than expected correlation between the two task types. Since false alarm rates are likely to be higher if participants are utilising recognition memory, this provides a possible avenue for experimental investigation of this explanation.

A similarly low correlation between N-back and CST was found in numerous previous studies (e.g., Jaeggi et al., 2010; Kane et al., 2007; Oberauer, 2005; Roberts & Gibson, 2002). One concern with a number of these studies is the use of non-comparable stimulus modality. For example, Kane et al. (2007) compared Operation Span (a CST that is numerical and language-based) with an N-back task with letter stimuli and then use the difference in findings between the two measures to suggest poor validity. This comparison was confounded by the non-shared numerical component of the CST. Therefore, the current study used two versions of each task type, one with verbal stimuli and one with spatial

stimuli. The low correlation in the current study, even for consistent modality replicates the low correlations found in past studies. Until further research can reveal the true cause of the low correlation, both tasks should be used. Doing so will mean the results will remain relevant when/if the debate is resolved and will also assist in investigating the cause of the low correlation.

A number of past studies investigating cognitive function in depression have employed tasks that may capture a number of specific cognitive functions. For example, while the WCST has commonly been used as a measure of set-shifting ability, it can also be considered to measure WM as participants must retain their 'set' in active memory (Merriam et al., 1999). Inconsistent and null findings are not surprising in such studies as there are multiple sources of extra variability that has the potential to obscure results since depressed patients need not necessarily be impaired in all cognitive domains. The current study aimed to use relatively focussed WM tasks (N-back and CST) and the lack of WM deficits may indicate intact WM function in depression as found by a number of previous studies (e.g., Barch et al., 2003; Grant et al., 2001; Purcell et al., 1997; Zakzanis et al., 1998). However, the current study's findings are at odds with other research that found impaired WM (e.g., Beats et al., 1996; Channon et al., 1993; Harvey et al., 2004; Landro et al., 2001; Nebes et al., 2000; Porter et al., 2003; Reppermund et al., 2008). Similar findings have been observed in past studies of WM but have identified increased brain activity during the performance of these tasks suggesting that compensatory brain activity may help to maintain intact performance (e.g., Fitzgerald et al., 2008; Ravnkilde et al., 2003; Rose et al., 2006). No cognitive task is ever going to be a pure measure of a particular cognitive ability. The current study's WM tasks also involved psychomotor skills, information processing speed, decision making, and attention, all aspects of cognitive function which have been proposed to be impaired in depression despite varying experimental support (see Chapter 3). Such sources

of variability are unlikely to ever be truly removed from cognitive studies. While functional imaging studies using subtraction methodology may be useful in localising structures involved in WM, the issue of interpreting possible compensatory activity during functional imaging studies of depression remains a concern.

Measuring Brain Activity

The results of the current study did not support past findings of relatively reduced left frontal activity in depression. However, if one looks closely at past findings, there is a high degree of variability in the presence and strength of this effect (Thibodeau et al., 2006). Moderating factors have been found to include reference site, EEG recording period, and definition of depression (Thibodeau et al., 2006; see Chapter 2).

The findings from the current study pose a further problem. Theoretically, the use of EEG asymmetry metrics should balance out individual differences and absolute differences caused by different recording systems. This was not the case in the current study as significant differences in asymmetry score, at all three recording locations, were found between the two systems. Therefore, equipment failure may have led to the finding that results could be influenced by the recording system used. This finding is far from conclusive as there was as indication that the groups recorded on the different systems may not have been equivalent and there were differences in how the reference was calculated. Further investigation is warranted. If different systems could lead to different findings, this could account for some of the inconsistencies observed between past studies.

One limitation of the current study was the use of relative asymmetry measures. Absolute alpha activity can be strongly influenced by individual differences such as skull thickness and differences in reference impedance. When using EEG to measure asymmetrical brain activity, the use of an asymmetric metric, to cancel out the influence of

such differences, is required. While the asymmetry metric is able to indicate relative dominance of left or right locations, it cannot specify where the abnormal brain activity is occurring. For example, relative right dominance can indicate reduced left activity or increased right activity. In the current study, the relationship between asymmetry score and memory performance was assessed and no clear pattern emerged. This could indicate that lateralisation of activity is unrelated to WM performance or could be a result of the use of the asymmetry score to determine relative activation. Lateralisation of activity has been found to relate to performance (e.g., Henriques & Davidson, 1997) but relative levels of activity may be less important than absolute alpha activity. Further, although resting asymmetry was used in the current study as a way to circumvent concerns regarding compensatory activity, Rogers et al. (2004) noted that interpreting resting EEG activity in depressed individuals is hindered by depressive rumination during the rest period which may lead to an increase in the right frontal activity since, as described by the circumplex model of emotion, right frontal activity is associated with negative thoughts and withdrawal-motivated emotions. Therefore, it is possible that previous studies finding increased resting right frontal activity in depressed participants may actually have been a result of depressive rumination occurring during the recording session.

Another possible cause for the lack of observed relationship between performance and cortical brain activity is that perhaps subcortical regions, not measured during EEG, may be more important for WM performance. Although spatial WM has been associated with right frontal activity and verbal WM has been associated with left frontal activity, this activity may not be necessary for successful accomplishment of the tasks, rather it may be supplementary. Use of fMRI could help to investigate this suggestion further but the cost and time involved may well be too great to prevent a large enough sample to be used to observe an effect.

A further issue, not commonly addressed in EEG research, relates to the rejection of artefacts. Since electrical activity produced by muscle and eye movements is much larger than electrical activity that can be recorded from the brain, and since electrical activity produced by eye movements can distort waveform analysis from scalp electrodes, especially at frontal sites, epochs containing such artefacts must be removed before data analysis can proceed. In some cases, participants may be fidgety or distracted by the eye electrodes showing in their peripheral vision resulting in a high number of artefacts. Despite requesting that participants remain as still as possible during the recording period, high numbers of artefacts can and did occur. How many artefacts are too many for the data to remain usable after artefact rejection has taken place? There does not seem to be any agreement or particular threshold or criteria for making this decision. Very few studies even mention the proportion of epochs rejected. As seen in the current study, the percentage of epochs that are retained can vary widely (refer to Appendix E).

Both depression and anxiety disorders can lead to psychomotor agitation and tension increasing the number of artefacts (Beck & Alford, 2009). Although there were no differences in the number of artefacts removed from the control and depressed participant groups in the current study, further consideration of this problem is required. Results based on a smaller amount of data are more likely to be influenced by random fluctuations or spurious data. Therefore, when more artefacts are rejected, the data may become less reliable. There was no correlation between the number of epochs rejected and the EEG asymmetry scores in the current study but this does not necessarily suggest that the data were not affected; only that they were not influenced in a systematic manner by artefact rejection. Further study is needed to determine the impact of rejection of a large proportion of artefacts and how this should be managed in future asymmetry research.

As outlined at the beginning of this section, the findings of the current study demonstrated remarkable inconsistency even with slightly different methods of assessing the same construct. Further, all effect sizes were relatively small although this may be a result of low power. Given the apparent small size and inconsistency of the asymmetry effects, the question of utility of the asymmetry measure comes into question. Unless the measures can be improved to make the data less noisy, a large sample may be required to see clearer trends in the data. The presence of inconsistencies reduces the ability of asymmetry scores to act as a biomarker for depression as proposed by Stewart et al. (2010). Additionally, TMS may be of limited use as a treatment, especially given evidence from the current study that asymmetry might not be related to functional deficits.

Conclusions

Despite attempting to account for a number of sources of variability, such as subtypes and anxiety, the findings from the current study only add to the already inconsistent literature regarding the presence of altered brain activity and cognitive deficits in depression. The inconsistencies regarding the presence and strength of both asymmetrical brain activity in depression, and cognitive impairment in depression suggests two possibilities. The first is that the true effect size is small and that a large sample size is required to detect it reliably. Although some smaller sample research has detected moderate effects, it is possible that these are chance findings and that the number of studies finding non-significant effects is underestimated due to publication bias. Recruiting large samples of clinically depressed participants for a relatively intensive data collection process is challenging so a key focus for further investigation should be to reduce the amount of noise in the data by addressing factors raised in the above discussion such as subtypes of anxiety, distinguishing between anxiety

and depression, and utilising multiple methods of measuring cognitive function. The current study addressed the possibility that subtypes of depression, characterised by abnormal activity in each of the quadrants of the brain, might account for some of the noise in previous studies. Although no support was found for this, it remains possible that other subtype systems could account for the inconsistencies and future research should address other proposed subtype systems to address this possibility. Another interpretation of the inconsistencies within the current study and in past studies is that resting frontal asymmetry in depression does not exist. It is possible that the observed right frontal dominance may be a result of rumination that might lead to increased right frontal activity during resting recordings. Alternatively, resting frontal asymmetry as a vulnerability marker for depression may not actually be related to functional performance if abnormal resting asymmetry does not persist during cognitive tasks.

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Appendix A

Copy of Depression History Survey

[The Blue Brain: The Effects of Asymmetric Brain Activity in Depression on Complex Short Term Memory

Participant Questionnaire

Please try to answer all questions to the best of your ability. If you are unable or do not wish to answer a question just leave it blank and continue on.

1) Are you Male/Female? (Please circle one)

2) How old are you?

3) Which hand do you write with?

Right/Left (please circle one)

4) Have you ever been diagnosed with depression?

If no, please continue to question 7.

Yes/No (Please circle one)

5) If yes to question 4 did you take any medication for depression?

If no, please continue to question 7.

Yes/No (please circle one)

6) If yes to question 5, which medication were you taking?

7) Have you ever been diagnosed with Anxiety Disorder?

Yes/No (please circle one)

8) Have you ever suffered a traumatic brain injury?

Yes/No (Please circle one)

Thanks for your time.

Please ensure you write your participation number on the top left of this page
(If you're unsure please ask the researcher)

Appendix B

Supplementary Descriptive Statistics

Table B-1
Descriptive Statistics for Asymmetry Metrics for Lateral and Medial Frontal Sites and Parietal site for Never, Currently, and Previously Depressed Groups

| Asymmetry | | | | |
|----------------|----------------------|----------|----------|-----------|
| Location | Group | <i>N</i> | <i>M</i> | <i>SD</i> |
| F7/F8 Lateral | Never Depressed | 30 | -0.15 | 0.22 |
| | Currently Depressed | 36 | -0.10 | 0.27 |
| | Previously Depressed | 11 | -0.07 | 0.26 |
| F3/F4 Medial | Never Depressed | 30 | 0.005 | 0.22 |
| | Currently Depressed | 36 | 0.09 | 0.26 |
| | Previously Depressed | 11 | 0.24 | 0.42 |
| P3/P4 Parietal | Never Depressed | 30 | 0.13 | 0.32 |
| | Currently Depressed | 35 | 0.13 | 0.32 |
| | Previously Depressed | 11 | 0.30 | 0.38 |

Table B-2.

Descriptive Statistics for Never, Currently, and Previously Depressed Groups Split by EEG System for Both Medial And Lateral Frontal Asymmetry Scores

| EEG System | Depressed Group | <i>N</i> | Medial Frontal | | | Lateral Frontal | | |
|------------|----------------------|----------|----------------|-----------|------------------------|-----------------|-----------|------------------------|
| | | | <i>M</i> | <i>SD</i> | <i>SD</i> ² | <i>M</i> | <i>SD</i> | <i>SD</i> ² |
| Neuroscan | Never Depressed | 16 | -0.08 | 0.11 | 0.01 | -0.21 | 0.26 | 0.07 |
| | Currently Depressed | 8 | -0.08 | 0.10 | 0.01 | -0.17 | 0.19 | 0.04 |
| | Previously Depressed | 4 | 0.20 | 0.56 | 0.31 | -0.26 | 0.33 | 0.11 |
| ADI | Never Depressed | 14 | 0.10 | 0.27 | 0.07 | -0.09 | 0.15 | 0.02 |
| | Currently Depressed | 28 | 0.13 | 0.27 | 0.07 | -0.07 | 0.29 | 0.08 |
| | Previously Depressed | 7 | 0.27 | 0.37 | 0.14 | 0.04 | 0.14 | 0.02 |

Table B-3.

Descriptive Statistics for High and Low Anxiety Depressed Groups and Non-Depressed Group's Parietal Asymmetry Scores When Grouped Using State or Trait Anxiety Scores

| Anxiety Group | <i>N</i> | State Anxiety | | | Trait Anxiety | | | |
|------------------------------|----------|---------------|-----------|------------------------|---------------|----------|-----------|------------------------|
| | | <i>M</i> | <i>SD</i> | <i>SD</i> ² | <i>N</i> | <i>M</i> | <i>SD</i> | <i>SD</i> ² |
| Low Anxiety Depressed Group | 9 | 0.08 | 0.40 | 0.16 | 9 | 0.10 | 0.42 | 0.18 |
| High Anxiety Depressed Group | 10 | 0.14 | 0.25 | 0.06 | 9 | 0.07 | 0.30 | 0.09 |
| Non-Depressed Group | 41 | 0.17 | 0.34 | 0.12 | 41 | 0.17 | 0.34 | 0.12 |

Note. Low sample sizes in depressed groups due to taking the top and bottom 25% of STAI scores for depressed participants.

Table B-4.
Descriptive Statistics for Working Memory Task Performance (z-Scores) in Currently, Never, and Previously Depressed Groups

| WM Task | Never Depressed | | Currently Depressed | | Previously Depressed | |
|-----------------------|-----------------|-----------|---------------------|-----------|----------------------|-----------|
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Verbal Span Absolute | 0.21 | 0.97 | -0.04 | 0.93 | -0.45 | 1.22 |
| Verbal Span Total | 0.23 | 0.97 | -0.05 | 0.96 | -0.48 | 1.11 |
| Spatial Span Absolute | -0.04 | 0.88 | 0.11 | 1.04 | -0.25 | 1.20 |
| Spatial Span Total | 0.06 | 0.88 | 0.08 | 1.05 | -0.42 | 1.15 |
| Verbal 2-back | 0.14 | 0.79 | -0.01 | 1.09 | -0.35 | 1.20 |
| Verbal 3-back | -0.08 | 0.67 | 0.16 | 1.03 | -0.31 | 1.55 |
| Verbal N-back Mean | 0.03 | 0.72 | 0.08 | 1.05 | -0.37 | 1.45 |
| Spatial 2-back | 0.13 | 0.66 | 0.00* | 1.16 | -0.36 | 1.21 |
| Spatial 3- back | 0.15 | 0.68 | 0.02 | 1.21 | -0.47 | 0.93 |
| Spatial N-back Mean | 0.14 | 0.63 | 0.01 | 1.20 | -0.43 | 1.07 |

Note. Never Depressed $N=31$, Currently Depressed $N=36$, Previously Depressed $N=11$

* $M=0.0002$

Table B-5.
z-Score Working Memory Task Descriptive Statistics for Depressed and Control Groups Subtyped by Medial Frontal Asymmetry Scores

| WM Task | Control Left | | Control Right | | Depressed Left | | Depressed Right | |
|-----------------------|--------------|-----------|---------------|-----------|----------------|-----------|-----------------|-----------|
| | Dominant | | Dominant | | Dominant | | Dominant | |
| | (N=22) | | (N=19) | | (N=20) | | (N=16) | |
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Verbal Span Total | -0.43 | 1.13 | 0.57 | 0.62 | -0.18 | 1.11 | 0.11 | 0.73 |
| Verbal Span Absolute | -0.40 | 1.08 | 0.53 | 0.87 | -0.12 | 1.03 | 0.06 | 0.81 |
| Spatial Span Total | -0.28 | 1.10 | 0.17 | 0.76 | 0.23 | 1.02 | -0.10 | 1.08 |
| Spatial Span Absolute | -0.26 | 1.04 | 0.07 | 0.89 | 0.19 | 0.87 | 0.01 | 1.24 |
| Verbal 2-back | -0.15 | 1.01 | 0.12 | 0.78 | 0.12 | 0.97 | -0.18 | 1.24 |
| Verbal 3-back | -0.48 | 0.91 | 0.20 | 0.92 | 0.05 | 1.13 | 0.30 | 0.91 |
| Verbal N-back Mean | -0.35 | 0.96 | 0.18 | 0.88 | 0.10 | 1.07 | 0.07 | 1.06 |
| Spatial 2-back | -0.12 | 0.95 | 0.11 | 0.75 | -0.02 | 1.25 | 0.02 | 1.08 |
| Spatial 3-back | -0.12 | 0.83 | 0.09 | 0.77 | -0.28 | 1.41 | 0.38 | 0.80 |
| Spatial N-back Mean | -0.12 | 0.88 | 0.10 | 0.73 | -0.15 | 1.36 | 0.21 | 0.96 |

Table B-6.
z-Score Working Memory Task Descriptive Statistics for Depressed and Control Groups Subtyped by Lateral Frontal Asymmetry Scores

| WM Task | Control Left | | Control Right | | Depressed Left | | Depressed Right | |
|-----------------------|--------------|-----------|---------------|-----------|----------------|-----------|-----------------|-----------|
| | Dominant | | Dominant | | Dominant | | Dominant | |
| | (N=15) | | (N=26) | | (N=13) | | (N=23) | |
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Verbal Span Total | -0.13 | 0.88 | -0.13 | 1.14 | 0.07 | 1.24 | -0.12 | 0.78 |
| Verbal Span Absolute | -0.32 | 1.01 | 0.23 | 1.09 | 0.18 | 1.09 | -0.17 | 0.81 |
| Spatial Span Total | -0.10 | 1.03 | -0.06 | 0.96 | 0.29 | 1.12 | -0.04 | 1.01 |
| Spatial Span Absolute | -0.06 | 1.06 | -0.13 | 0.94 | 0.35 | 1.11 | -0.03 | 1.00 |
| Verbal 2-back | -0.16 | 1.10 | 0.05 | 0.79 | 0.23 | 0.99 | -0.15 | 1.15 |
| Verbal 3-back | -0.52 | 1.04 | 0.04 | 0.87 | 0.33 | 0.71 | 0.06 | 1.18 |
| Verbal N-back Mean | -0.38 | 1.13 | 0.05 | 0.81 | 0.32 | 0.83 | -0.05 | 1.15 |
| Spatial 2-back | -0.05 | 0.75 | 0.01 | 0.93 | -0.01 | 1.44 | 0.01 | 1.01 |
| Spatial 3-back | 0.07 | 0.63 | -0.07 | 0.89 | -0.12 | 1.58 | 0.09 | 0.98 |
| Spatial N-back Mean | 0.01 | 0.66 | -0.03 | 0.90 | -0.07 | 1.56 | 0.05 | 0.98 |

Table B-7.
z-Score Working Memory Task Descriptive Statistics for Depressed and Control Groups Subtyped by Parietal Asymmetry Scores

| WM Task | Control Left | | Control Right | | Depressed Left | | Depressed Right | |
|-----------------------|--------------|-----------|---------------|-----------|----------------|-----------|-----------------|-----------|
| | Dominant | | Dominant | | Dominant | | Dominant | |
| | (N=31) | | (N=10) | | (N=23) | | (N=12) | |
| | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> | <i>M</i> | <i>SD</i> |
| Verbal Span Total | -0.08 | 1.01 | 0.37 | 1.15 | -0.24 | 1.08 | 0.35 | 0.61 |
| Verbal Span Absolute | -0.11 | 1.03 | 0.45 | 1.19 | -0.18 | 1.00 | 0.31 | 0.68 |
| Spatial Span Total | -0.04 | 1.03 | -0.17 | 0.85 | -0.04 | 1.11 | 0.25 | 0.95 |
| Spatial Span Absolute | -0.06 | 0.97 | -0.23 | 1.03 | -0.14 | 0.94 | 0.57 | 1.15 |
| Verbal 2-back | 0.03 | 0.96 | -0.20 | 0.73 | -0.04 | 1.16 | 0.16 | 0.95 |
| Verbal 3-back | -0.17 | 1.04 | -0.15 | 0.69 | 0.06 | 1.22 | 0.38 | 0.56 |
| Verbal N-back Mean | -0.07 | 1.02 | -0.20 | 0.70 | 0.01 | 1.21 | 0.30 | 0.68 |
| Spatial 2-back | -0.03 | 0.94 | 0.03 | 0.56 | -0.11 | 1.27 | 0.24 | 0.99 |
| Spatial 3-back | -0.01 | 0.80 | -0.07 | 0.81 | -0.21 | 1.40 | 0.47 | 0.65 |
| Spatial N-back Mean | -0.20 | 0.86 | -0.02 | 0.69 | -0.17 | 1.35 | 0.37 | 0.83 |

Table B-8.
Descriptive Statistics for Depression and Anxiety Inventories in the Never, Currently, and Previously Depressed Groups

| Group | BDI-II | HDI-SF | State Anxiety | Trait Anxiety |
|---------------------|---------------|---------------|---------------|---------------|
| | <i>M (SD)</i> | <i>M (SD)</i> | <i>M (SD)</i> | <i>M (SD)</i> |
| Never | | | | |
| Depressed (N=31) | 5.26 (3.74) | 3.03 (1.97) | 30.45 (6.28) | 34.48 (7.05) |
| Currently | | | | |
| Depressed (N=35) | 25.58 (9.33) | 12.68 (5.00) | 45.19 (11.90) | 57.56 (11.26) |
| Previously | | | | |
| Depressed (N=11) | 6.81 (4.38) | 4.45 (2.38) | 36.82 (7.65) | 41.27 (7.27) |

Appendix C

Data Distributions

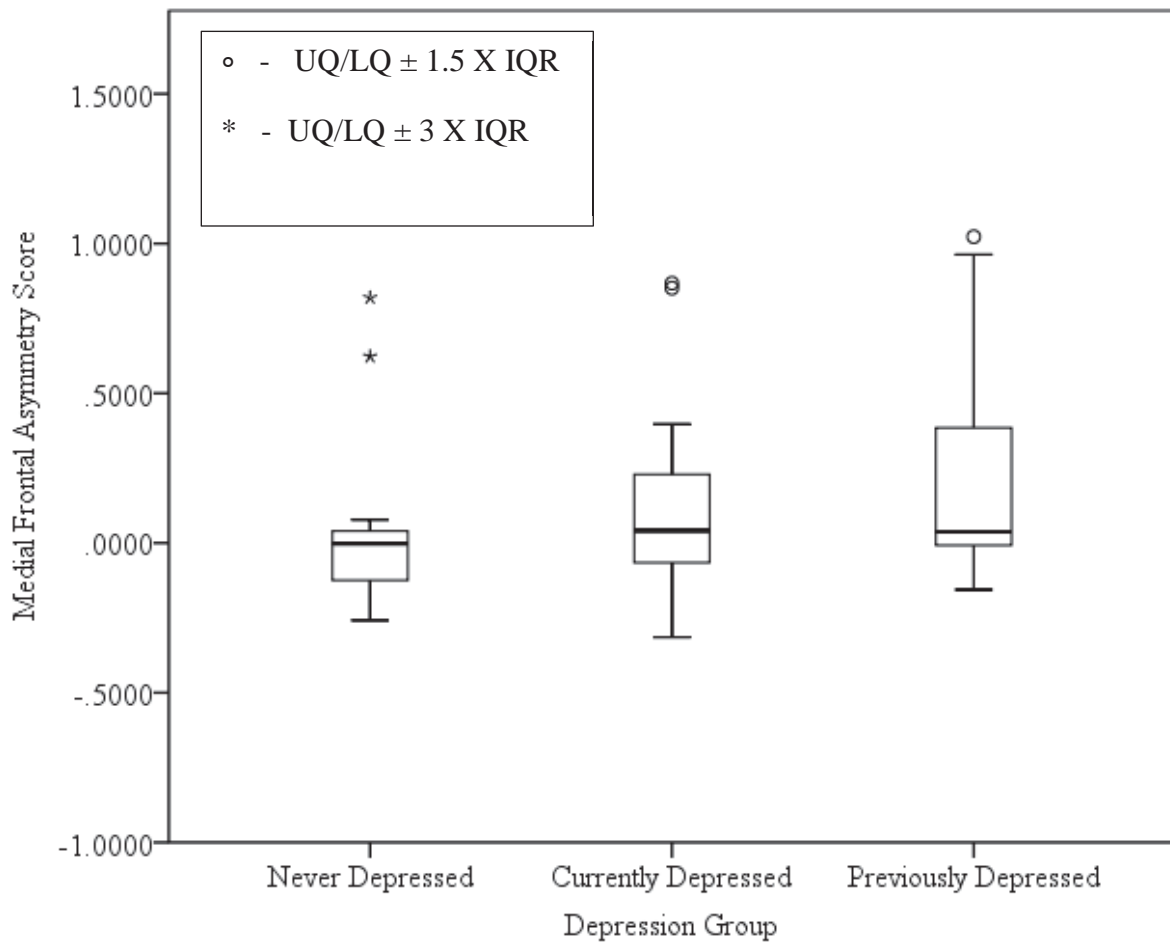


Figure C-1. Distribution of Medial Frontal Asymmetry Scores in the Never, Currently, and Previously Depressed Groups.

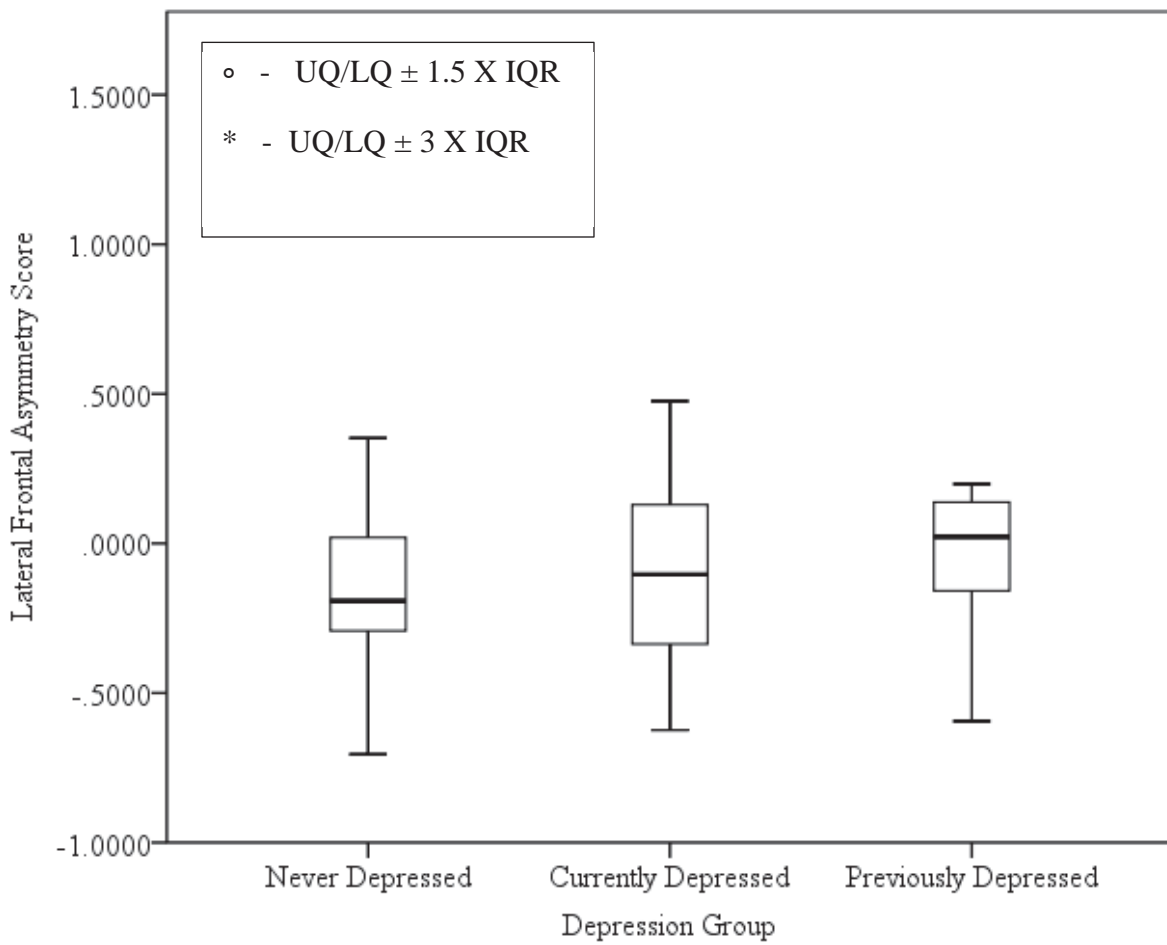


Figure C-2. Distribution of Lateral Frontal Asymmetry Scores in the Never, Currently, and Previously Depressed Groups.

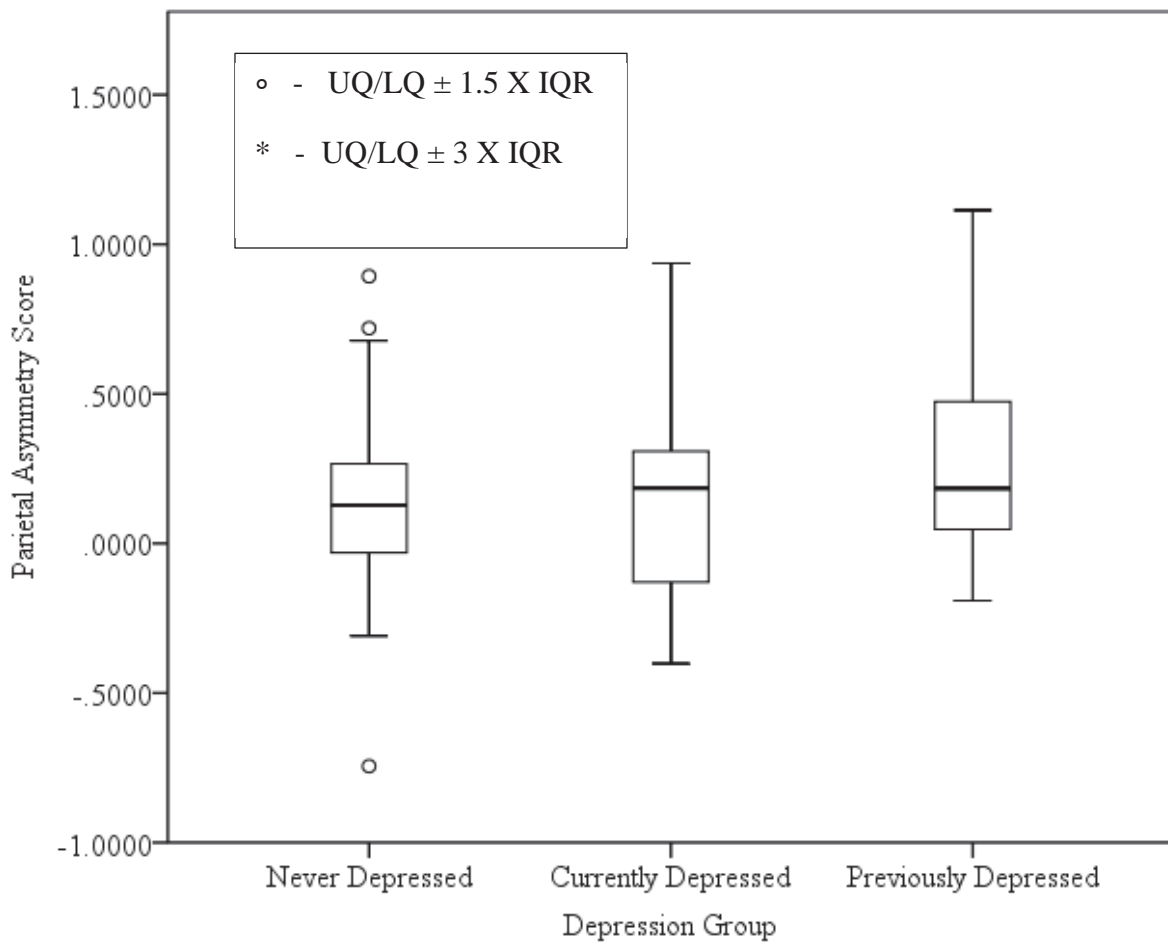


Figure C-3. Distribution of Parietal Asymmetry Scores in the Never, Currently, and Previously Depressed Groups.

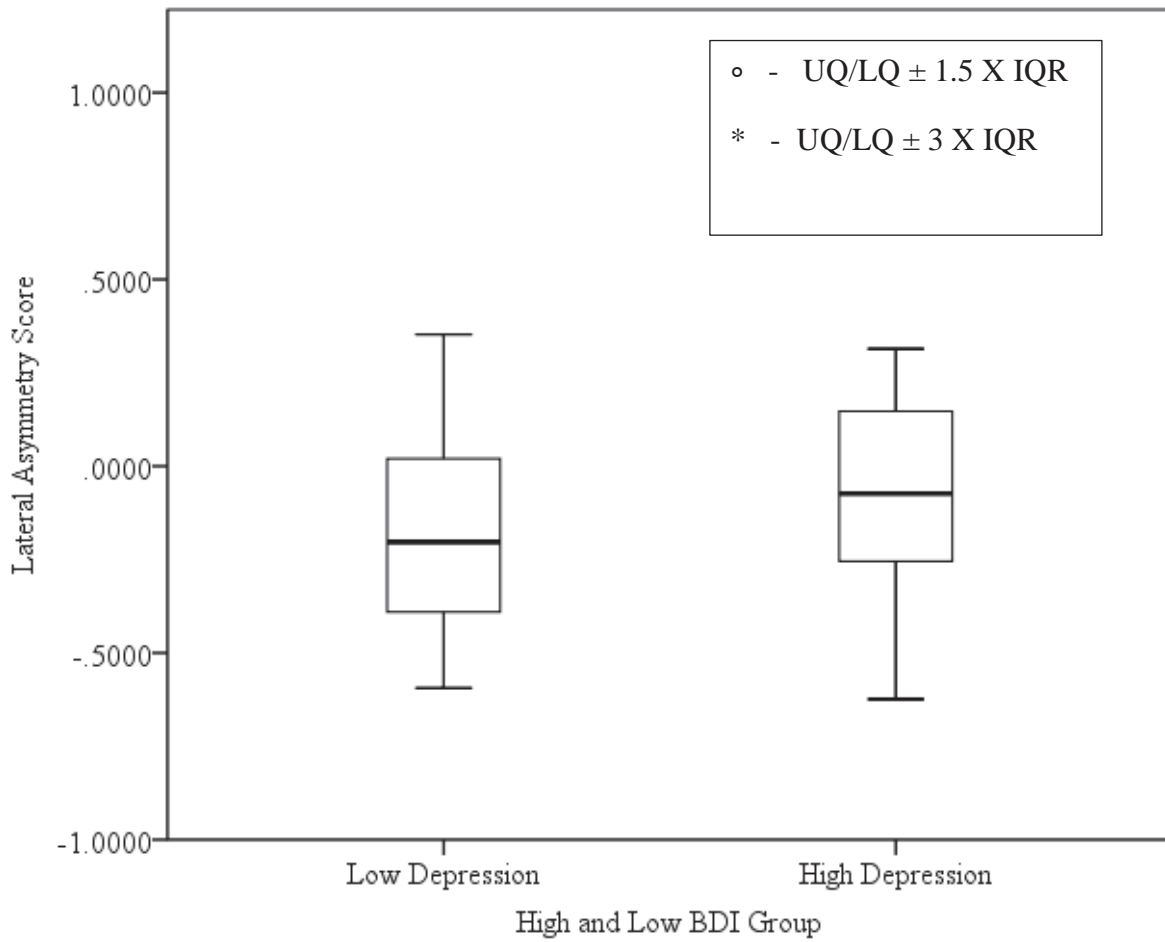


Figure C-4. Distribution of Lateral Frontal Asymmetry Scores in the Low and High Depression groups.

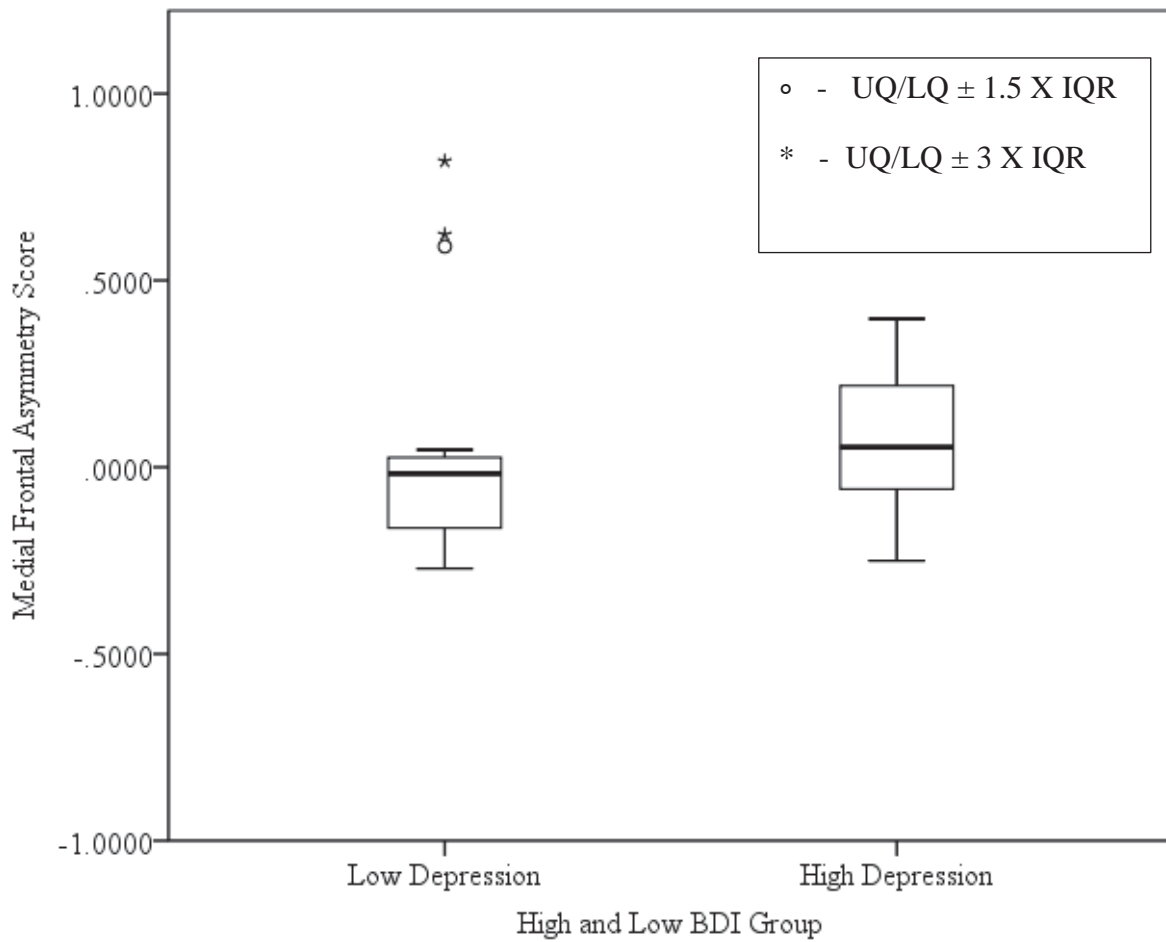


Figure C-5. Distribution of Medial Frontal Asymmetry Scores in the Low and High Depression groups.

Appendix D

Comparisons of EEG asymmetry scores between EEG recording systems

Due to equipment failure, two EEG systems were used during the collection of these data. Despite no obvious theoretical reason, there appears to be significant differences between the asymmetry scores recorded on the two systems. The original Neuroscan system consistently recorded relatively more right dominant activity as displayed in Table D-1.

Table D-1
Descriptive Statistics for Comparison of Neuroscan and ADI EEG Recording Systems

| | Neuroscan | | | ADI | | |
|---------------------------------|-----------|-----------|----------|----------|-----------|----------|
| | <i>M</i> | <i>SD</i> | <i>N</i> | <i>M</i> | <i>SD</i> | <i>N</i> |
| Lateral Frontal Asymmetry Score | -0.20 | 0.24 | 28 | -0.06 | 0.24 | 49 |
| Medial Frontal Asymmetry Score | -0.04 | 0.23 | 28 | 0.14 | 0.29 | 49 |
| Parietal Asymmetry Score | 0.07 | 0.33 | 28 | 0.20 | 0.32 | 48 |
| Percentage of Epochs Retained | 53.73 | 19.65 | 22 | 58.65 | 16.05 | 49 |

A significant difference between ADI and Neuroscan systems was found for both lateral frontal ($t(75)=-2.43$, $p=.02$, $d=0.58$) and medial frontal ($t(75)=-2.95$, $p=.004$, $d=0.70$) asymmetry scores with large effect sizes. A similar effect was apparent at the parietal recording sites ($t(74)=-1.74$, $p=.09$, $d=0.41$) with a moderate effect size. To ensure that these differences did not arise due to differences in the number of epochs retained following artefact removal, a t -test was conducted comparing the mean percentage of epochs retained (averaged across the four recording blocks) and no significant differences were observed

($t(69)=-1.11, p=.27, d=0.29$). However, a weak/moderate effect size indicated that more epochs were retained on the ADI system than the Neuroscan system. This could indicate that the data recorded on the ADI system was more reliable as the asymmetry scores were based on a greater number of epochs but it is unclear why this difference may have occurred. It may be a result of the smaller number of participants collected on the Neuroscan system. As a result, individual participants' data that required substantial artefact removal, are likely to have influenced the mean results more than in the ADI system results.

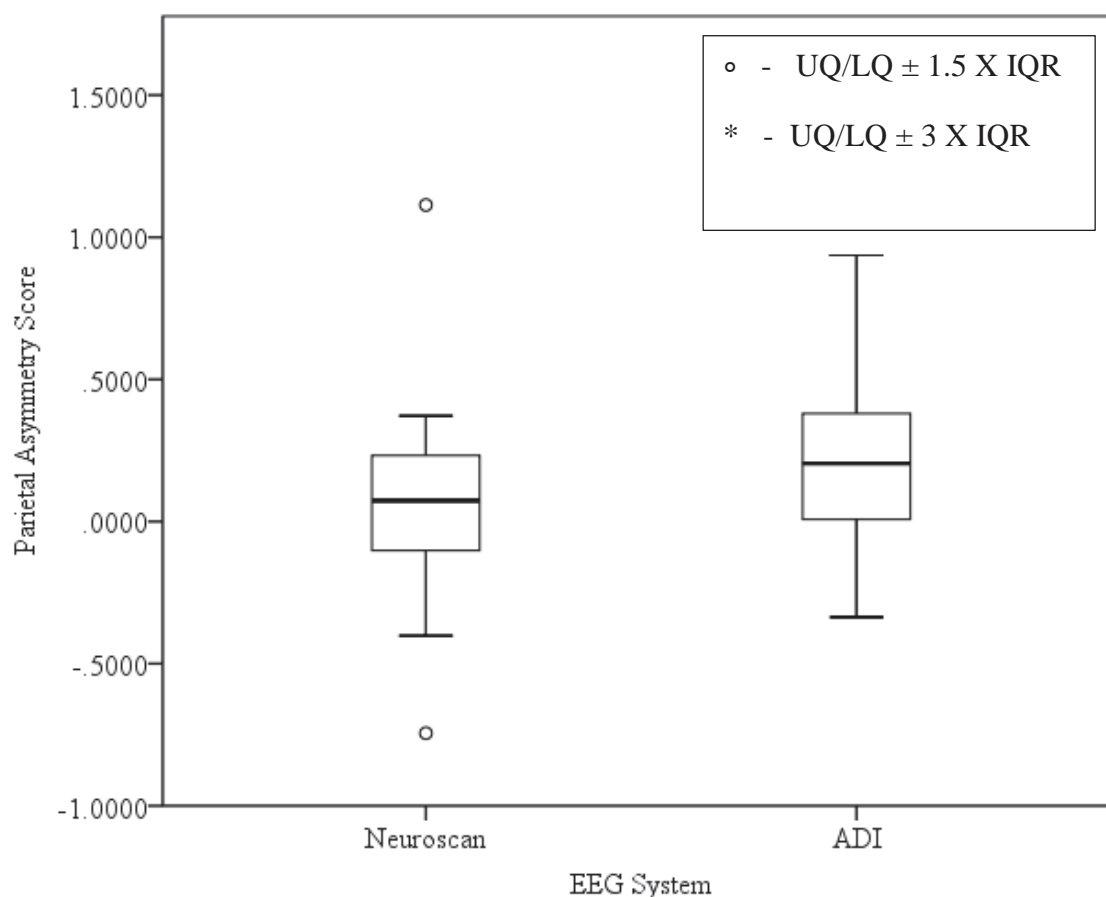


Figure D-1. A Comparison of the Distribution of Parietal Asymmetry Scores Recorded on the Neuroscan and ADI EEG-Systems.

A visual comparison of the distributions of the asymmetry scores for all three recording sites on the Neuroscan and ADI system is provided in Figures D-1, D-2, and D-3.

Despite the Neuroscan system consistently recording lower asymmetry scores, the data from both systems do show substantial overlap. Therefore, it is unclear whether the differences in the distributions are a result of genuine differences in the recorded data or partly due to the smaller number of scores examined on the Neuroscan system. It is also possible that the participants collected on the original Neuroscan system were different from the participants recorded on the ADI system. Since previous research has indicated a correlation between asymmetry scores and season (Peterson & Harmon-Jones, 2009), possible order effects may have occurred since the Neuroscan data collection occurred primarily during Autumn 2013 while the ADI data were primarily recorded during Spring 2013 (See Figure D-4 for a comparison of recording season). While some previous studies have described a possible moderating effect of season on EEG alpha asymmetry (Peterson & Harmon-Jones, 2009), other studies have not been able to replicate this finding (Velo, Stewart, Hasler, Towers, & Allen, 2012) so it is unclear the extent to which recording season may have influenced the data. Additionally, although alpha asymmetry is thought to be a relatively stable, trait-like metric, other factors correlated with time of year such as study-related stress may also have influenced the recordings.

In Figures D-1 to D-3, extreme scores are indicated by circles defined as points more than 1.5 times further than the IQR from the upper or lower quartile. The most extreme scores are indicated by stars and are defined as being more than 3 times further than the IQR from the upper or lower quartile. The extreme scores identified were still within the tail-end of the distribution usually recorded with asymmetry scores which makes it impossible to tell if they are genuine data points at the tail-end of the expected distribution or whether they are abnormalities that should be removed from the analysis. To check to see if the presence of these extreme scores may account for the differences observed between the EEG recording systems, the comparison of EEG asymmetry scores between the two systems was repeated

with the extreme scores excluded. Note that there were no extreme scores to remove for the lateral frontal recording site. Once extreme scores were removed, the effect size of the system difference for both medial frontal ($t(68) = -4.06, p = .000, d = 1.00$) and parietal ($t(72) = -2.03, p = .05, d = 0.49$) recording sites actually became larger which suggests that the extreme scores were not responsible for the differences between the recording systems (see Table D-2 for descriptive statistics). Since the extreme scores were in the tail-end of what is expected, and there is no reason to suspect these recordings were abnormal/outliers, these data-points have not been excluded from any other analysis in this report.

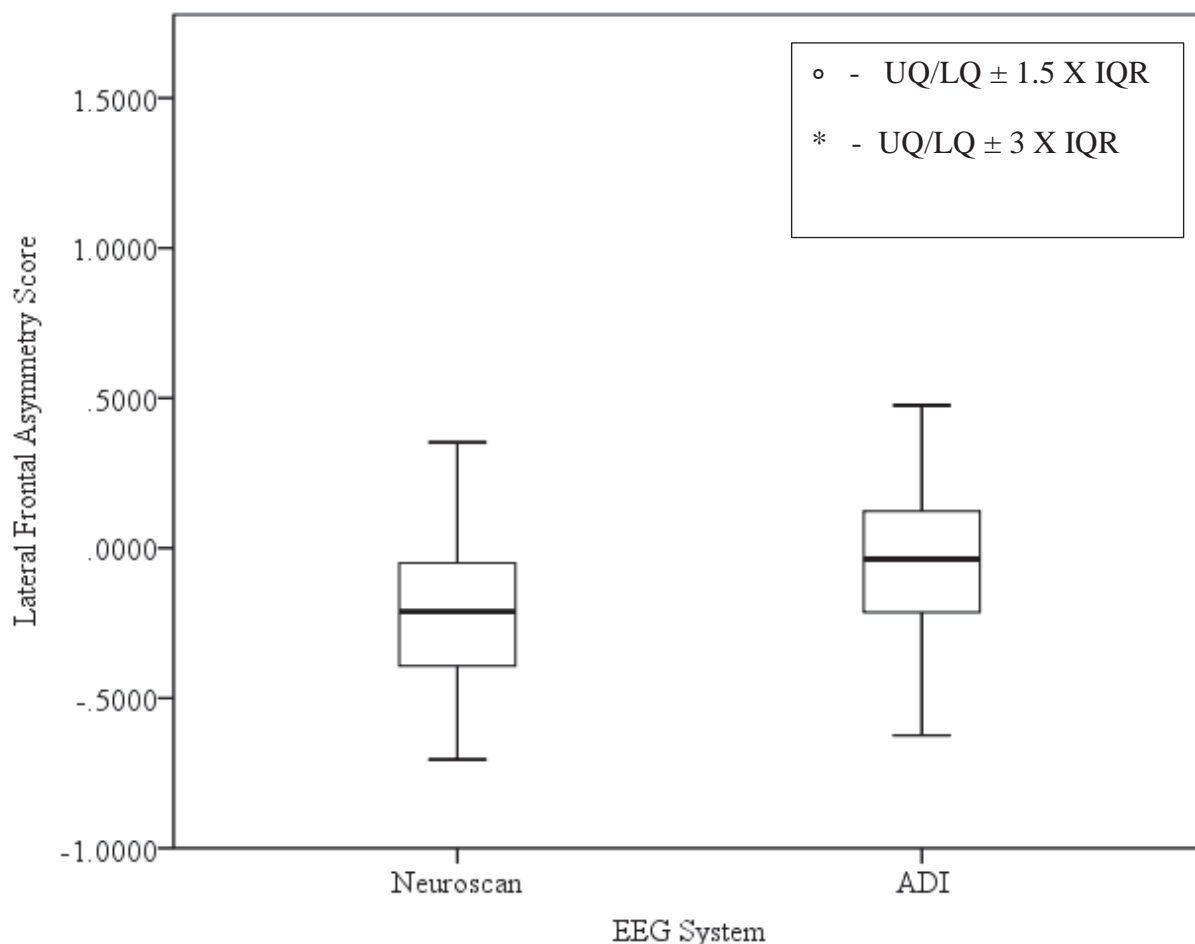


Figure D-2. A Comparison of the Distribution of Lateral Frontal Asymmetry Scores Recorded on the Neuroscan and ADI EEG Recording Systems.

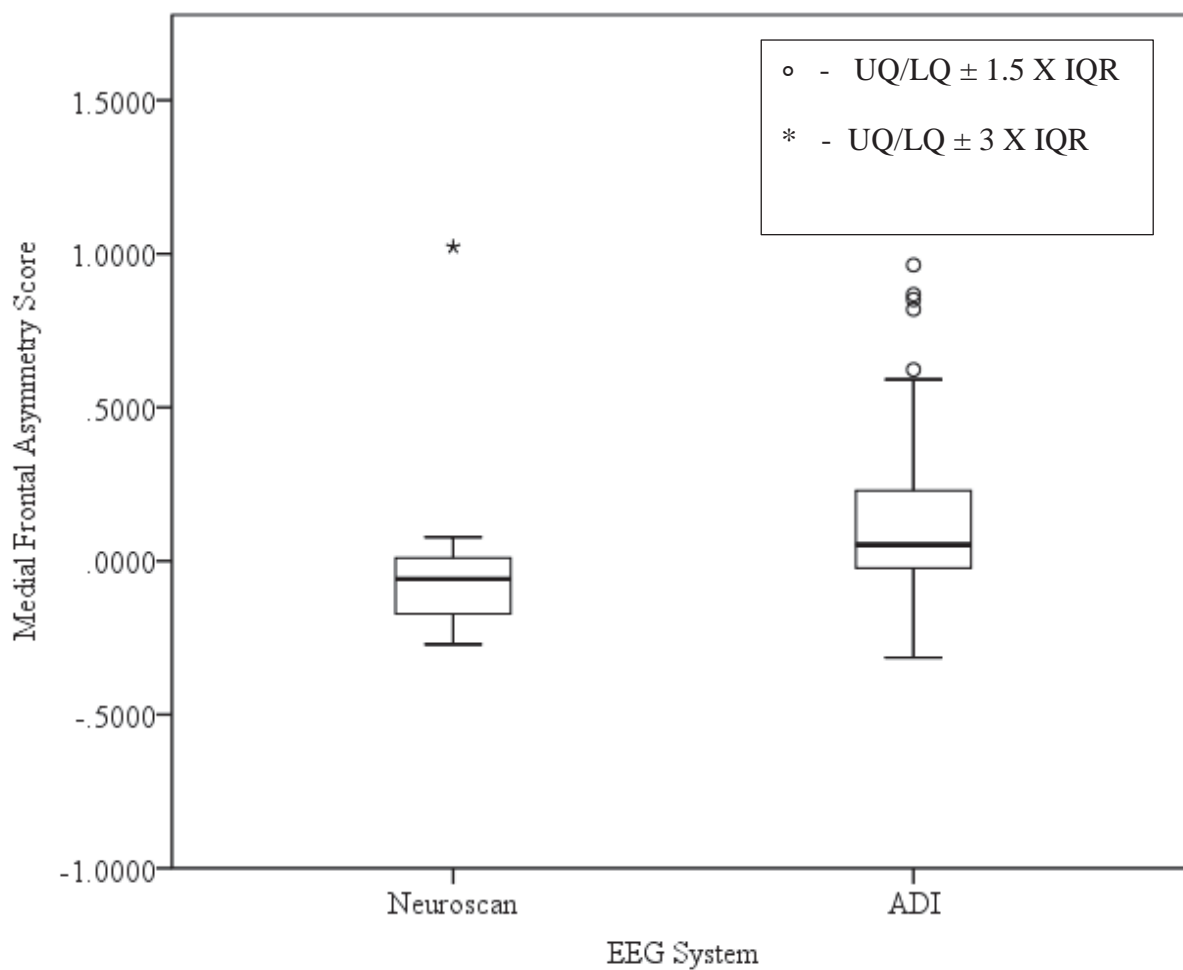


Figure D-3. A Comparison of the Distribution of Medial Frontal Asymmetry Scores Recorded on the Neuroscan and ADI EEG Recording Systems.

Table D-2

Descriptive Statistics for Comparison of Neuroscan and ADI EEG Recording Systems With Extreme Scores Removed

| | Neuroscan | | | ADI | | |
|--------------------------------|-----------|-----------|----------|----------|-----------|----------|
| | <i>M</i> | <i>SD</i> | <i>N</i> | <i>M</i> | <i>SD</i> | <i>N</i> |
| Medial Frontal Asymmetry Score | -0.08 | 0.10 | 27 | 0.05 | 0.16 | 43 |
| Parietal Asymmetry Score | 0.06 | 0.21 | 26 | 0.20 | 0.32 | 48 |

To help clarify the potential effect of the EEG system differences on the asymmetry scores, the frequency of left and right dominant participants was calculated for both systems (refer to Table D-3). Unsurprisingly, there were a substantially greater proportion of right dominant participants on the Neuroscan system.

Table D-3

Comparison of Left and Right Dominant Asymmetry Scores for Neuroscan and ADI Recording Systems for Medial, Lateral, and Parietal Recording Sites

| | | Left Dominant | | Right Dominant | |
|----------|-----------|---------------|-------|----------------|-------|
| | | N | % | N | % |
| Medial | Neuroscan | 8 | 28.57 | 20 | 71.43 |
| | ADI | 34 | 69.39 | 15 | 30.61 |
| Lateral | Neuroscan | 5 | 17.86 | 23 | 82.14 |
| | ADI | 23 | 46.94 | 26 | 53.06 |
| Parietal | Neuroscan | 17 | 60.71 | 11 | 39.29 |
| | ADI | 37 | 77.08 | 11 | 22.92 |

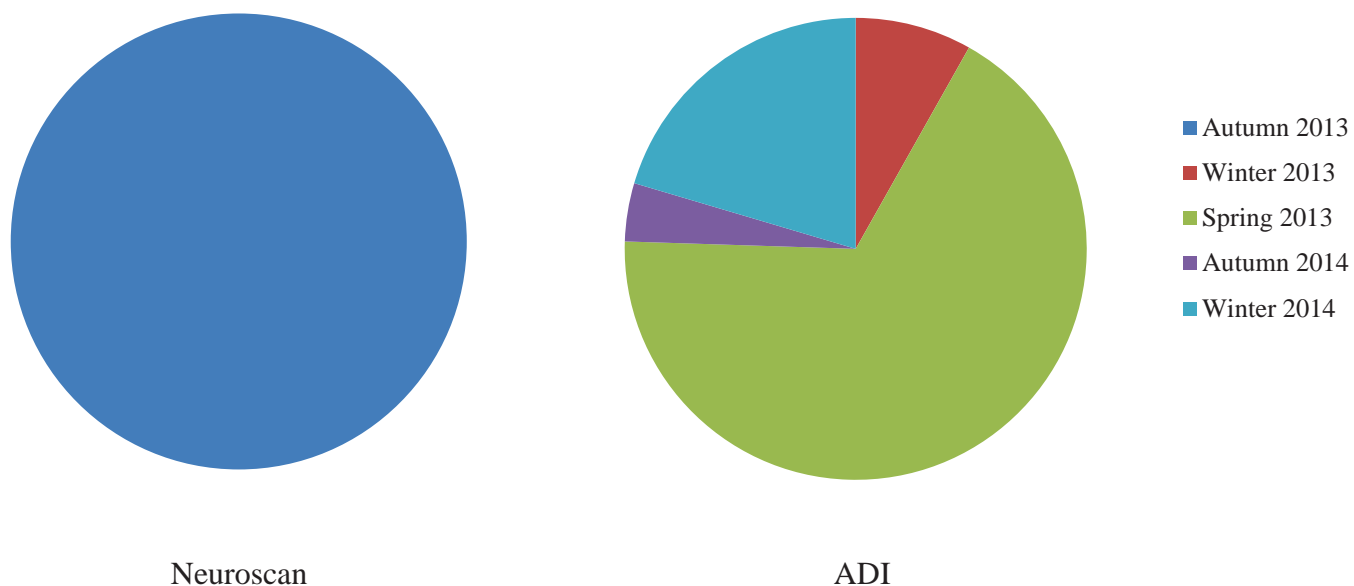


Figure D-4. A comparison of season of collection for the Neuroscan and ADI EEG systems.

It is possible that the participants whose data was collected on the Neuroscan and ADI systems may have been different in some other variable that could account for the system differences. In order to investigate this possibility, the participants recorded on the two systems were compared in terms of their age, BDI-II scores, HDI-SF scores, State Anxiety scores, and Trait Anxiety Scores. There were no differences in the average age of participants recorded on the two systems ($t(75)=0.64, p=.53, d=0.15$). However, all other analyses revealed substantial group differences. A comparison of the participants sampled using the first and second systems revealed a significant difference in BDI-II scores ($t(74.68)=-2.84, p=.01, d=0.67$) with participants on the ADI system ($N=49, M=17.57, SD=13.33$) scoring significantly higher on the BDI-II than the participants tested using the Neuroscan system ($N=28, M=10.64, SD=8.08$) with a moderate/strong effect size. Note that Levene's test of homogeneity of variance was violated ($F=12.73, p=.001$) so the corrected test using the Welch-Satterthwaite method was employed. Similar results were observed with the HDI-SF scores with participants on the ADI system ($N=49, M=9.07, SD=6.56$) showing significantly higher scores on the HDI-SF than participants recorded using the Neuroscan system ($N=28, M=5.44, SD=3.89$) ($t(74.86)=-3.05, p=.003, d=0.72$) with a large effect size. Levene's test was also violated for the HDI-SF analysis ($F=9.97, p=.002$) so the Welch-Satterthwaite method was used.

A significant difference was also found in trait anxiety with participants recorded using the ADI system ($N=49, M=48.71, SD=15.05$) scoring significantly higher on the trait anxiety measure than those recorded on the Neuroscan system ($N=28, M=41.89, SD=11.85$) ($t(67.47)=-2.20, p=.03, d=0.52$) indicating a moderate effect size. A weaker difference was also present in state anxiety ($t(75)=-1.19, p=.24, d=0.28$). There were no age differences between the participants recorded on the two system ($t(75)=0.64, p=.53, d=0.15$).

There are three interpretations of the differences in EEG asymmetry scores found on recordings made on the different systems. Firstly, the difference may be a result of the differences in the participants recorded between the two systems. Participants recorded on the ADI system were more symptomatic in terms of their depression and anxiety levels. Since depression and anxiety are both thought to influence asymmetry scores, it is possible that the difference between the systems was a result of these participant differences. Secondly, it is possible that the differences may be chance effects as a result of the lower number of participants recorded on the Neuroscan system.

Finally, and perhaps most problematic, is the possibility that there are genuine differences in the EEG asymmetry scores recorded on the different systems. The asymmetry metric should cancel out differences in absolute values due to different recording systems. Therefore, it is unclear what could be the cause of such differences. One possibility is the slight difference in the way the linked-mastoid reference site was computed. The Neuroscan system, a specialist EEG recording system, has a function to computationally link the mastoid electrodes. However, the ADI system had limited electrode ports available and this necessitated the use of a physically linked-mastoid electrode. Pivik et al. (1993) noted that this method can be less reliable as slight differences in impedance between the left and right mastoid electrodes can lead to bias in the asymmetry scores. Every effort was made to ensure that impedance was matched between these positions to minimise the effect of this. Furthermore, research has demonstrated that once the electrode impedances of the two reference electrodes are matched, there does not seem to be any differences between recording made using physically or computer-linked mastoids (e.g., Miller, Lutzenberger, & Elber, 1991; Senulis & Davidson, 1989). Residual differences in impedance could account for the observed differences between the recordings.

Appendix E

Epoch Analysis

As revealed in Figure E-1, there was considerable variation in the percentage of epochs that were retained after artefact rejection.

There was no relationship between the total number of epochs retained and asymmetry scores at lateral frontal ($r(71)=.01, p=.94$), medial frontal ($r(71)=.11, p=.37$) or parietal ($r(70)=.12, p=.32$).

There were no differences in the percentage of epochs retained between the never, currently, and previously depressed groups ($F(2,68)=.91, p=.41$).

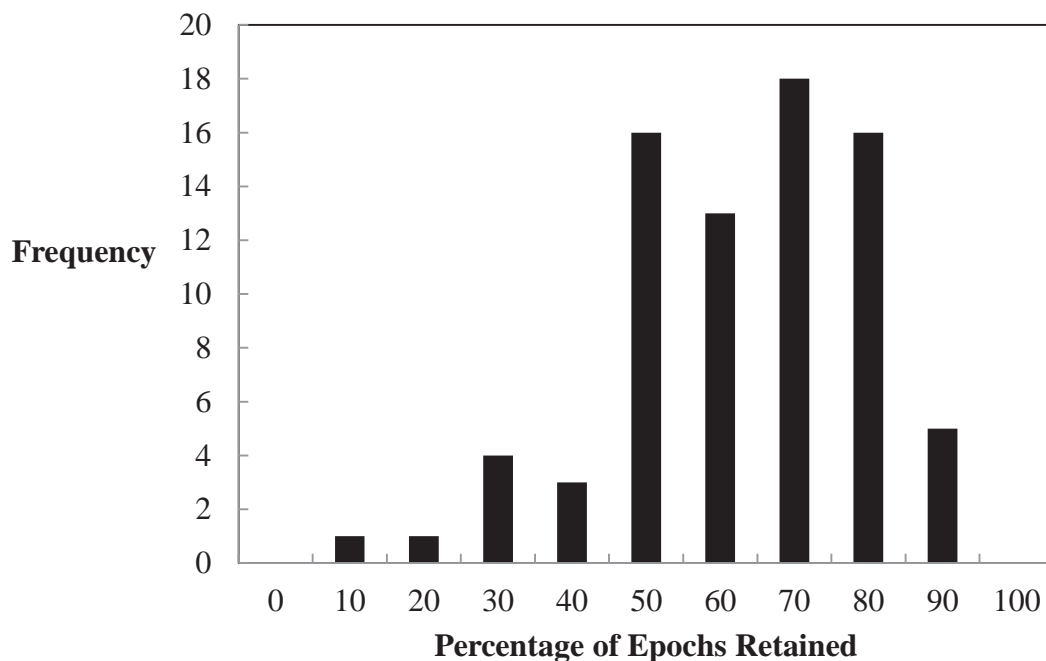


Figure E-1. Frequency Distribution of Average Percentage of Epochs Retained for EEG Data.

Appendix F

Distribution of Depression and Anxiety Inventory Scores

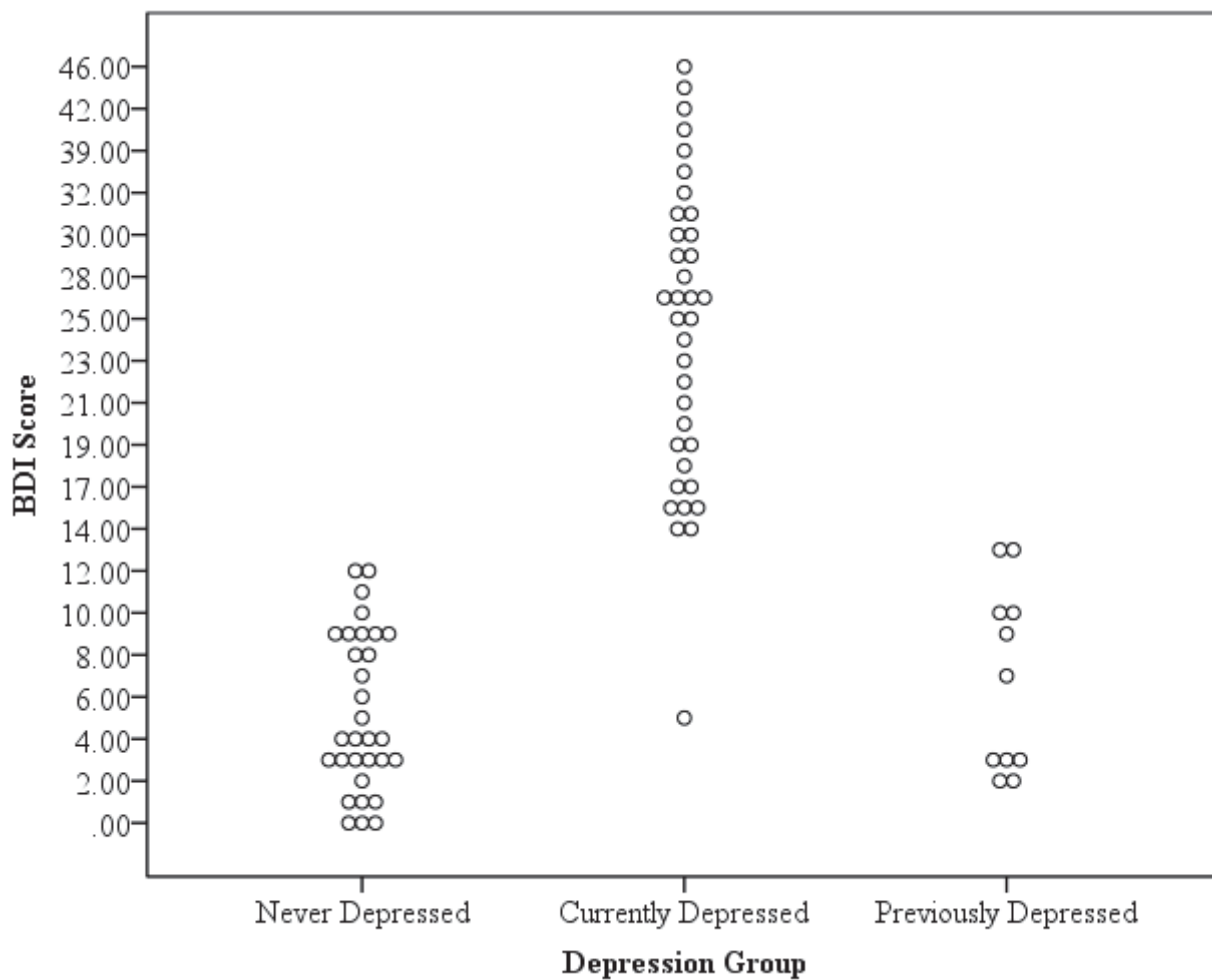


Figure F-1. Scatterplot depicting BDI scores for the Never, Currently, and Previously Depressed participant groups.

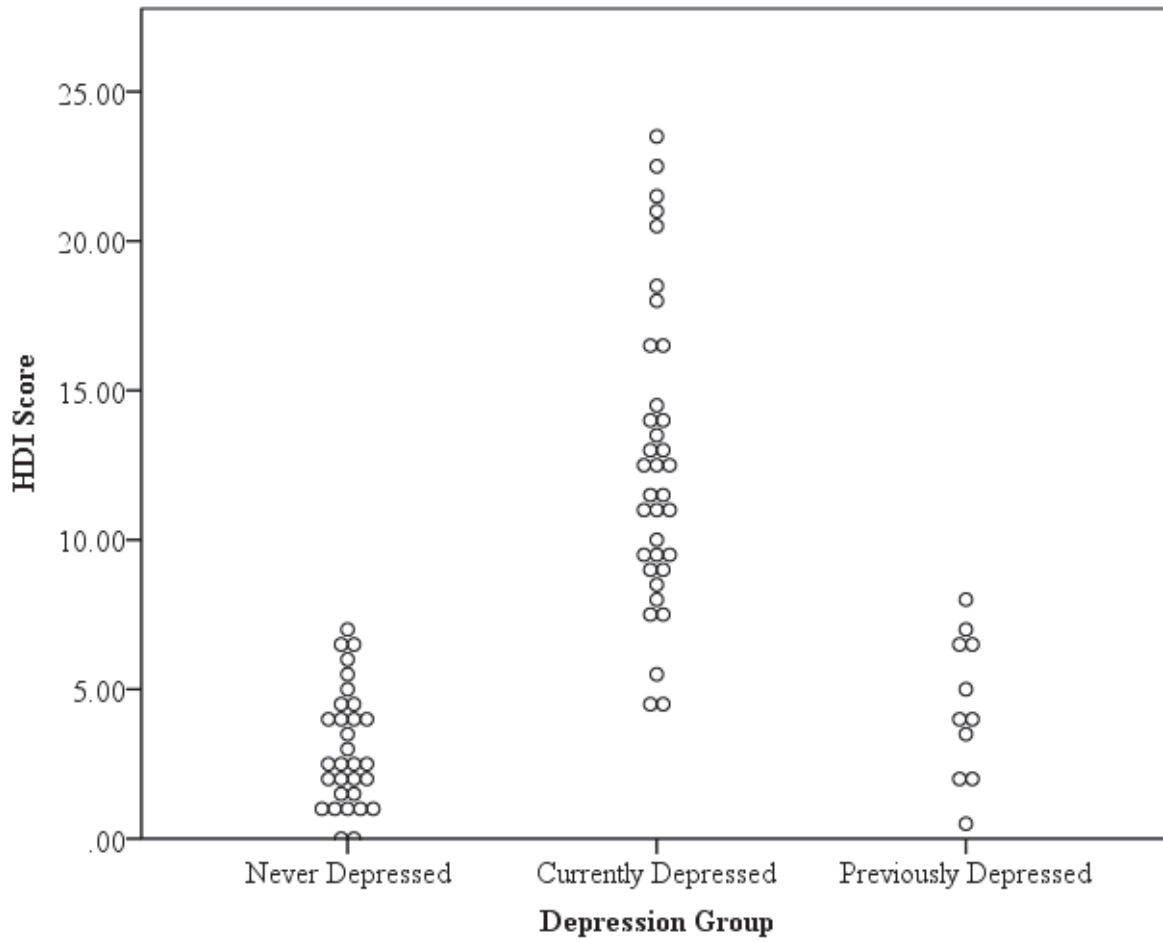


Figure F-2. Scatterplot depicting HDI scores for the Never, Currently, and Previously Depressed participant groups.

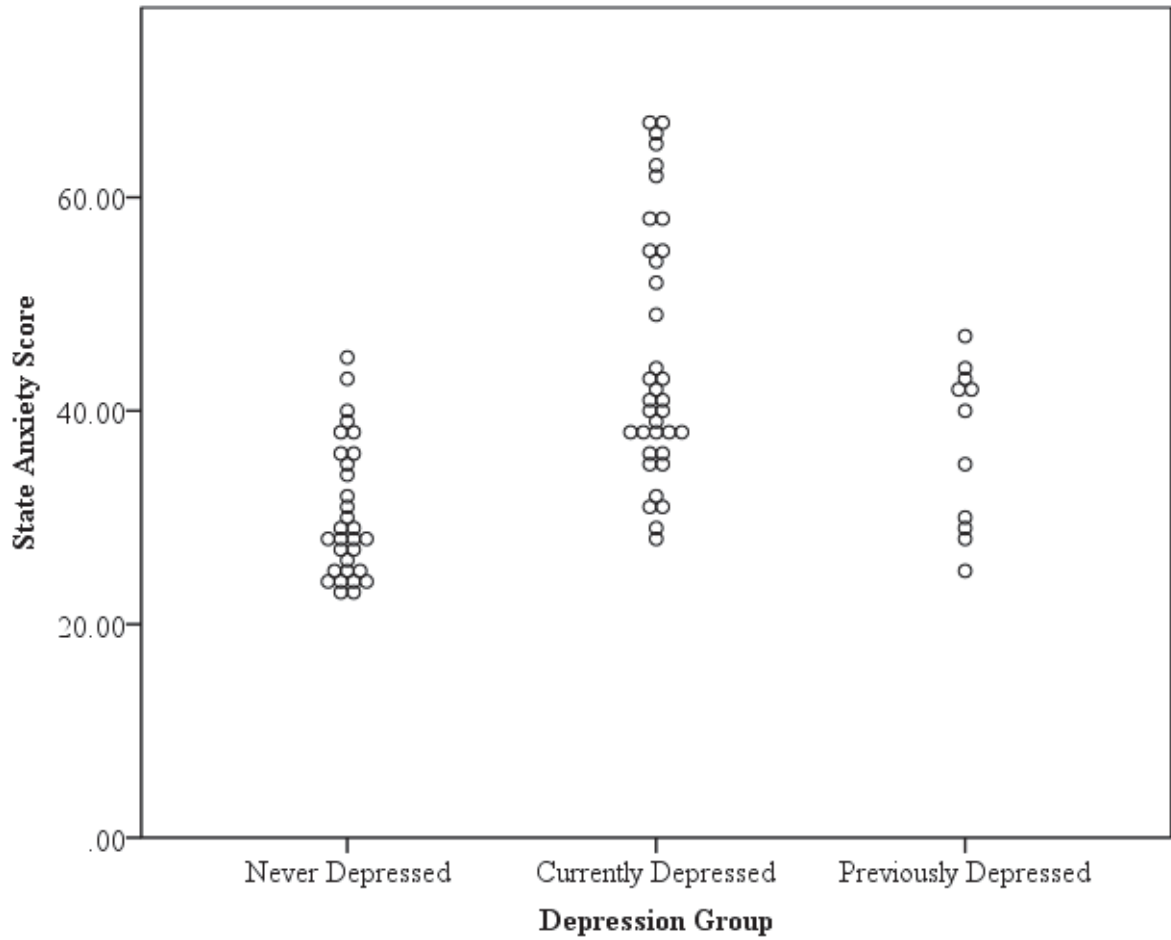


Figure F-3. Scatterplot depicting State Anxiety scores for the Never, Currently, and Previously Depressed participant groups.

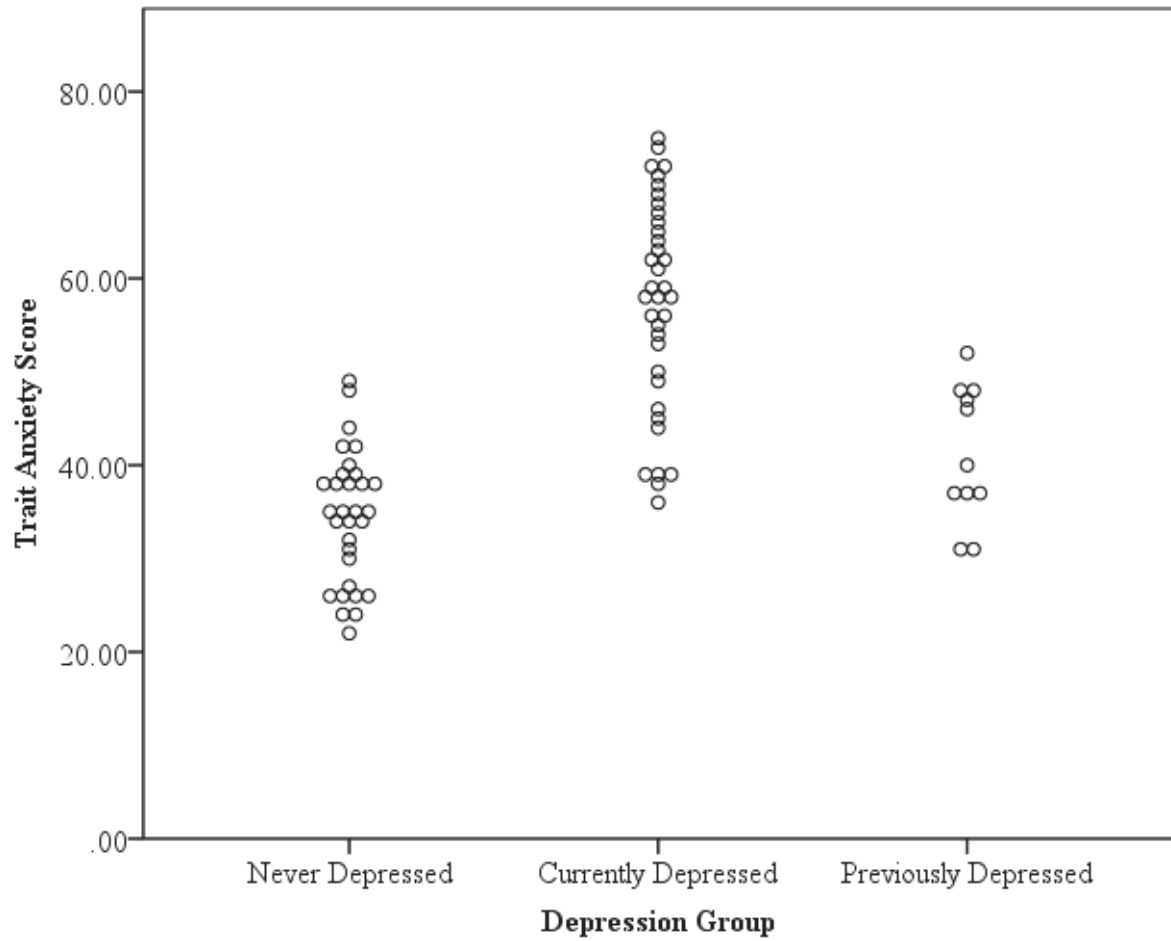


Figure F-4. Scatterplot depicting Trait Anxiety scores for the Never, Currently, and Previously Depressed participant groups.

