Systematic Review of the Literature, and an Investigation of the Roles of Severity, Gender and Cerebral Sites, in the relationship between Alpha Electroencephalographic Asymmetry and Depression

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Abstract

The approach-withdrawal model of depression hypothesizes that depression is characterized by: (i) behavioural withdrawal from negative aversive stimuli (which is associated with increased activation of the right frontal lobe) and (ii) reduced interaction with positive pleasant stimuli (which is evidenced by reduced activation of the left frontal lobe). Therefore, depressed individuals show greater activation in the right *vs* the left frontal lobes. However, experimental findings in this field of research have shown some inconsistencies in depressed participants.

To investigate these inconsistencies, this thesis focused on two tasks. First, a comprehensive review of the literature on the occurrence of alpha EEG asymmetry in depression was undertaken. From this, three important issues which affect the occurrence of alpha EEG asymmetry were identified *vis-à-vis* the roles of: (i) depression severity, (ii) gender, and (iii) cerebral locations where alpha asymmetry occurs (i.e., frontal, temporal, parietal and occipital sites). Therefore, the second section of this thesis comprises an investigation of the relationship between alpha EEG asymmetry and these three issues.

Alpha EEG asymmetry was measured in a community sample of 100 adult individuals (46 males and 54 females) by measuring their baseline EEG under two experimental conditions (i.e., eyes opened and eyes closed, for 3 minutes each). With the aid of the Zung Self-rating Depression Scale (SDS), participants were classified into a "clinically depressed" group (SDS raw scores of 40+) and a "non-clinically depressed" group (SDS raw scores of <40); they were also re-classified into a "severe depression" group (SDS raw scores of 50+) and a "not-severe depression" group (SDS raw scores of <50). Statistical analyses (*t*-tests, ANOVAs and MANOVAs) were performed on the data collected to test for the presence of significant differences in EEG activity across hemispheres.

The findings from this study suggested that: (a) in the absence of depression, significant alpha EEG asymmetry was not observed in the community sample (across all cerebral sites); (b) in the absence of depression, men and women did not exhibit significantly different patterns of alpha asymmetry at the frontal site, although the presence of the "opposite" kind of alpha asymmetry (represented by 'positive' asymmetry scores) differentiated men and women at some temporal, parietal and occipital sites; (c) the

presence of frontal alpha asymmetry significantly differentiated severely depressed individuals from not-severely depressed individuals (the latter showed a lack of alpha asymmetry); and (d) a significant interaction effect was observed between depression severity and frontal alpha asymmetry as a result of gender (i.e., significant frontal alpha asymmetry differentiated severely depressed females from not-severely depressed females, but severely depressed males did not differ from not-severely depressed males).

The findings from this study provide some evidence in support of the approach-withdrawal model of depression, principally at the frontal sites and in severely depressed individuals. Also, gender played a significant role in the occurrence of frontal alpha EEG asymmetry in depressed individuals in this study. Thus, frontal alpha asymmetry which represents an increased activation of the right frontal lobe (increased withdrawal) and a decreased activation of the left frontal lobe (decreased engagement) may provide a valid explanation for the behavioural withdrawal from negative aversive stimuli or stressors (coupled with less interaction with positive stimuli) which depressed individuals display, and it may also serve as a possible biomarker for MDD.

Certification

I, Emmanuel Aderemi, JESULOLA, certify that the substance of this thesis has not already been submitted for any degree or diploma and is not currently being submitted for such.

I certify that, to the best of my knowledge, all of the sources used and assistance received has been acknowledged.

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Signature

Publication arising from this Thesis

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List of Abbreviations

ACTH:	Adrenocorticotropin Hormone
ADHD:	Attention Deficit Hyperactive Disorder
ANOVA:	Analysis of Variance
BAS:	Behavioural Activation System
BATHE:	Background, Affect, Trouble, Handling, Empathy
BAT:	Behavioural Activation Therapy
BDI:	Beck Depression Inventory
CAR:	Common Average Referencing
CBT:	Cognitive Behaviour Therapy
CES-D:	Center for Epidemiological Studies scale
CRF:	Corticotropin-Releasing Factor
CRP:	C-Reactive Protein
CSF:	Cerebrospianal Fluid
CSQ-N:	Cognitive Style Questionnaire-negative events composite
CSF:	Colony Stimting Factors
CT scan:	Computed Axial Tomography Scan
DA:	Dopamine
DSM:	Diagnostic and Statistical Manual of Mental Disorders
ECT:	Electroconvulsive Therapy
EEG:	Electroencephalography
FLA:	Frontal Lobe hemispheric Asymmetry
fMRINF:	Functional Magnetic Resonance Imaging Feedback
fMRI:	Functional Magnetic Resonance Imaging
FTT:	Fast Fourier Transformation
GBI:	General Behavior Inventory
GH:	Growth Hormone
HPA:	Hypothalamus-Pituitary-Adrenal
ICD:	International Classification of Diseases
INF:	Interferons
IL:	Interleukins
IPT:	Interpersonal Psychotherapy
MDD:	Major Depressive Disorder

MDE:	Major Depressive Episode
MAOIs:	Monoamine Oxidase Inhibitors
MRI:	Magnetic Resonance Imaging
MMPI:	Minnesota Multiphasic Personality Inventory
MANOVA:	Multivariate Analysis of Variance
NA:	Negative Affectivity
NE:	Norepinephrine (NE)
PDD:	Persistent Depressive Disorder
PA:	Positive Affectivity
PET:	Positron Emission Tomography
PTSD:	Post-Traumatic Stress Disorder
PDT:	Psychodynamic Therapy
PST:	Problem-Solving Therapy
rTMS:	Repetitive Transcranial Magnetic Stimulation
5HT:	Serotonin (5-hydroxytryptamine)
SPECT:	Single Photon Emission Computed Tomography
SWICKIR:	Somatic symptoms, Worries, Irritability, Concentration, Keyed up, Initial insomnia, Relaxation difficulties
SOAP:	Subjective, Objective, Assessment and Plan
TSH:	Thyroid Stimulating Hormone (Tyrotropin)
TMS:	Trans-cranial Magnetic Stimulation
TCAs:	Tricyclic and Tetracyclic Antidepressants
TNF:	Tumour Necrosis Factors
TRH:	Tyrotropin Releasing Hormone
UNE:	University of New England
WHO:	World Health Organization
SDS:	Zung Self Rating Depression Scale

Appendices

Appendix 1: Detailed descriptions of the studies which investigated the relationship between resting and task-related frontal EEG asymmetry and depression

Appendix 2: Detailed descriptions of the studies which investigated the relationship between frontal EEG asymmetry and depression with other co-morbid psychological disorders

Appendix 3: Detailed descriptions of the studies which investigated the influence of therapeutic interventions on alpha EEG asymmetry

Appendix 4: Study questionnaire

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CHAPTER ONE
OVERVIEW OF THESIS

1.1 Overview of research study

1.1 Overview of research study

Elucidation of the pathophysiology of depression has led to the investigation of electrical activity in the brains of depressed individuals with the aid of electroencephalographic (EEG) measurements. Findings from this body of research have identified frontal EEG asymmetry as a marker for depression. This is because, as opposed to non-depressed individuals, depressed individuals have been reported to show relatively greater electrical activity in their right frontal lobes than in their left frontal lobes.

According to the approach-withdrawal model of depression, the activation of the left prefrontal cortex reflects the activation of the *behavioural approach* system (responsible for engaging with pleasant stimuli) and the activation of the right prefrontal cortex reflects the activation of the *behavioural withdrawal* system (responsible for withdrawing from aversive stimuli). Therefore, because depressed individuals are less engaged and more withdrawn than non-depressed individuals, they tend to activate the left frontal lobe less, while they activate the right frontal lobe more. The reduced left frontal brain activity coupled with increased right frontal brain activity is the basis for the alpha EEG asymmetry seen in depressed individuals. The focus of this thesis was to further explore the findings of alpha EEG asymmetry in depression.

This thesis has been structured into two major parts; firstly, a comprehensive review of the literature on alpha EEG asymmetry in depression was carried out. From this, some inconsistencies regarding certain factors which influence the finding of alpha asymmetry in depression were evident. In broad terms, the areas of controversy included: the impact of depression severity on the association between alpha asymmetry and depression; the role of gender in the finding of alpha EEG asymmetry in depression, and the precise cerebral site where alpha asymmetry occurs in depression. Secondly, an investigation of these issues (i.e., the roles of depression severity, gender and cerebral sites) was then carried out and the findings were interpreted in the light of the previous reports on these issues.

In Chapter 2, a general introduction on the topic of depression is presented. Here, the prevalence, effects, categories and diagnostic criteria of major depression were discussed, and detailed descriptions of the current theories of depression

pathophysiology, treatment options for depression, depression comorbidities with anxiety, and theoretical models of depression were presented. Also, neuroimaging procedures (in particular EEG) which are commonly used in depression research were also described with their advantages and disadvantages.

The comprehensive review of the literature on alpha EEG asymmetry in depression is presented in Chapter 3. Following this exercise, the research investigation was designed as an exploratory process through which the roles of depression severity, gender and cerebral sites were investigated as regards the occurrence of alpha asymmetry in depression, to further understanding on the role which alpha asymmetry plays in the neurobiology/pathophysiology of depression. Here, appropriate research questions were generated in order to address these identified issues of controversy. These research questions were subsequently addressed in chapters 4, 5 and 6.

As presented in Chapter 4, the experimentation involved recruiting 100 adult individuals (46 males and 54 females) from the community to participate in the study. Following ethics approval by the Human Research Ethics Committee of the University of New England, appropriate informed consent was obtained from all 100 participants who then had their resting EEG measured for a total of 6 minutes under two commonly utilized experimental conditions (i.e., eyes opened and eyes closed). There were no side effects or hazardous sequels following EEG measurements and all participants gave usable EEG data. With the aid of the Zung Self-rating Depression Scale (SDS), the participant cohorts were first classified into a "clinically depressed" group (SDS raw scores of 40+) and a "non-clinically depressed" group (SDS raw scores of <40), and then re-classified into a "severe depression" group (SDS raw scores of 50+) and a "not-severe depression" group (SDS raw scores of <50).

In Chapter 5, a series of statistical analysis of the data collected (including appropriate data transformation, *t*-tests, ANOVAs and MANOVAs) were performed in order to address all aspects of the research questions which were generated. Finally, in Chapter 6, the significant findings were reported and interpreted accordingly, and the appropriate conclusions regarding alpha asymmetry and the roles of depression severity, gender and cerebral sites were derived and discussed, with a description of the study's limitations, issues for future research and the clinical implications of these results.

Part A: Introduction to Depression and Systematic Review of the Literature on Alpha EEG asymmetry in depression.

CHAPTER TWO

THE NATURE OF DEPRESSION

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2.1.3 Depression in Australia

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2.2.3 Morbidity and Mortality

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2.7.3 Implications of comorbid occurrence of Depression and Anxiety
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2.1 Introduction

2.1.1 What is depression?

Depression is a common mental disorder that affects people irrespective of age-group, race, ethnicity and gender, resulting in adverse effects on physical health, human relationships and cognitive function, with attendant disability and increasing disease burden (Waraich, Goldner et al. 2004; Lyness, Heo et al. 2006; Alonso, Petukhova et al. 2010; Cuijpers, Beekman et al. 2012). The term depression is used in many different ways to describe transient and mild conditions of low mood experienced by most people at varying times in their lifetime, through to severe psychiatric disorders (AIHW 2013). In the community, depression is believed to be a condition that generally comes and goes, and it is more likely to occur or be experienced at certain stages of a person's life cycle (AIHW 2013). Although some types of depression such as dysthymic disorder and major depressive disorder are believed to be affected or influenced by genetic and biological factors, other types such as minor depression and major depressive episodes maybe considered as responses to major life events (APA 2000; AIHW 2013).

However, depression as described by the World Health Organization (WHO) is a mood disorder characterized by specific symptoms including sadness, loss of interest, anhedonia (loss of pleasure) and lack of appetite, feelings of guilt, low self-esteem or self-worth, sleep disturbance, feelings of tiredness, and poor concentration (WHO 2012). Individuals suffering from depression describe varying degrees of helplessness and hopelessness, inability to concentrate, insomnia, loss of appetite, loss of interest in what they usually find pleasurable, feelings of extreme sadness and guilt, which could be accompanied by thoughts of death. Depression can be recurrent or long-lasting resulting in substantial impairment in ability to function (Marcus, Yasamy et al. 2012; WHO 2012).

2.1.2 Prevalence of Depression

Globally, more than 350 million people of all ages suffer from depression (WHO 2012). The World Mental Health Survey conducted in 17 countries found that 1 in 17 people reported at least one episode of depression in the previous year (Kessler and Ustun 2008). As shown in Table 1 below, the estimated global point prevalence of Major Depressive Disorder (MDD) as presented by Ferrari and colleagues was 4.7%

(44–5.0 %) and the pooled annual incidence was stated as 3.0% (2.4–3.8 %) (Ferrari, Somerville et al. 2013). Depression often starts at adolescent or young adult age, and it generally affects women more than men, with women of child bearing age worst affected due to about 10 – 20 % of women experiencing post-partum depression (WHO 2012).

Table 1: Predicted point prevalence of Major Depressive Disorder (MDD) by regions of the world (adapted from Ferrari *et al.*, 2013).

World Regions	Predicted Point Prevalence % (95% Uncertainty)	Number of Studies (n)
Africa/Middle East	6.6 (5.3–8.3)	21
Asia Pacific	5.6 (4.2–7.4)	8
Asia South	8.6 (5.2–14.0)	6
Australasia	4.1 (2.9–5.7)	9
Eastern/Central Europe	5.1 (4.2–6.1)	6
East/Southeast Asia	4.0 (3.4–4.6)	10
North America	3.7 (3.1–4.3)	19
South America	4.0 (3.5–4.7)	13
Western Europe	4.7 (4.2–5.1)	33
All regions	4.7 (4.4–5.0)	125

2.1.3 Depression in Australia

In any given year in Australia, one in five (20%) Australians aged 16-85 will experience a mental illness and almost half of the population of Australians (45%) will experience a mental illness in their lifetime (ABS 2009). Common mental illnesses in young Australians are: anxiety disorders (14%), depressive disorders (6%) and substance use disorders (5%) (Kitchener and Jorm 2009). Significantly, depression has a high lifetime prevalence in Australia - one in seven Australians (14 %) will experience depression in their lifetime, and in rural communities of Australia, the prevalence of depression is a little lower (10%) (ABS 2009; Kitchener and Jorm 2009). Generally, the onset of mental illness in Australia is around mid-to-late adolescence and Australian youth (18-24 years old) have the highest prevalence of

mental illness of any age group in the country, with one in four young Australians (26%) experiencing a mental illness every year (ABS 2009).

2.2 Effects of Depression

2.2.1 Quality of Life, Family and Societal Functions

Depending on the severity of the disease, depression significantly affects both the physical health and the quality of life of affected individuals. It results in negative impacts on physical functioning such that affected individuals are unable to effectively fulfil their social functions (Alonso, Petukhova et al. 2010) and family functions (Hasche, Morrow-Howell et al. 2010). Sadly, up to 80% of depressed people have some form of impairment in their daily functioning (Pratt and Brody 2008).

Depression does not only impair parental functioning, it also generates negative parenting behaviours and maladaptive interactions between the parent and the child, and these may result in poor upbringing and poor development (Lovejoy, Graczyk et al. 2000; Tronick and Reck 2009; Wilson and Durbin 2010). In the same vein, depression has been associated with low probability of getting married and a higher propensity for separation and divorce for men and women alike (Kessler and Walters 1998; Butterworth and Rodgers 2008). Also, there is a strong association between depression and marital dissatisfaction and marital discord both in men and women (Culp and Beach 1998; Whisman 1999), and depression is both a risk maker and a predictor of marital violence (both perpetration and victimization) (Riggs, Caulfield et al. 2000; Lorber and O'Leary 2004; Lehrer, Buka et al. 2006; Fang, Keating et al. 2010).

In addition, due to poor physical and emotional health, depression causes pain and reduced vitality, inability to cope with challenges and daily life activities, poor general health perceptions and limitations on social functioning (Brenes 2007; Hasche, Morrow-Howell et al. 2010). Studies on the long-term effects of depression on children or adults who suffer from depression show that depressed people are more likely to have lower educational attainment (primarily due to termination of education), fewer working days (due to absenteeism) and a much lower income when compared with healthy individuals, plus a huge lifetime financial loss for families

who have a depressed family member (Breslau, Lane et al. 2008; Ford, Clark et al. 2010; Levinson, Lakoma et al. 2010; Smith and Smith 2010; Breslau, Miller et al. 2011). In its most severe form, depression can ultimately lead to suicide, with about 1 million lives lost due to suicide every year (WHO 2012; WHO 2012).

2.2.2 Productivity and Economy

Cognitive, emotional, and social skills resources (which are significantly affected by depression) are essential requirements for effective functioning, sustenance and growth of the economy of any given society, and the direct and indirect effects of depression on the economy are enormous and alarming in all ramifications (Insel 2008). For instance, productivity in the workplace is significantly reduced with depression. Depressed people on average, lose about 6 hours of productive work in a week (Stewart, Ricci et al. 2003) and depression accounts for close to 20% of lost work days in total (Sohn, Ahn et al. 2013). Also, depressed people are seven times more likely to be unemployed leading to a considerable reduction in the workforce and available human resources in any given economy (Lerner, Adler et al. 2004).

Absenteeism and short-term disability account for up to 50% loss of work productivity, with depressed workers twice more likely to take sick days than healthy counterparts, and depressed workers have more short-term disability days than healthy workers (Kessler, Barber et al. 1999; Druss, Schlesinger et al. 2001; Adler, McLaughlin et al. 2006; Greener and Guest 2007). Even when at work, the productivity of depressed individuals is greatly impaired, this is as a result of less ability to concentrate, lower performance efficiency, and poor ability to organize their work, and these findings are directly related to the severity of the disease, with more severe forms of depression having the worse outcome (Dewa, Hoch et al. 2003; Birnbaum, Kessler et al. 2010). When estimated, the overall lost work performance due to depression could cost an economy as much as between $30.1 billion and $51.5 billion annually, this clearly highlights the cost effects of depression on the productivity and the overall work output of any given economy (Greenberg, Kessler et al. 2003; Stewart, Ricci et al. 2003).

2.2.3 Morbidity and Mortality

The vast majority of research undertaken on depression and its association with other diseases (especially chronic medical conditions) suggests that depression increases both risk for the development of other diseases and also worsens the prognosis, with increased mortality (Manuel, Schultz et al. 2002; Von Korff, Scott et al. 2009; Alonso, Vilagut et al. 2011; Walker, Hansen et al. 2014). Available data from multiple clinical samples and epidemiological surveys have demonstrated that depression is a significant risk factor for the development of chronic physical illnesses such as hypertension, diabetes, asthma, arthritis, chronic respiratory disorders, chronic pain, and cardiovascular diseases (Derogatis, Morrow et al. 1983; Wells, Golding et al. 1989; Dew 1998; Nemeroff 1998; Nemeroff, Musselman et al. 1998; Anderson, Freedland et al. 2001; Manuel, Schultz et al. 2002; McWilliams, Cox et al. 2003; Chapman, Perry et al. 2005; Scott, Bruffaerts et al. 2007; Von Korff, Scott et al. 2009; Alonso, Vilagut et al. 2011).

While it is yet uncertain if depression is a causal factor for most of these chronic physical conditions, available evidences demonstrate that, if depression is present in the setting of chronic diseases, the prevalence, severity, impairments and mortality risk of these chronic diseases increase substantially (Peyrot and Rubin 1997; Gillen, Tennen et al. 2001; Mancuso, Rincon et al. 2001; Lesperance, Frasure-Smith et al. 2002; Barth, Schumacher et al. 2004; Van Melle, De Jonge et al. 2004; Gump, Matthews et al. 2005), and depression alone has been shown to predict the onset of diseases such as stroke, coronary artery disease, heart attack, diabetes and even some forms of malignancy (Ohira, Iso et al. 2001; Carnethon, Kinder et al. 2003; Wulsin and Singal 2003; Van der Kooy, Van Hout et al. 2007; Scherrer, Virgo et al. 2009; Gross, Gallo et al. 2010). However, these findings may not be surprising considering that individuals who suffer from depression are more likely to have poor personal health behaviours such as increased rates of smoking and alcohol consumption (Davis, Uezato et al. 2008), they are more likely to be obese (Cizza 2011), they are more likely to abuse drugs in addition to having low compliance with prescribed medications (Ziegelstein, Fauerbach et al. 2000; Schlenk, Dunbar-Jacob et al. 2004) plus there is an increased occurrence of impaired immune function in association with depressive illnesses (Kiecolt-Glaser and Glaser 2002).

In addition, the clinical course of a chronic disease is affected significantly if depression occurs as a comorbidity (Peyrot and Rubin 1997; Gillen, Tennen et al. 2001; Mancuso, Rincon et al. 2001), primarily because depressed individuals may not adhere to treatment regimens both for the chronic condition and also for depression (Breitbart, Rosenfeld et al. 2000; Ziegelstein, Fauerbach et al. 2000; Cluley and Cochrane 2001), more so, depression is associated with an increase in completed suicides (Bostwick and Pankratz 2000; Moller 2003; Rihmer 2007). Taken together, these findings may largely explain the increased risk of mortality associated with depression (Carney, Freedland et al. 2002; Cuijpers and Schoevers 2004; Davis, Uezato et al. 2008), although, the severity of the existing chronic disease has been implicated in the increased mortality risk found in people with chronic medical conditions and comorbid depression (Lesperance, Frasure-Smith et al. 2002; Barth, Schumacher et al. 2004; Gump, Matthews et al. 2005).

2.2.4 Disability and Disease Burden

Most often, the total impact or burden of a disease is measured by the financial cost, morbidity, mortality, and in particular the disability which results from the disease (often expressed as number of years of life lost due to ill-health, disability or early death) (AIHW 2013). On a global scale, depression contributes significantly to the total burden of disease and the disability and complications associated with depression plus the increased cost in treatment and health services use is concerning (Ustun, Ayuso-Mateos et al. 2004; WHO 2008). In terms of total years lost due to disability, depression remains the leading cause of disability worldwide (WHO 2008; WHO 2012), in fact, the World Health Organization Global Burden of Disease Survey estimates that by the year 2020, major depression will be second only to ischemic heart disease in the amount of disability experienced by sufferers (WHO 2008).

The projections of global mortality and burden of disease from 2002 to 2030 also suggest that unipolar depressive disorders will account for 5.7 % of Disability Adjusted Life Years (DALYs) ranking highest as a cause of disability in High-income countries such as the United States, UK and Australia, and ranking second highest to HIV/AIDS in middle-income countries (Mathers and Loncar 2006). The World Health Organization estimates that by 2030, depression will be the number one health concern in both developed and developing countries of the world (WHO 2008). In

Australia, depression has the third highest burden of all diseases accounting for about 13.3% of all disease burdens, and it is the number one cause of non-fatal disability in Australia (24%) (AIHW 2007). By implication, in Australia, people with depression live with this disability for a higher number of years than people suffering from other non-fatal diseases such as hearing loss and dementia (AIHW 2007).

2.2.5 Financial Implications

The financial implications of depression are alarming. Globally, the estimated cost of mental health over the next 20 years is US$16 trillion, and as reported by the WHO, the global depression's financial burden (which ranked fourth in 2000) will increase by 2020 to be the second most costly disease in the world (WHO 2008; Tomlinson 2013). In the United States, the cost of depression including productivity loss and increased medical expenses is stated as $83 billion each year; this value exceeds the costs of the war in Afghanistan alone (Greenberg, Kessler et al. 2003). In the UK, high levels of depression cost the UK economy almost £11 billion each year in lost earnings, in demands on the health service and in drug prescriptions (Paul, Sujith et al. 2008).

According to the Australian Bureau of Statistics (2009), mental health claims in Australia cost an estimated A$20 billion per year (ABS 2009). As a single entity, it was estimated that depression costs the Australian economy about $12.6 billion yearly and accounts for the loss of productivity worth six million working days in addition to the significant personal and social costs to affected individuals and their families (DHA 2005). Annually, depression-associated disability costs the Australian economy $14.9 billion while the treatment of depression costs the Australian community over $600 million each year (DHA 2005).

2.3 Definition, Categories and Diagnostic Criteria of Depression

Globally, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) are the most recognized sources for the purpose of definition, categorization and diagnosis of depression (WHO 2010; APA 2013).

Taking the ICD system first, according to the latest edition (the ICD-10), a depressive episode is identified by the presence of selected symptoms including: low mood, feelings of guilt and worthlessness, reduced energy, decreased activity, psychomotor retardation or agitation, loss of libido, reduced capacity for interest and enjoyment, sleep disturbance, reduced concentration, diminished appetite, weight loss, low self-esteem, reduced self-confidence and marked tiredness even after minimum effort (WHO 2010). Based on the number and severity of these symptoms, a depressive episode could be classified as mild, moderate or severe (with or without psychotic symptoms) and any of these categories could be recurrent (meaning that, there are repeated episodes of depression without any history of independent episodes of mood elevation and increased energy)(WHO 2010).

The DSM system's description of depression is almost identical to the ICD. According to the latest edition of that system, in the DSM V (fifth edition), depression is described as a disorder in which the primary symptom or predominant feature is a disturbance in mood, with inappropriate, exaggerated, or limited range of feelings, (typified by crying, low mood and frequent suicidal ideations)(APA 2013). Thus, an appropriate classification of depression will require the presence of depressive symptoms only and will also exclude manic, hypomanic, psychotic and schizoaffective symptoms. Therefore, depression categories will include; Major Depressive Episode (MDE), the Depressive disorders (otherwise termed 'unipolar depression' comprising Major Depressive Disorder (MDD) and Dysthymic disorder) and the Bipolar disorder with a current Major Depressive Episode (APA 2000; APA 2013). Other newly introduced depression categories in the DSM include; Disruptive Mood Dysregulation Disorder, Other Specified Depressive Disorder (this includes Recurrent brief depression; Short-duration depressive episode and Depressive episode with insufficient symptoms), Unspecified Depressive Disorder, Substance/medication-induced Depressive Disorder and Depressive Disorder Due to Another Medical Condition (APA 2013).

Of the above mentioned depression categories, MDD which is one of the most common types of depression (Kessler, Petukhova et al. 2012; Kessler 2012), and the most extensively studied type (APA 2013), and it is described below in detail, with the other depression categories being summarized in Tables 3 and 4.

2.3.1 Major Depressive Disorder (MDD)

In clinical presentation, MDD is typified by episodes of more persistent and pervasive disturbances in mood and varying degrees of accompanying depressive symptoms (AIHW 2007), and importantly, the symptoms of depression in MDD occur exclusively without previous history of manic, mixed, or hypomanic episodes. MDD also excludes episodes of substance-induced mood disorder and mood disorder due to a general medical condition (WHO 2010; APA 2013).

According to the DSM V, MDD is a mood disorder characterized or evidenced by one or more major depressive episodes, in which there is the presence of depressed mood or loss of interest (or both) for at least 2 weeks, with four accompanying symptoms of depression (or three, if both depressed mood and loss of interest are present). The additional symptoms which could present with varying degrees of severity include: change in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts (APA 2013)(APA 2013). The full criteria used for the diagnosis of a MDD in clinical settings are presented below (adapted from the DSM V) (APA 2013).

Diagnostic Criteria for Major Depressive Disorder

A. *Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The symptoms that are clearly attributable to another medical condition are excluded.*

1. *Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)*

2. *Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).*

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

4. *Insomnia or hypersomnia nearly every day.*

5. *Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).*

6. *Fatigue or loss of energy nearly every day.*

7. *Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).*

8. *Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).*

9. *Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.*

B. *The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.*

C. *The episode is not attributable to the physiological effects of a substance or to another medical condition.*

***Note:* Criteria A–C represents a major depressive episode (MDE).**

D. *The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.*

E. *There has never been a manic episode or a hypomanic episode.*

2.3.2 Descriptive features of MDD

2.3.2.1 Prevalence and age at onset

The average age of onset of MDD is in the mid-20s, although MDD may occur at any age including late adulthood (Kessler, Berglund et al. 2003). First-degree biological relatives are at greater risk (about four times) of developing MDD than the general population (Sullivan, Neale et al. 2000; Kessler, Berglund et al. 2003). The lifetime prevalence and the twelve-month prevalence of MDD is in the range of 1.5% to 19.0% and 0.8% to 7% respectively (Kessler, Berglund et al. 2003; Bromet, Andrade et al. 2011; Kessler, Petukhova et al. 2012), while the overall weighted prevalence or 30 day prevalence of current major depression is between 2.2 % and 4.9 % (Blazer 1994; Wilhelm, Mitchell et al. 2003). Women experience three-fold higher rates of MDD than men (Kessler *et al.,* 2003), and the prevalence of MDD is much higher in individuals with chronic medical conditions (APA 2013).

2.3.2.2 Associated factors

A number of factors such as psychosocial events (including adverse childhood experiences and traumas during childhood), chronic general medical conditions and substance dependence/abuse, especially Alcohol or Cocaine, have been implicated in precipitating and exacerbating MDD (Chapman, Perry et al. 2005; APA 2013). Also, if underlying personality disorder, anxiety and substance use disorders are present the likelihood of the chronicity of depressive symptoms increases, with associated decreased likelihood of achieving complete remission of symptoms (APA 2013).

In addition, the presence of chronic or severe general medical conditions such as diabetes, myocardial infarction, malignancies or carcinomas and stroke do not only serve as risk factors for the development of MDD, but also make the management more difficult and the prognosis worse. Conversely, these chronic medical conditions are more difficult to manage in the presence of MDD (APA 2000; APA 2013).

2.3.2.3 Risk of suicide

About 15% of individuals with severe MDD commit suicide, and this may partly explain the high mortality associated with MDD (APA 2000). Suicide attempts and outcomes are worse in individuals who are males (Male to Female ratio of 3:1), single, living alone and with underlying borderline personality disorder (Oquendo, Barrera et al. 2004; Tondo, Lepri et al. 2007). Previous history of failed suicide

threats or attempts is a major risk for future completed suicide (Oquendo, Barrera et al. 2004; Tondo, Lepri et al. 2007), and the risk of suicidal behaviour is significantly increased with recurrent or refractory depression and depression with comorbid alcohol abuse (Oquendo, Barrera et al. 2004; Tondo, Lepri et al. 2007).

2.3.2.4 Clinical course

In any individual, the course of MDD could be complete remission (no residual mood disorder or depressive symptoms for at least 2 months, or the presence of only one or two mild symptoms), partial remission (some symptoms are still present but they do not meet full criteria for MDD) or persistence (symptoms that are sufficiently severe to meet the criteria for a full MDD are still present) (WHO 2010; APA 2013). A diagnosis of recurrent MDD is made once all the criteria for MDD are met with the presence of two or more Major Depressive Episodes (MDEs), and these episodes must have been separated by an interval of at least 2 consecutive months in which the criteria for MDD are not met (WHO 2010; APA 2013). However, the course of MDD in any individual is greatly influenced by the severity of the initial episode and the presence of chronic general medical conditions (WHO 2010; APA 2013).

2.3.2.5 Specifiers for MDD

According to the DSM V, it is important to specify the severity of the current status of MDD, especially because of treatment planning (APA 2013). Specifying severity is based on: how many depressive symptoms are present in excess of criteria requirements; what is the degree of intensity or severity of these symptoms; and what is the extent of the accompanying functional disability. Therefore, a mild form of MDD will have few or no depressive symptoms in excess of MDD criteria requirements, and these symptoms are of less intensity with minor impairment in functioning. Severe MDD will have depressive symptoms above criteria requirements, and these symptoms are of higher intensity with greater impairment in functioning. The symptoms of moderate MDD stand somewhere in between those of mild and severe MDD. However, a good clinical judgement is required because this is somewhat subjective (APA 2013).

Additional specifiers which can be used to describe current MDD in clinical presentation include: anxious distress, melancholic features, mixed features, atypical

features, psychotic features, catatonic features, seasonal pattern and peripartum onset (WHO 2010; APA 2013). For instance, if features of anxious distress are present and the patient also meets the criteria for MDD, a diagnosis of MDD with anxious distress is made, rather than MDD alone. The descriptions of these additional specifiers are summarized in Table 2.

Table 2: Descriptive features of MDD specifiers.

Anxious distress	Melancholic features	Mixed features	Atypical features	Psychotic features	Catatonic features	Peripartum onset	Seasonal Pattern
At least two of the following symptoms are present during the majority of days of a MDD: - Feeling keyed up or tense. - Feeling unusually restless. - Difficulty concentrating because of worry. - Fear that something awful may happen. - Feeling that the individual might lose control of himself or herself.	**One of the following is present during the most severe period of the current episode:** - Loss of pleasure in all, or almost all, activities. - Lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens). **Three (or more) of the following:** - A distinct quality of depressed mood characterized by profound despondency, despair, and/or moroseness or by so-called empty mood. - Depression that is regularly worse in the morning. - Early-morning awakening (i.e., at least 2 hours before usual awakening). - Marked psychomotor agitation or retardation. - Significant anorexia or weight loss. - Excessive or inappropriate guilt.	**At least three of the following manic/hypomanic symptoms are present nearly every day during the majority of days of a MDD:** - Elevated, expansive mood. - Inflated self-esteem or grandiosity. - More talkative than usual or pressure to keep talking. - Flight of ideas or subjective experience that thoughts are racing. - Increase in energy or goal-directed activity. - Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments). - Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).	**The following features predominate during the majority of days of the current or most recent MDD:** - Mood reactivity (i.e., mood brightens in response to actual or potential positive events). **Two (or more) of the following**: - Significant weight gain or increase in appetite. - Hypersomnia. - Leaden paralysis (i.e., heavy, leaden feelings in arms or legs). - A long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment. **During this period, criteria are not met for** "with **melancholic** features" or "with **catatonia**" **during the same episode**.	**Delusions and/or hallucinations are present.** **With mood-congruent psychotic features**: The content of all delusions and hallucinations is consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. ***OR*** **With mood-incongruent psychotic features:** The content of the delusions or hallucinations does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or the content is a mixture of mood-incongruent and mood-congruent themes.	**At least three of the following catatonic features are present during most of the period of MDD:** - Stupor (i.e., no psychomotor activity; not actively relating to environment). - Catalepsy (i.e., passive induction of a posture held against gravity). - Waxy flexibility (i.e., slight, even resistance to positioning by examiner). - Mutism (i.e., no, or very little, verbal response [exclude if known aphasia]). - Negativism (i.e., opposition or no response to instructions or external stimuli). - Posturing (i.e., spontaneous and active maintenance of a posture against gravity). - Mannerism (i.e., odd, circumstantial caricature of normal actions). - Stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements). - Agitation, not influenced by external stimuli. - Grimacing. - Echolalia (i.e., mimicking another's speech). - Echopraxia (i.e., mimicking another's movements).	**This is applicable in MDD if onset of mood symptoms occurs during pregnancy or in the four weeks following delivery.**	**The following Criteria must be met:** - There has been a regular temporal relationship between the onset of major depressive episodes in MDD and a particular time of the year (e.g., in the fall or winter). - Cases in which there is an obvious effect of seasonally related psychosocial stressors (e.g., regularly being unemployed every winter) are excluded. - Full remissions (or a change from major depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring). - In the last 2 years, two MDEs have occurred that demonstrate the temporal seasonal relationships defined above and no non-seasonal MDE have occurred during that same period. - Seasonal MDE (as described above) substantially outnumber the non-seasonal MDEs that may have occurred over the individual's lifetime.

The combination of the MDD specifiers (comprising the degree of severity and presence of additional non-depressive features) could give any of the following classifications of the current clinical status of MDD:

- mild, moderate or severe major depression without psychotic symptoms;
- severe major depression with psychotic symptoms;
- MDD with melancholia
- MDD with catatonia and
- Chronic MDD (full criteria for a MDE have been met continuously for at least the past 2 years) (WHO 2010; APA 2013).

2.3.3 MDD and other related depression categories

As opposed to MDE in which there is a single episode of depressed state defined by the presence of either depressed mood or loss of interest/pleasure (or both) for at least 2 weeks, with additional accompanying symptoms of depression, MDD is a disorder which is described by the presence of one or more MDEs in varying severity, duration and persistence (APA 2013). In other words, MDE is an integral part of MDD.

Similarly, MDD should not be confused with Persistent Depressive Disorder, PDD (Dysthymia). Notably, there is the prominent presence of low interest and self-criticism in PDD and vegetative symptoms such as sleep disturbance, poor appetite, weight change, and psychomotor symptoms are less common in PDD than in MDD (APA 2000). More importantly, MDD is differentiated from PDD by the fact that in MDD, depressed mood occurs nearly every day during a period of two weeks, whereas in PDD, the mood disturbance occurs more days than not during a two-year period (1 year for children), and this is usually accompanied by at least two additional depressive symptoms (as opposed to four additional depressive symptoms in MDD), thus, full criteria for a major depressive episode are not met in PDD (APA 2013). Therefore, PDD can be described as MDD of a lesser intensity, which lasts for a longer duration. However, a chronic form of MDD could also occur, in which case, the full criteria for a major depressive episode which typifies MDD have been met continuously for at least the past 2 years, leading to a diagnosis of Chronic MDD (WHO 2010; APA 2013). The full diagnostic criteria and descriptive features of PDD are presented in Tables 3 and 4.

Considering the high co-occurrence of depression and general medical conditions (Derogatis, Morrow et al. 1983; Dew 1998; Anderson and Phelps 2001; Chapman, Perry et al. 2005; Alonso, Vilagut et al. 2011), it is also necessary to differentiate MDD due to another medical condition from pure MDD. Essentially, a diagnosis of MDD due to another medical condition is considered if an individual with a pre-existing medical condition presents with a history of prominent and persistent periods of depressed mood or markedly diminished interest or pleasure in all, or nearly all activities, and this event is clearly and fully attributed to the direct physiological effects of the pre-existing medical condition (APA 2013).

The list of medical conditions that have the propensity to induce major depression is somewhat endless (Cohen 1980; Starkman, Schteingart et al. 1981; Haskett 1985; Sacks, Peterson et al. 1990; Banks and Kerns 1996; Sadovnick, Remick et al. 1996; Borson, Claypoole et al. 1998; Jiang, Krishnan et al. 2002; Jorge, Robinson et al. 2004; Kunik, Roundy et al. 2005; Levin, McCauley et al. 2005; Siegert and Abernethy 2005; Elderona and Whooley 2013; Akena, Kadamab et al. 2015; Neupane, Panthi et al. 2015), thus in clinical practice, the principal concern in distinguishing MDD from MDD due to a medical condition is the ability to confirm that a prominent and persistent mood disturbance is actually and entirely due to a general medical condition. Hence, the identification of a physiological mechanism which can be used to establish or explain whether the mood disturbance is etiologically related to the general medical condition is essential (APA 2013).

Apart from establishing an etiological association, a careful and comprehensive assessment of other multiple factors is also required in making the right judgment as regards to diagnosing MDD due to another medical condition (APA 2013). Useful pointers which can provide help in this area include: the presence of a temporal association between the onset, exacerbation, or remission of the general medical condition and that of the mood disturbance; the presence of features which are atypical of primary mood disorders such as atypical age at onset, atypical course or absence of family history of mood disorders; literature evidence which suggests that there can be a direct association between the general medical condition in question and the development of mood symptoms; and more importantly, available clinical evidences (including history, physical examination and laboratory findings) which

indicate that the mood disturbance is the direct pathophysiological outcome of a known medical condition which is now present in the patient (APA 2013). The full diagnostic criteria and descriptive features of MDD due to a medical condition are presented in Tables 3 and 4.

Table 3: Diagnostic Criteria for other Depression Categories (Adapted from APA 2013).

Depression Categories	Description	Diagnostic Criteria
Persistent depressive disorder (Dysthymia)	The main feature of dysthymic disorder is the presence of depressed mood for more days than not for at least 2 years (1 year for children), and this is usually accompanied by at least two additional depressive symptoms that do not meet criteria for a MDE. Symptoms of low interest and self-criticism are very prominent in Dysthymia, and individuals often see themselves as incapable and uninteresting, however, vegetative symptoms such as sleep disturbance, poor appetite, weight change, and psychomotor symptoms are less common in PDD.	A. Depressed mood for most of the day, for more days than not, as indicated by either subjective account or observation by others, for at least 2 years. In children and adolescents, mood can be irritable and duration must be at least 1 year. B. Presence, while depressed, of two (or more) of the following: 1. Poor appetite or overeating. 2. Insomnia or hypersomnia. 3. Low energy or fatigue. 4. Low self-esteem. 5. Poor concentration or difficulty making decisions. 6. Feelings of hopelessness. C. During the 2-year period (1 year for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 months at a time. D. Criteria for a major depressive disorder may be continuously present for 2 years. E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder. F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder. G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g. hypothyroidism). H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Bipolar I Disorder, current episode is MDE	This characterized by the presence or history of a current MDE (in the absence of symptoms of mania, hypomania and Schizoaffective disorders), but with a previous history of any of Manic episodes or Mixed episodes. Also, the current depressive symptoms (mood disorder) are not superimposed on any of Schizophrenia, Schizophreniform disorder and Delusional disorder, neither are they explained by substance use or existing general medical condition.	A. Currently (or most recently) in a MDE B. There has previously been at least one Manic episode or Mixed Episode. C. The occurrence of the manic, mixed and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
Premenstrual dysphoric disorder	This is typified by the presence of depressive symptoms (such as depressed mood, marked anxiety, marked affective lability and	A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week post-menses. B. One (or more) of the following symptoms must be present:

	decreased interest in activities) which are severe enough to markedly interfere with work, school, or regular activities for at least a year, and these symptoms are present in most menstrual cycles. Specifically, the symptoms occur regularly during the last week of the luteal phase, they resolve within a few days after menstruation commences and they are entirely absent for at least 1 week post-menses.	1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection). 2. Marked irritability or anger or increased interpersonal conflicts. 3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts. 4. Marked anxiety, tension, and/or feelings of being keyed up or on edge. C. One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above. 1. Decreased interest in usual activities (e.g., work, school, friends, hobbies). 2. Subjective difficulty in concentration. 3. Lethargy, easy fatigability, or marked lack of energy. 4. Marked change in appetite; overeating; or specific food cravings. 5. Hypersomnia or insomnia. 6. A sense of being overwhelmed or out of control. 7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain. **Note:** The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year. D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home). E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders). F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (**Note**: The diagnosis may be made provisionally prior to this confirmation.) G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).
Substance/medication-induced depressive disorder	This disorder is characterized by the occurrence of symptoms of depressive disorder (e.g., MDD) in the presence of use of a particular substance or medication, but depressive symptoms are not better explained by an independent depressive disorder. The onset of depressive symptoms is associated with the ingestion, injection, or inhalation of a specific substance or medication which can include any drug of abuse, toxins, psychotropic medication or any other medication (usually during or within 1 month after the substance use).	A. A prominent and persistent disturbance in mood that predominates in the clinical picture and is characterized by depressed mood or markedly diminished interest or pleasure in all, or almost all, activities. B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2): 1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication. 2. The involved substance/medication is capable of producing the symptoms in Criterion A. C. The disturbance is not better explained by a depressive disorder that is not substance/medication-induced. Such evidence of an independent depressive disorder could include the following: The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced depressive disorder (e.g., a history of recurrent non-substance/medication-related episodes). D. The disturbance does not occur exclusively during the course of a delirium. E. The disturbance causes clinically significant distress or

		impairment in social, occupational, or other important areas of functioning. **Note**: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.
Depressive disorder due to another medical condition	Essentially, a diagnosis of depressive disorder due to another medical condition is considered if an individual with a pre-existing medical condition presents with a history of prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all activities, and this event is thought to be related to the direct physiological effects of a pre-existing medical condition.	A. A prominent and persistent period of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities that predominates in the clinical picture. B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition. C. The disturbance is not better explained by another mental disorder (e.g., adjustment disorder, with depressed mood, in which the stressor is a serious medical condition). D. The disturbance does not occur exclusively during the course of a delirium. E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Table 4: Descriptive Features of other Depression categories (Adapted from APA 2013)

Depression Categories	Features				
	Age at Onset	**Prevalence**	**Female: Male**	**Hereditary**	**Suicide Risk**
Persistent depressive disorder (Dysthymia)	< 21 (Early onset) ≥ 21 (Late onset)	0.5%	2-3: 1(Adulthood) 1:1 (Adolescence)	Commoner among first-degree biological relatives of individuals with MDD. First-degree relatives of individuals with Dysthymic disorder are at a greater risk of developing both Dysthymic disorder and MDD.	Associated with higher rates of suicidal behaviours (similar to MDD)
Bipolar I Disorder, current episode is MDE	20 years	0.6%	1:1.1	10-fold increased risk of developing Bipolar I disorder among adult relatives of individuals with bipolar I and bipolar II disorders.	More likely to experience more suicidal ideation and attempts than other types of Bipolar I disorder
Premenstrual dysphoric disorder	Any point after menarche	1.8% and 5.8%	Not specified	Heritability of premenstrual dysphoric disorder is unknown.	Not specified
Substance/medication-induced depressive disorder	Related to medication use	0.26%	Not specified	Not specified	No perceptible increased risk of suicidal behaviour or ideation across all adult age groups. Risk for patients ages 18–24 is higher but not significantly.
Depressive disorder due to another medical condition	Not specified	Not specified	Gender differences pertain to those associated with the medical condition. The female to male ratio is greater in diseases that are more common in women (e.g., systemic lupus erythematosus), but lesser in diseases that are commoner in men (e.g., stroke).	Not specified	Suicide risk is assumed to be the same or greater than that for MDD

2.3.4 Summary of the differences between DSM IV and DSM V in the classification and diagnosis of depression.

The DSM V was introduced in May 2013 to replace the DSM-IV-TR. Apart from introducing the word "hopeless" as one of the descriptions of the state of depressed mood, there are no major diagnostic criteria changes in the classification and diagnosis of depression in the newly published DSM V. However, there are classification re-arrangements, re-naming and introduction of new diagnoses, and exclusion of some diagnoses from the class of depressive disorders in the DSM V. For instance, the class of "mood disorder" has been excluded from DSM V and Depressive and Bipolar Disorders now stand alone as separate sections. Also, as mentioned earlier, the diagnosis of MDE is now an integral component of MDD in the DSM V while Dysthymic Disorder (DSM IV) is now termed Persistent Depressive Disorder (APA 2013).

The sub categories of Post-psychotic Depressive Disorder of Schizophrenia and MDE superimposed on any of Delusional Disorder, Schizophrenia and Psychotic Disorder Not Otherwise Specified have been excluded from DSM V; new diagnosing categories including Disruptive Mood Dysregulation Disorder, Substance/medication-induced Depressive Disorder and Depressive Disorder due to Another Medical condition have been introduced. Also, the components of Depressive Disorder Not Otherwise Specified in DSM IV have been re-organized into three separate classes which are now recognized as distinct diagnoses; these include Premenstrual Dysphoric Disorder, Other Specified Depressive Disorder (this group includes Short Duration Depressive Episode, Recurrent Brief Depression, and Depressive Episode with Insufficient Symptoms) and Unspecified Depressive Disorder (APA 2013).

Overall, by classification re-arrangements, re-naming and introduction of new diagnoses and the re-organizing of the previous DSM IV unspecified category into separate distinct diagnoses, the DSM V gives room for more specific diagnoses, thus making it more diagnosis specific.

2.4 Pathophysiology of Depression

Despite continued research in neurophysiology and neuropsychiatry which has resulted in an increasing understanding of the pathophysiology of depression, the precise mechanism(s) by which depression develops is yet to be completely

understood, and this is partly because depression is somewhat a heterogeneous disorder with a complex phenomenon with possibly multiple aetiologies (Brigitta 2002; Nemeroff 2008).

Currently recognized mechanisms which aim at explaining the pathophysiology of depression include; the Biogenic amine hypothesis, Dysregulation of the hypothalamic-pituitary-adrenal axis and Genetic and Environmental factors (Brigitta 2002; Nemeroff 2008). Other possible contributors include, increased inflammatory cytokines secretion (immunologic factors), elevated levels of corticotrophin-releasing factor, and abnormalities of second messenger systems (Connor and Leonard 1998; Hammen 2005; Sharpley and Agnew 2011).

2.4.1 The Biogenic Amine Hypothesis

Vast connections of the noradrenergic, serotonergic, and dopaminergic neurons exist in the brain and their projections into many areas of the brain is well established (Snell 2010). Noradrenergic neurons spread from the region of the brain stem to almost all brain areas (where noradrenaline modulates the function of the prefrontal cortex where the processing of working memory regulates behaviour and attention) and it also plays a role in the acquisition of emotionally-arousing memories (Delgardo and Morena 2006). Serotonin which innervates all brain areas is known to be the largest cohesive neurotransmitter system in the brain (Chen and Zhuang 2003; Delgardo and Morena 2006), while Dopamine modulates activities in brain regions which sub-serve the functions of reward and motivation, working memory and attention (Chen and Zhuang 2003; Delgardo and Morena 2006).

It is evident that monoaminergic systems are responsible for many behavioural symptoms of depression, such as low mood, vigilance, reduced motivation, fatigue, and psychomotor agitation or retardation (Stahl 1998; Stahl 1998). Alterations in serotonin levels in the brain have been linked to changes in behavioural and somatic functions (including appetite, sleep, sex, pain response, body temperature and circadian rhythm) that are seen in depression (Maes and Meltzer 1995), and various post-mortem studies have demonstrated low levels of serotonin in the brains of depressed patients as opposed to non-depressed patients (Stanley, Virgilio et al. 1982; Perry, Marshall et al. 1983; Stockmeier 2003). Similarly, abnormalities in dopamine

have been linked to impaired motivation, concentration and aggression (Dongju, Christopher et al. 2008), while low levels of noradrenaline (together with serotonin and dopamine) mediate a broad spectrum of depressive symptoms including sex, appetite, aggression, concentration, interest and motivation (Maes and Meltzer 1995; Stahl 1998; Landén and Thase 2006; Dongju, Christopher et al. 2008).

Most brain functions fundamentally depend on the presence and actions of various neurotransmitters at the pre- and post-synaptic membranes of the billions of neurons in the brain, and there is evidence in support of the role of specific neurotransmitters in the development and clinical manifestations of depression (Brigitta 2002; Nemeroff 2008). This hypothesis is also known as the "monoamine hypothesis" and proposes that the reduced availability of three major monoamine neurotransmitters —serotonin (5-hydroxytryptamine, 5HT), norepinephrine (NE), and dopamine (DA) in the brain results in decreased neurotransmission and impaired cognitive performance which may lead to depression (Stahl 1998; Rang, Dale et al. 2007). The functional deficiency of monoamines seen in depression could also result from decreased protein transporter functions and abnormalities in the neurotransmitter receptor function (Brigitta 2002).

2.4.1.1 Functional Deficiency of Monoamines

As explained by the proponents of the monoamine hypothesis, the functional deficiency of these monoamine neurotransmitters is majorly brought about by the degrading effects of the monoamine oxidases in the synaptic cleft (Stahl 1998; Brigitta 2002; Rang, Dale et al. 2007; Nemeroff 2008). This is supported by experimental findings of increased monoamine oxidase enzyme activity in depressed individuals (Brigitta 2002; Nemeroff 2008). The continuous actions of these enzyme systems result in a significant reduction in the availability of the biogenic amines, thus resulting in the decreased neurotransmission seen in depression (Stahl 1998; Stahl 1998; Brigitta 2002; Rang, Dale et al. 2007; Nemeroff 2008)(Brigitta 2002; Nemeroff 2008; Rang *et al.,* 2007; Stahl 1998). This primarily is the basis for the application of anti-oxidase agents as antidepressant medications in the management of depressive illnesses, with a view to restoring the low levels of monoamine neurotransmitters (Schildkraut 1965; Coppen 1967; Matussek 1972; Stahl 1998; Rang, Dale et al. 2007).

2.4.1.2 Decrease Transport Protein Function

As with most cell-to-cell communication in the human body systems, transport proteins play a crucial role in nerve-nerve communications and monoaminergic transmissions (Lesch, Wolozin et al. 1993; Owens and Nemeroff 1994). The activities of transport proteins in the brain help to enhance or facilitate the reuptake of neurotransmitters into the pre-synaptic neurons so that neurotransmitters can be available for continuous neurotransmission (Leonard 2000; Brigitta 2002). By facilitating neurotransmitter re-uptake, transport proteins help reduce the availability of neurotransmitters in the synaptic cleft, thus decreasing the amount of monoamoine neurotransmitters that are degraded by the monoamine oxidase enzymes (Brigitta 2002). A decrease in transport protein function (mostly due to a decrease in the number of transporters) is believed to contribute to the reduced monoamine neurotransmitter seen in depression, and interestingly, decreased protein transporter functions have been found in depression, thus highlighting their role in the development of depression (Drevets, Videen et al. 1992; Lesch, Wolozin et al. 1993; Owens and Nemeroff 1994; Mann, Malone et al. 1996; Drevets, Frank et al. 1999; Leonard 2000; Zill, Baghai et al. 2000; Brigitta 2002).

2.4.1.3 Abnormalities of Receptor Functions

Abnormality in neurotransmitter functions which leads to the impaired transmission seen in depression can also arise from changes in receptor functions (Leonard 2000; Brigitta 2002). These abnormalities could either be an inability to couple neurotransmitters to receptors (usually due to decreased affinity to receptors by neurotransmitters or decreases in number of receptors) or changes in the downstream signal transduction cascade which result in ineffective or abnormal transmission (Brigitta 2002). A number of bio-molecular experiments have demonstrated some abnormalities in receptor function in depressed individuals. For example, alterations in the numbers and affinity of serotonin receptors (5-HT1 and 5-HT2) in the brain, and super-sensitivity of presynaptic $\alpha 2$-adrenoceptors (which modulate the release of NE in the brain) have been reported in depressed individuals (Hrdina, Bakish et al. 1997; Leonard 2000). Also, alterations in G-proteins and protein kinases (major players in signal transduction cascades) have been found at multiple sites of the cAMP pathway in several studies using peripheral cell model systems and post-

mortem brain tissue samples (Duman, Malberg et al. 1999; Feighner 1999; Manji, McNamara et al. 1999; Coull, Lowther et al. 2000).

2.4.2 Genetic Factors

Apart from family, twin and adoption studies which provide convincing evidence that genetics play an important role in the aetiology of depressive disorders, epidemiological evidence also provides strong arguments for a genetic contribution to the development of depression (Akiskal, King et al. 1981; Scott, Barker et al. 1988; Craddock, Khodel et al. 1995; Berrettini 1999; Malhi, Moore et al. 2000; Jones and Craddock 2001; Souery, Rivelli et al. 2001; Klein, Shankman et al. 2004; Mondimore, Zandi et al. 2006), with heritability significantly greater in women than in men (Kendler, Gardner et al. 2001), a finding that corroborates the reported higher incidence and prevalence of most forms of depression in women (Yatham, Srisurapanont et al. 1997; APA 2000; APA 2013).

A number of genes have been associated with the development of depression (mostly in MDD) (López León, Croes et al. 2005; Kang, Hahn et al. 2007; Irie, Masaki et al. 2008; Lopez-Leon, Janssens et al. 2008; Dong, Wong et al. 2009; Hong, Taylor et al. 2009). However, only a few polymorphisms in some genes have been shown to have significant relationships with MDD (López León, Croes et al. 2005; Lopez-Leon, Janssens et al. 2008). Some of these genes include the apolipoprotein E (APOE ε2 and APOE ε4), guanine nucleotide-binding protein (GND3), methylenetetrahydrofolate reductase (MTHFR 677T), dopamine transporter (SLC6A3), the serotonin transporter (SLC6A4) and the dopamine receptor gene (DRD 4) (López León, Croes et al. 2005; Lopez-Leon, Janssens et al. 2008).

Recent research on the role of these genes (also described as "MDD susceptibility genes") in the development of depression has provided more information on the specific associations of these genes with depression (López León, Croes et al. 2005; Lopez-Leon, Janssens et al. 2008; Sharpley 2011). For example, apolipoprotein E, which is believed to have deleterious effects on cognition (Guyton and Hall 2006), has been shown to have significant association with depression (Irie, Masaki et al. 2008; Yuan, Zhang et al. 2010). Of the four isoforms of APOE, APOE ε2 and APOE

ε4 have been well studied, and APOE ε4 has been implicated in the development of depression as it shows a significant association with reduced brain anatomical structure (Qiu, Taylor et al. 2009; Yuan, Zhang et al. 2010) and function (Irie, Masaki et al. 2008) in depressed individuals, although some studies show no significant correlates between APOE and depression (Elovainio, Puttonen et al. 2008; Surtees, Wainwright et al. 2009). On the other hand, APOE ε2 is believed to function as a protective gene for MDD (López León, Croes et al. 2005; Lopez-Leon, Janssens et al. 2008).

Similarly, the gene DRD 4 which codes for dopamine receptors has been shown to be more highly expressed in individuals with current MDD (Guo and Tillman 2009) and also in post mortem samples of depressed individuals (Xiang, Szebeni et al. 2008).Carriers of the gene SCL6A4, demonstrate significantly greater amygdala activity and higher response to unpleasant, emotional and social stress stimuli than non-carriers (Dannlowski, Ohrmann et al. 2007; Heinz, Smolka et al. 2007; Segers 2007; Smolka, Buhler et al. 2007). A summary of the associations of these genes with MDD is presented in Table 5 which was adapted from (López León, Croes et al. 2005; Lopez-Leon, Janssens et al. 2008). Interestingly, some of these genes (e.g., GNB3, SCL6A3, SLC6A4) are the target of some therapeutic interventions in the treatment of depression (Zhou, Zhen et al. 2007; Karg, Burmeister et al. 2011), thus buttressing the significant role of genetic factors in the genesis of depression.

Table 5: Summary Findings for Links Between Six Polymorphisms and MDD (Adapted from Lopez-Leon *et al.*, 2005; Lopez-Leon *et al.*, 2008).

Polymorphism	Number of Studies conducted	Participants	Outcome: Odds Ratio for Depression (Confidence Interval)
DRD4	5	318 Depressed, 814 Control	1.73 (1.29-2.32)
APOE ε2	7	827 Depressed, 1,616 Control	0.72 (0.51-1.0)
GNB3	3	375 Depressed, 492 Control	1.38 (1.13-1.69)
MTHFR	6	875 Depressed, 3,859 Control	1.20 (1.07-1.34)
SCL6A3	3	151 Depressed, 272 Control	2.06 (1.25-3.40)
SLC6A4	24	3,752 Depressed, 5,707 Control	1.11 (1.04-1.19)

2.4.3 Environmental Stress Factors

The influence of environmental stress and adverse life events on the development of depression has previously been documented, and most researchers report an excess of severely threatening life events before the onset of depression (Brown, Harris et al. 1994; Paykel, Cooper et al. 1996; Paykel 2011). Notable life events that precede depression include (but are not limited to): death of a spouse, divorce and marital separation, loss of job or redundancy and retirement, unwanted pregnancy, social isolation, rape, childhood abuse, fighting and war and major accidents (Brown, Harris et al. 1994; Brown, Schulberg et al. 1996; Paykel, Cooper et al. 1996; Kessler 1997; Kendler, Kuhn et al. 2005). These stressful life events have been shown to reduce improvement and increase the probability of relapse of depression (Brown, Harris et al. 1994; Paykel, Cooper et al. 1996; Paykel 2011).

It is known that the stress system and depression share many common mediators and circuitries (Gold, Goodwin et al. 1988) and stress has a significant role in precipitating and influencing the clinical course of depression (Kendler and Halberstadt 2013). The absence of stress may confer some protection against the development of depression (Kendler and Halberstadt 2013), thus, depression could be explained as a possible outcome of the dysregulation of the stress response system (Gold, Goodwin et al. 1988; Gold, Goodwin et al. 1988; Gold, Drevets et al. 2002). Evidence from experimental animal studies suggest that stress induces structural and functional changes in the brain (Dranovsky and Hen 2006; Rajkowska, O'Dwyer et al.

2007; Rajkowska and Miguel-Hidalgo 2007 ; Duman 2009). Following exposure to various stressors, structural changes in the dentate gyrus, prefrontal cortex, amygdala, hippocampus and nucleus accumbens have been shown to contribute to the development of depression (Dranovsky and Hen 2006; Rajkowska, O'Dwyer et al. 2007; Rajkowska and Miguel-Hidalgo 2007 ; Duman 2009).

Studies of monozygotic twins have been used to demonstrate the role of environmental stressors in the development of depression (Kendler and Gardner 2001; Kendler, Gardner et al. 2001; Keller, Neale et al. 2007). Differences in the complexity of life events or environmental experiences in monozygotic twins discordant for major depression have been found to be related to the development of depression in the affected twin (Kendler and Gardner 2001; Kendler, Gardner et al. 2001; Keller, Neale et al. 2007). Examples of such stressors include: the traumatic loss of a romantic relationship, unhappy marriage, divorce, traumatic brain injury (which significantly reduced cognitive function), guilt (resulting from individual actions that significantly affect other people, e.g., loss of life), occupational stress, job loss and failure in a chosen career (Kendler and Gardner 2001; Kendler, Gardner et al. 2001; Keller, Neale et al. 2007). More importantly, a higher number of stressful life events and the continuity of stressors over a long period of time are MORE common in the affected twin (Kendler and Gardner 2001; Keller, Neale et al. 2007). Further, the type and duration of the stressor may also influence the phenotype of the depressive episode (Keller, Neale et al. 2007).

While available evidence suggests that both acute and chronic stressful life events can influence the onset and recurrence of major depression (Kessler 1997), positive life events such as marriage and supportive relationships, birth of a baby, academic and career success, availability of other social supports, acceptance of gifts and donations, financial independence and other financial support, have been reported to improve the clinical outcomes of depression, and they may also confer some sort of protection against the development of depression (Cohen and Hoberman 1983; Cohen, Kamarck et al. 1983 ; Brown, Harris et al. 1994; Paykel, Cooper et al. 1996; Johnson, Han et al. 1998; Paykel 2011).

2.4.4 Endocrine Factors

A number of abnormalities in the human endocrine system have been identified as possible contributors to the etiology of depression. These include altered levels of Growth hormone, abnormalities in Thyroid hormone secretion and function, and dysfunctions in the Hypothalamus-Pituitary-Adrenal (HPA) axis (Thase and Howland 1995; Brigitta 2002; Segerstrom and Miller 2004). A brief explanations of the possible mechanisms by which these endocrine disturbances may result in depression are provided below.

2.4.4.1 Growth Hormone (GH)

For over three decades, the role of pituitary hormones such as GH in the development of depression has been previously investigated via their influence (direct and indirect) on the noradrenergic system (Brigitta 2002). Specifically, GH release (stimulated by catecholaminergic mechanisms) (Guyton and Hall 2006), is defective in depression and GH responses in depressed patients have been shown to be different from healthy controls (Charney, Heninger et al. 1984; Matussek 1988; Anand and Charney 2000). In fact, following GH challenge tests (using apomorphine and clonidine), patients with recurrent major depression exhibited 'flat' or 'blunted' GH responses as opposed to healthy subjects who demonstrated adequate GH release (Charney, Heninger et al. 1984; Hoehe, Valido et al. 1986; Matussek 1988; Anand and Charney 2000). Although, this could be viewed as a decrease in DA receptors sensitivity and α2-adrenoceptors sensitivity, a further challenge with different α2-adrenoceptor–selective agents produced an adequate increase in GH secretion, suggesting that an intrinsic abnormality in the GH system was responsible for the flat response, thus implicating GH in depression (Anand and Charney, 2000). Interestingly, blunted GH response to clonidine has been shown as a trait marker for depression, even after recovery (Charney, Heninger et al. 1984; Hoehe, Valido et al. 1986). However, the precise mechanism by which dysfunction in GH response results in depression remains largely unknown.

2.4.4.2 Thyroid Hormones

The active forms of thyroid hormones are tri-iodothyronine (T3) and tetra-iodothyronine (T4), which are produced from the thyroid gland by the stimulating effect of the pituitary hormone, Thyroid Stimulating Hormone (TSH, also called

Tyrotropin), whose secretion is under the influence of the hypothalamic hormone, Tyrotropin Releasing Hormone (TRH) (Guyton and Hall 2006). Thyroid hormones (T3 and T4) function primarily in regulating the overall metabolism in the human body (Guyton and Hall 2006) and previous experimental findings on thyroid function and depression have suggested that alterations in thyroid function could be a possible link to the development of depression (Duval, Mokrani et al. 1999; Gur, Lerer et al. 1999; Altshuler, Bauer et al. 2001). Some symptoms of depression such as weight loss, sleep disturbance and psychomotor agitation could be attributed to thyroid function abnormalities (Duval, Mokrani et al. 1999; Gur, Lerer et al. 1999; Altshuler, Bauer et al. 2001) (Thase and Howland 1995). Similarly, the administration of tri-iodothyronine (T3) has been shown to be an effective adjunctive therapy for many patients with depression (Duval, Mokrani et al. 1999; Altshuler, Bauer et al. 2001). While the precise mechanism by which thyroid hormone abnormalities contribute to the genesis of depression is yet to be fully elucidated, the findings of increased cortical serotonin secretion following application of thyroid hormone may suggest that thyroid hormones act indirectly through the serotoninergic system (Gur, Lerer et al. 1999). However, some researchers have suggested that thyroid hormones act as co-transmitters to NE in the adrenergic nervous system. Thus, thyroid hormone dysfunction may act indirectly through serotoninergic and/or adrenergic systems to produce symptoms of depression (Gordon, Kaminski et al. 1999; Altshuler, Bauer et al. 2001; Brigitta 2002).

2.4.4.3 Hypothalamus-pituitary-adrenal (HPA) Axis

Various endocrinology researchers have indicated that dysfunctions in the hypothalamus-pituitary- adrenal (HPA) axis make significant contributions to the development of depression (Board and Wadeson 1957; Sachar, Hellman et al. 1970). Following intensive investigation and analysis of the HPA system, findings revealed that depressed individuals have: hyper-secretion of hypothalamic corticotropin-releasing factor (CRF) and cortisol, dysfunctional glucocorticoid feedback mechanism, inadequate suppression of the HPA axis in response to exogenous glucocorticoid administration, and impaired corticosteroid receptor signalling (Holsboer, Liebl et al. 1982; Holsboer, Gerken et al. 1986; Rubin, Poland et al. 1989; Holsboer and Barden 1996; Holsboer 2000).

Some depressive symptoms such as excessive guilt and hopelessness, decreased appetite, weight loss, decreased sexual behaviour, disrupted sleep, and altered psychomotor activity, have been linked with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Heinrichs, Menzaghi et al. 1995; Gillespie and Nemeroff 2005). This may partly explain why patients with Cushing's disease or syndrome (a clinical condition in which there is hyper-secretion of cortisol) often experience varying severities of depression (Brigitta 2002; Guyton and Hall 2006; Nemeroff 2008).

CRF plays a major role in controlling or regulating the activity of the HPA axis (Herman and Cullinan 1997; Guyton and Hall 2006; Smith and Vale 2006). It is produced by neurons of the paraventricular nuclei of the hypothalamus which secrete CRF into the hypothalamo-hypophyseal portal system, from where it is transported by blood vessels into the anterior pituitary (Herman and Cullinan 1997; Guyton and Hall 2006; Smith and Vale 2006). Its action is to increase adrenocorticotropin hormone (ACTH) secretion from the corticotrophs of the anterior pituitary, and ACTH then stimulates the release of cortisol from the adrenal gland. Thus, CRF controls HPA axis activity (Herman and Cullinan 1997; Guyton and Hall 2006; Smith and Vale 2006). However, CRF is also found in a significant proportion in extrahypothalamic brain regions and it is believed that it functions as a neurotransmitter in concert with the hypothalamic CRF system to co-ordinate the behavioural, autonomic, endocrine, and immune responses to stress, and this function may underlie its role in the development of depression (Gillespie and Nemeroff 2005; Nemeroff 2008).

Apart from the many laboratory animal studies which demonstrated some signs and symptoms of depression (including decreased appetite and weight loss, decreased sexual behaviour, disrupted sleep, and altered psychomotor activity) following the direct administration of CRF into the central nervous system of laboratory animals (Heinrichs, Menzaghi et al. 1995), depressed patients have also been found to exhibit elevated concentrations of CRF in their Cerebrospinal fluid (CSF) samples (Nemeroff, Widerlo¨ v et al. 1984). Similarly, post-mortem studies of depressed individuals showed a significantly decreased CRF receptor density in the frontal cortex, reduced expression of CRF1 receptor mRNA and increased CRF concentrations in the brain as opposed to non-depressed control subjects (Merali, Du

et al. 2004). Furthermore, a significant reduction in the high CRF concentrations in the CSF of depressed individuals have been found in successive treatment of depression following the use of electroconvulsive therapy (ECT) or the Selective Serotonin Reuptake Inhibitor (SSRI), fluoxetine (Nemeroff, Bissette et al. 1991). Also, the use of CRF-antagonist (R121919) has been shown to reduce symptoms of major depression in clinical trials (Kunzel, Zobel et al. 2003; Held, Kunzel et al. 2004; Kunzel, Ising et al. 2005). In addition, persistently elevated CRF concentrations in the CSF of depressed patients have been shown to be associated with higher rates of early relapse (Nemeroff 2008). These findings implicate chronic CRF hyper-secretion in the observed HPA axis alterations in depressed patients.

In addition, the hyperactivity of the HPA axis seen in depression is also evidenced by the demonstrated failure to suppress plasma cortisol concentrations after exogenous glucocorticoid administration in depressed individuals, (Holsboer, Liebl et al. 1982; Holsboer, Gerken et al. 1986; Holsboer and Barden 1996). As a result of this HPA hyperactivity and failure of suppression of cortisol secretion, depressed individuals show significantly higher levels of cortisol both in plasma and saliva samples when compared with non-depressed subjects (Gibbons 1966; Halbreich and Asnis 1985; Gillespie and Nemeroff 2005; Vreeburg and Hoogendijk 2009). The impaired feedback regulation in the HPA axis which results in higher levels of cortisol in depressed subjects has been shown to be associated with the intensity and severity of depression, and when this dysfunctional glucocorticoid feedback mechanism persists; there is a significant-risk for relapse of depressive symptoms (Ising, Kunzel et al. 2005; Nemeroff 2008). Hence, the use of antiglucocorticoids in order to inhibit cortisol synthesis is a valid therapeutic option which has been shown to yield expected results both in animal and human studies (Ising and Zimmerman 2007; Surget and Saxe 2008).

2.4.5 Immunologic Factors (Role of Cytokines)

Cytokines are chemical inflammatory mediators which are secreted by lymphoid cells (mostly white blood cells) primarily in response to foreign or invading pathogenic antigens, and they function as regulators of all other immune cells (lymphocytes, monocytes, neutrophils, basophils, eosinophils and natural killer cells) which are involved in the process of inflammation in the body (Dinarello 1997; Hildebrand,

Pape et al. 2005; Song, Halbreich et al. 2009). They include: interferons (INF), interleukins (IL), colony stimulating factors (CSF) and others (e.g., tumour necrosis factors, TNF, C-reactive protein (CRP) and serum amyloid proteins) (Dinarello 1997; Song, Halbreich et al. 2009). By actions, cytokines could either be pro-inflammatory or anti-inflammatory. Pro-inflammatory cytokines include IL-1, IL-6 and TNF, while IL-4, IL-8, IL-10 and IL-13 are anti-inflammatory in action (Dinarello 1997; Song, Halbreich et al. 2009).

The idea that immune factors (cytokines) could have a possible role in the development of depression seems to have resulted from various studies linking chronic stress (a major factor in depression pathology) with reduced or suppressed immune function (Dhabhar 2000; McEwan 2000). This has led to investigations seeking to find the link between immune factors and depression. A number of possible mechanisms have been proposed as direct or indirect links between depression and cytokines (Sharpley and Agnew 2011). These mechanisms are presented in summary in Table 6.

Table 6: Mechanisms by which immune factors contribute to the development of depression.

Proposed Mechanism	Research Evidence	Cytokines implicated	Sources
Elevated levels of pro-inflammatory cytokines contributes to depression (mostly by a dose-response relationship)	1. Melancholic depressed patient show increasing elevated interleukin levels with increasing severity. 2. Increased level of cytokines in CSF and blood samples of depressed individuals with no comorbid medical condition. 3. Depression was associated with elevated levels of pro-inflammatory cytokines in patients with metabolic syndrome who have higher incidences of depression than healthy individuals. 4. Significantly higher levels of cytokines have been expressed in sweat samples of currently depressed women than women in remission. 5. Peripherally administered pro-inflammatory cytokines in adults produces increase inflammatory responses in the CNS associated with increased incidence of depression. 6. Large, multiple, well controlled studies have shown increased cytokines and vascular adhesion molecules in depressed individuals as opposed to non-depressed individuals. 7. Meta-analysis on studies of depression and inflammatory cytokines has reported significant relationships between depression and cytokines.	1. IL-1, IL-2, TNF. 2. IL-6, CRP, IL-1, TNF. 3. CRP and IL-6. 4. IL-1α, IL-1β, IL-6, IL-8, TNF α. 5. IFN α. 6. CRP, IL-1, IL-6, TNF. 7. CRP, IL-1, IL-6, TNF, IL-1ra.	1. Hayley *et al.*, 2005. 2. Raison *et al.*, 2006 (list of 20 studies). 3. Capuron *et al.*, 2008. 4. Cizza *et al.*, 2008. 5. Raison *et al.*, 2009. 6. Glassman and Miller 2007. 7. Howren *et al.*, 2009; Dowlati *et al.*, 2010.
Specific cytokines produce and induce symptomatology of MDD	1. Cytokines have been used to induce a 'depressive-like' state in experimental animals. 2. Administration of cytokines as immunotherapeutic agents induce sufficient symptoms which qualify for the diagnosis of MDD.	1. IL-1β and TNF α. 2. IL-2, IFN-α.	1. Dantzer *et al.*, 2007. 2. Dunn 2008; Hayley *et al.*, 2005.
Cytokines act as potential link for stress induced depression	1. Stress induced increased pro-inflammatory cytokines interfere with brain neuroplasticity and monoamine activity to produce depression. 2. Pro-inflammatory cytokines convert tryptophan (serotonin precursor) to other metabolites, thus reducing the production of Serotonin, thus resulting in depression.	1. IL-1, IL-6, TNF. 2. IFN- γ; IL-2.	1. Hayley *et al.*, 2005. 2. Dantzer *et al.*, 2007; Dinan 2008.

	3. Pro-inflammatory cytokines significantly activate the HPA axis by increasing glucocorticoid receptor resistance, resulting in failure of down regulation of CRH and Cortisol.	3. IL-1β and TNF α.	3. Dantzer *et al.*, 2007.
Antidepressant therapy suppresses the activation of inflammatory response	1. Most studies on antidepressants and inflammatory cytokines have shown that application of antidepressants significantly reduces cytokine concentrations in depressed patients undergoing treatments.	1. CRP and serum amyloid A.	1. Kling *et al.*, 2007; Miller *et al.*, 2009 (a review of 20 studies).
	2. Antidepressant therapy in breast cancer patients with depression reduces inflammatory indices such as white blood cell count, number of neutrophils and helper/suppressor ratio.	2. IL-1, IL-2, IL-6, CRP, TNF.	2. Thornton *et al.*, 2009.

However, as presented in the review by Raison and associates (Raison, Capuron et al. 2006), some studies on immune factors and depression found contrasting results; while some studies found no association between inflammation and depression and or depression severity, and some studies demonstrated an inverse relationship between inflammatory cytokines and depression. In addition, a few studies which demonstrated an association between inflammatory cytokines and depression were noted to have been confounded by other factors such as personality, gender or body mass index (Raison, Capuron et al. 2006; Miller, Maletic et al. 2009). Also, the application of anti-inflammatory drugs (e.g Cyclo-oxygenase inhibitors) in depression was ineffective in resolving the symptoms of depression, suggesting that inflammatory factors are not solely responsible for depression (Dunn 2008). Thus, these inconsistencies may imply that the association between inflammatory factors and development of depression is not a simple mathematical correlate by which cytokines might be implicated as a primary cause of depression. Rather, a complex association may underlie the link between inflammatory factors and development of depression (Dinan 2008; Dunn 2008).

As suggested by Sharpley (2013), the complex link between depression and inflammatory factors may partly be explained by the 'Sickness behaviour' concept. This concept explains that, as part of the normal immunologic response to infections, pro-inflammatory cytokines (such as IL-1β and TNFα) which act on widespread

receptors in the brain initiate a combination of behavioural responses including hyperthermia, nausea, loss of appetite, sleep disturbances, anhedonia, easy fatigability and loss of interest in social and physical environments (Dantzer, O'Connor et al. 2007). These sickness behaviours, which make affected individuals become socially withdrawn, are believed to confer some advantages to the affected individuals in that they are able to conserve energy which assists them in coping better with the illness. But in severe cases the sickness behaviours may be sufficient enough to constitute the symptomatology of MDD, not only because they result in social withdrawal, but because they have been shown in laboratory animals to produce depressive symptoms similar to those in humans with MDD (Dantzer, O'Connor et al. 2007). In addition, they have been found to produce both sufficient symptoms that warrant the diagnosis of MDD in patients treated with immunotherapeutic cytokines (Hayley, Poulter et al. 2005; Dunn 2008). More importantly, some other cytokines (e.g., IL-10) have anti-inflammatory actions, and they serve as regulators of the immune response by inhibiting excessive production and signaling of other pro-inflammatory cytokines, thus an imbalance in the activities of opposing groups of cytokines may contribute to the genesis of depression (Dantzer, O'Connor et al. 2007).

However, because pro-inflammatory cytokines are also known to induce certain symptoms which are not constituents of MDD (e.g., hyperthermia and hypomotility) (Kent, Bluthe et al. 1992), depression may therefore be seen as a subset of a broader sickness behavioural response as a result of the actions of inflammatory cytokines (Sharpley and Agnew 2011).

2.4.6 Link between genetic, environmental, endocrine and immunologic factors in the development of depression

Generally, the findings of genetic studies on depression suggest that the heritability of depression is somewhat variable and does not follow a classical Mendelian pattern. Therefore, the presence of a single gene locus may not explain all the increased intra-familial risk for the development of the different types of depression (Brigitta 2002; Nemeroff 2008). Also, as mentioned earlier, the association between immunological factors and depression does not completely explain why depression develops; neither does the presence of environmental stressors alone nor the hyperactivity of the HPA

axis singly explain the genesis of depression. Therefore, just as it is reiterated in most literatures on the pathophysiology of depression, it is most likely that depression is a complex disorder in which an interplay of genetic, environmental, immunologic and endocrine factors contribute to the development of the disorder (Brigitta 2002; Nemeroff 2008; Sharpley and Bitsika 2010).

Interestingly, there is an apparent pathway which has been identified as a link between the contributing factors in the development of depression (Raison, Capuron et al. 2006; Sharpley and Bitsika 2010). This is the HPA axis and this has been described as the 'Diasthesis-Stress hypothesis" (Charney 2004; Bear, Connors et al. 2007). existing postulate is that environmental stressors acting through immunologic response and heritable genetic factors initiate structural and functional changes in many brain regions, resulting in dysfunctional neurotransmission which then manifest as a combination of symptoms which manifest as depression (Charney 2004; Bear, Connors et al. 2007) (Sharpley and Bitsika 2010; Sharpley and Agnew 2011)

By direct and indirect action on the brain, hypercortisolaemia (from hyperactivity of the HPA axis) causes structural and functional changes in brain regions, especially in the prefrontal cortex, hippocampus and amygdala, areas which are believed to be involved in the development of psychological, cognitive, physical and emotional symptoms of depression (Levin, Heller et al. 2007; MacQueen, Yucel et al. 2008; van Eijndhoven, van Wingen et al. 2009). Structural and functional changes such as alterations in the connectivity between certain brain regions (e.g., prefrontal cortex and amygdala), neurogenesis and increased dendritic branching resulting in volume increases in areas like the amygdala, and cell apoptosis resulting in decreased volume of the prefrontal cortex and hippocampus, have been attributed to hypercortisolaemia (Levin, Heller et al. 2007; MacQueen, Yucel et al. 2008; van Eijndhoven, van Wingen et al. 2009). These changes in the brain generate emotional and behavioural symptomatology including apathy, mood disturbance, cognitive dysfunction, withdrawal and anhedonia, which are seen in depression (Bolling, Kohlenberg et al. 1999; Nitschke and Mackiewicz 2005; Quirk and Gehlert 2006; Kanter, Busch et al. 2008; Schlosser, Wagner et al. 2008; APA 2013). Thus, the HPA axis occupies a significant position in the pathophysiology of depression.

Sharpley and Bitsika (2010) argued that heritable genetic factors do not act as a 'solo' factor. Rather, they have a reciprocal interaction with environmental stressors. In other words, environmental measures and life events tend to be influenced or 'contaminated' by genetic components (Malhi, Moore et al. 2000). Therefore, environmental stressors activate the HPA axis, resulting in hyperactivity of the axis, the result of which is increased CRF secretion leading to hypercortisolaemia seen in depression (Nemeroff, Widerlo¨ v et al. 1984; Merali, Du et al. 2004; Segerstrom and Miller 2004; Gillespie and Nemeroff 2005; Fiocco, Wan et al. 2006; Du, Wang et al. 2009).

Certain genes which are known to activate the secretion of CRH from the hypothalamus have been shown to be significantly more expressed in depressed individuals than non-depressed subjects (Wang, Kamphuis et al. 2008). By implication, genetic factors acting through the HPA axis result in excessive secretion of CRH and cortisol, the effects of which are structural and functional changes in brain regions which then contribute to depression (Wang, Kamphuis et al. 2008). However, because genes do not act alone, the presence of some 'plasticity genes' implies that affected individuals are more predisposed to having significantly higher depressive response to environmental stressors than non-carriers (Belsky, Jonassaint et al. 2009). Hence, environmental factors acting indirectly through genetic factors cause hyperactivity of the HPA axis which results in depression.

It is also known that increased pro-inflammatory cytokines (immunologic factors) directly produce depressive symptomatology by reducing Serotonin production and by interfering with brain neuroplasticity and monoamine activity (Hayley, Poulter et al. 2005; Dantzer, O'Connor et al. 2007; Dinan 2008). Pro-inflammatory cytokines significantly activate the HPA axis by increasing glucocorticoid receptor resistance, resulting in failure of down-regulation of CRF and consequently hyper-secretion of cortisol; thus, immunologic factors cause depression indirectly through the HPA axis (Dantzer, O'Connor et al. 2007). However, as proposed by Raison et al. (2006), it is also plausible that psychological or environmental stressors act through the HPA axis principally by increasing hypothalamic CRF production which then increases the production and activity of pro-inflammatory cytokines, the actions of which directly or indirectly result in depression.

Overall, the stress induced hyperactivity of the HPA axis is the major neurobiological link between these contributing factors and the development of depressive symptoms (Sharpley and Bitsika 2010).

2.5 Clinical content Subtypes of Depression

Generally in clinical practice and research, depression is most often viewed as a disorder with a "unitary construct", by which it is assumed that most forms of depression may be explained by similar underlying pathophysiology, and also amendable to similar therapeutic interventions (Sharpley and Bitsika 2013). This assumption is more pronounced when the DSM is used to make a diagnosis of major depression (Sharpley and Bitsika 2013). Thus, a casual use of the DSM criteria in diagnosing major depression (without paying attention to details of the presenting symptoms) may result in an inappropriate identification and differentiation of the possible clinical content subtypes of depression an individual is presenting (Sharpley, Bitsika et al. 2013; Sharpley and Bitsika 2013).

Also, the DSM module of diagnosing major depression appears to be more focused on the number of symptoms present (which in turn is used to determine the severity of depression), with little allowance for the clinical significance of each contributing symptom, probably assuming that most symptoms make a similar contribution to overall depression status (APA 2013). This limitation in the use of the DSM system for depression diagnosis in recognizing the contribution of each presenting symptom has been previously identified (Widiger, Hurt et al. 1984; Sharpley and Bitsika 2013). Improvement such as differential weighting of symptoms and the consideration of the diagnostic efficiency of symptoms (either single or combined) in the diagnosis of depression has been suggested (Widiger, Hurt et al. 1984).

Following the work of Ostergaard and associates who calculated the possible mathematical combinations of the qualifying symptoms of MDE criteria to be 1,497 (Ostergaard, Jensen et al. 2011), the arguments against viewing depression as a unitary construct (Luyten, Blatt et al. 2006; Parker and Parker 2006; Ghaemi and Vohringer 2011) have been further strengthened and intensified, and available evidence also suggests that the pathophysiology of depression may vary not only in terms of the *number and severity of symptoms* present, but also in the *underlying*

behavioural and neurobiological mechanisms involved, and (consequently) in the appropriate treatment options required (Sharpley and Bitsika 2010; Sharpley and Bitsika 2013; Sharpley, Bitska et al. 2013). Thus, depression is most unlikely to be a phenomenon which can be completely explained as a unitary construct.

Furthermore, in contrast to a unitary construct model of depression, the symptomatologies for major depression (MDE and MDD) consist of several key aspects such as cognition, somatic and emotional diagnostic criteria (Clark and Watson 1991; Hassler, Drevets et al. 2004; APA 2013; Sharpley and Bitsika 2013; Sharpley, Bitska et al. 2013). The recognition of these key aspects as distinct features suggests that (i) depression is a complex combination of different groups of symptoms which may be associated with specific stressors (Bitsika and Sharpley 2012; Sharpley and Bitsika 2013; Sharpley, Bitska et al. 2013), and (ii) that the combinations of depressive symptoms may vary from one individual to another (Hassler, Drevets et al. 2004; Bitsika and Sharpley 2012; Sharpley and Bitsika 2013). This concept of a "*multiple construct*" for depression highlights the possibility of differing pathophysiology in the development of depression, and it may also provide an explanation as to why some types of depression do not respond to conventional therapeutic interventions (Sharpley and Bitsika 2010; Bitsika and Sharpley 2012).

The key symptoms of MDD have been used as the basis for classifying major depression into five depression subtypes: Melancholic depression, Depressed Mood, Anhedonic, Cognitive and Somatic depression (Bitsika and Sharpley 2012; Sharpley and Bitsika 2013; Sutin, Terraccino et al. 2013). As shown in Table 7, each of these identified subtypes of depression has different combinations of symptoms, differing underlying behavioural and neurobiological mechanisms, and different treatment options (Bitsika and Sharpley 2012; Sharpley, Bitska et al. 2013). This model of depression which recognizes major depression subtypes based on different combinations of symptoms and underlying pathophysiology has the advantage of ensuring that precise diagnosis and subtyping of major depression is made, and that the specific treatment option which is appropriate for the subtype is chosen, and this will most likely result in overall improvement in treatment outcome (Hassler, Drevets et al. 2004; Ghaemi and Vohringer 2011; Bitsika and Sharpley 2012; Sharpley, Bitsika et al. 2013; Sharpley and Bitsika 2013; Sharpley, Bitska et al. 2013). By

implication, in clinical practice, the conscious awareness of the possibility of clinical content subtypes of major depression may result in clinicians taking a more careful and thorough history, and ensuring that more detailed information about patients' depressive illness is recorded in order to fully characterize the specific depression subtypes, with a view to providing the recommended appropriate treatment, and as such, achieving the best treatment outcome (Sharpley and Bitsika 2013).

Table 7: Descriptive Feature and Treatment Options for four Clinical Content Subtypes of Depression (adapted from Sharpley and Bitsika 2013).

Clinical content subtype	DSM diagnostic criteria (Symptoms)*	Extensions to diagnostic criteria	Underlying behavioural and neurobiological mechanisms (Pathophysiology)	Treatment option
Depressed mood	1. Depressed mood most of the day, nearly every day, from subjective report (e.g., feels sad and empty) or observations made by others (e.g., appears tearful)[#].	1. Irritability (especially in children or adolescents), persistent anger, angry outbursts, blaming others, exaggerated frustration over minor events. Sad, hopeless, discouraged, "down in the dumps", feeling "blah" or having no feelings, feeling anxious. Sadness may be replaced by somatic complaints (bodily aches and pains).	* Functional changes in prefrontal cortex, hippocampus and amygdala induced by elevated serum cortisol and elevated HPA axis function. * Reduced serotonin levels in the brain due to prolonged psychological stress which influences serotonin release and uptake.	1. Antidepressants which re-establish serotoninergic functions e.g., Selective serotonin reuptake inhibitors (SSRI). 2. Psychotherapy
	2. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.	2. Unrealistic guilt or feelings of worthlessness over minor failures; misinterpretation of neutral or trivial daily events as evidence of major personal defects; may take responsibility for untoward events; delusional sense of responsibility for unfortunate world events; self-blame for illness.		
	3. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a suicide plan for committing suicide.	3. Thoughts that others would be better off if the depressed person were dead; suicidal thoughts and plans can vary in frequency, intensity and lethality; a desire to give up in the face of perceived insurmountable obstacles, or an intense wish to end a very painful emotional state.		
Anhedonia	1. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day[#].	1. Less interested in hobbies, sports or previously-enjoyed activities. Social and/or sexual loss of interest or desire.	* Imbalance in catecholaminergic systems (mainly dopamine). * Reduction in dopamine receptors in the brain	1. Antidepressants. 2. Transcranial magnetic stimulation. 3. 'Modern' psychotherapy (Behavioural Activation Therapy)
Somatic	1. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.	1. May feel as if they have to force themselves to eat. May crave sweets or other specific foods.	* "Sickness behaviour" in response to uncontrollable and unavoidable stressors, resulting in behaviours that meet somatic criteria. * Irregularities or dysfunction in physiological aspects of behaviour (including changes in diet, sleep and exercise) act as precursors of somatic symptoms of depression	1. Pharmacotherapy. 2. Psychotherapy (e.g., Insomnia focused). 3. Dietary and Nutritional supplementation (e.g., Omega-3 essential fatty acis, folate, iron, zinc, vitamins B12 and B6, selenium). 4. Re-establishing Exercise routine.
	2. Insomnia or hypersomnia nearly every day.	2. Initial insomnia less common than middle insomnia (waking during the night) or terminal insomnia (unable to return to sleep). Hypersomnia may be oversleeping at night or during the day.		
	3. Psychomotor agitation or retardation nearly every day observable by others.	3. Agitation: Inability to sit still. Pacing, handwringing, pulling or rubbing the skin, clothing or other objects. Retardation: slowed speech, slowed thinking, slow body movements; pauses before answering; soft speech, lack of inflection in speech; reduced		

	4. Fatigue or loss of energy nearly every day.	speaking frequency and amount, reduced content variation. 4. Tiredness, often without physical exertion; small tasks (such as dressing) require major effort; efficiency of completing tasks is reduced.		
Cognitive	1. Diminished ability to think or concentrate, or indecisiveness, nearly every day.	1. Easily distracted; complain of memory difficulties sometimes mistaken for dementia; inability to complete previous-manageable complex intellectual tasks; major drop in grades if studying.	* Stress induced HPA hyperactivity and hypercortisolaemia produce apoptotic reduction in the number and length of apical dendrites in the prefrontal cortex, resulting in impairment in attentional processes. * Stress induced HPA hyperactivity and hypercortisolaemia produce apoptotic reduction in the density of hippocampal pyramidal neurons and overall hippocampal volume. This result in in impairment of memory-retrieval process. * Hypercortisolaemia produce increased structural and functional changes in the amygdala (e.g., increased dendritic growth in pyramidal and stellate basolateral amygdala neurons, increased amygdala volume, enhanced synaptic connectivity and neuronal plasticity). During times of chronic stress, apart from overriding the effect of prefrontal cortex rational evaluation of stressors, the amygdala activates hypothalamic and brainstem stress pathway which results in increased catecholamine levels (noradrenaline and dopamine), and this in turn strengthens fear conditioning circuits in the amygdala, and contributes to the emotion-based decision making seen in depression.	1. Pharmacological treatment to improve cognition e.g., Protein Phosphatase 1 and 2B to improve memory. 2. Antidepressants e.g., SSRI. 3. Cognitive behaviour therapy. 4. Mindfulness therapy. 5. Psychodynamic psychotherapy. 6. 'Attention bias modification'. 7. Neurofeedback e.g., functional magnetic resonance imaging feedback (fMRINF). 8. Transcranial magnetic stimulation (TMS).

Note:

These are the principal symptoms of which at least one must be present with additional four other symptoms (or three if both principal symptoms are present), before a diagnosis of major depression is made.

* Diagnostic criteria symptoms are not listed in any particular order, but they are assigned to the major depression subtypes they belong.

2.5.1 Melancholic Depression

The fifth clinical content subtype of major depression identified as Melancholic depression is actually described in the DSM V as a specifier of MDD (APA 2013). It is identified by the presence of melancholic features characterized by extreme and persistent anhedonia (with lack of reactivity to usually pleasurable stimuli and near-complete absence of the capacity for pleasure), plus marked psychomotor agitation or retardation, significant anorexia or weight loss, excessive or inappropriate guilt, depression that is regularly worse in the morning with early-morning awakening (i.e., at least 2 hours before usual awakening), and a distinct quality of depressed mood (characterized by profound despondency, despair, and hopelessness) (Sharpley, Bitska et al. 2011; Bitsika and Sharpley 2012; APA 2013).

The underlying behavioural and neurobiological mechanisms that explain melancholic depression include: HPA axis dysfunction (which influences emotions) and the sympathetic nervous system (which produces symptoms of guilt and hopelessness, thyroid axis abnormalities which contribute to weight loss, sleep disturbances and psychomotor agitation or retardation, altered circadian rhythms resulting in sleep disturbances, and functional irregularities in the left dorsolateral prefrontal cortex causing depressed mood (Sharpley, Bitska et al. 2011). The recommended treatment options for melancholic depression include: pharmacotherapy (SSRI and Tricyclic antidepressants), and repetitive transcranial magnetic stimulation (Baeken, De Raedt et al. 2011).

2.6 Treatment of Depression

Clinical interventions which are instituted for the purpose of treating depression include: Pharmacotherapy (use of antidepressant medication), Psychotherapy, interventions that institute changes in brain structure and function (e.g., Electroconvulsive therapy (ECT), Trans-cranial magnetic stimulation (TMS) and Functional magnetic resonance imaging feedback (fMRINF), and Adjunct therapies (e.g. Diet, Exercise and Resilience training). These are briefly discussed below.

2.6.1 Pharmacotherapy (Antidepressants)

Antidepressants are commonly used medications in the treatment of depression. They include the Monoamine Oxidase Inhibitors (MAOIs), the Tricyclic and Tetracyclic antidepressants (TCAs), the Reuptake inhibitors and the Glutamatergic and GABAnergic drugs.

The MAOIs are believed to restore the levels of the three monoamines (serotonin, noradrenaline and dopamine) throughout the body, and the increase in these monoamines result in an increase in motor function and mood elevation (Hay and Linkowski 2004; Rang, Dale et al. 2007; NIMH 2010). Examples of MAOIs include phenelzine, tranylcypromine, moclobemide, trazodone, hyperforin, mirtazapine and mianserin (Hay and Linkowski 2004; Rang, Dale et al. 2007; NIMH 2010).

The TCAs are a closely-related class of drugs because they contain three or four cyclic hydrocarbon rings (Hay and Linkowski 2004; Peveler, Kendrick et al. 2005; Rang, Dale et al. 2007; NIMH 2010). Their mode of action is through the inhibition of transporter proteins that uptake serotonin and noradrenaline from the synaptic cleft, thereby making these monoamines more available for neurotransmission, and as a result, they facilitate mood elevation and reduction in somatic symptoms of depression (Rang, Dale et al. 2007; NIMH 2010). Examples of TCAs include imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, protriptyline, amoxapine, doxepine and maprotiline (Peveler, Kendrick et al. 2005; Rang, Dale et al. 2007; NIMH 2010).

The Reuptake inhibitors include the Selective serotonin reuptake inhibitors (SSRIs), Noradrenaline reuptake inhibitors (NRIs), and the combined Serotonin and Noradrenaline reuptake inhibitors (SNRIs). These are the most popular and mostly prescribed antidepressants especially in primary health care (Shelton and Lester 2006; Olfson and Marcus 2009), probably due to having fewer side effects which make them better tolerated by most patients (Arroll, Macgillivray et al. 2005; Olfson and Marcus 2009). The mode of action of reuptake inhibitors is via the inhibition of the process by which serotonin and noradrenaline are returned back into the presynaptic neuron, thus making these neurotransmitters more available for neurotransmission (Rang, Dale et al. 2007; NIMH 2010). They have been used effectively in the

treatment of moderate depression, but they are not so effective for severe depression, in which case MOAIs and TCAs are preferred (Arroll, Macgillivray et al. 2005; Rang, Dale et al. 2007; NIMH 2010).

Apart from the fact that most antidepressants have a long onset of action (it could take up to several weeks before antidepressant effects are seen) (Rang, Dale et al. 2007; NIMH 2010), the cost implications and the deleterious side effects of the use of antidepressants (which include nausea, anorexia, loss of libido, hypotension, hyperthermia, tremors, insomnia, weight gain, dry mouth, blurred vision, urinary retention, headaches, constipation, drowsiness, sedation, confusion and difficulty with concentrating) (Hay and Linkowski 2004; Arroll, Macgillivray et al. 2005; Rang, Dale et al. 2007; Olfson and Marcus 2009; NIMH 2010), are major concerns about the use of these medications in the treatment of depression.

More importantly, there are arguments about the efficacy of antidepressant medications in depression treatment (Kirsch, Moore et al. 2002; Kirsch, Scoboria et al. 2002; Moncrieff and Kirsch 2005; Ruhe and Mason 2007; Bruhl and Kaffenberger 2010; Moncrieff, Wessely et al. 2010). While some authors have suggested that antidepressant medications are significantly better than placebo, and that they are altogether effective and important in the management of depression (Hollon and Thase 2002; Thase and Denko 2008; Wichers and Barge-Schaapveld 2008; Bruhl and Kaffenberger 2010; Fournier and DeRubeis 2010), others have queried the effectiveness of these medications, indicating that a large proportion of depressed patients (sometimes up to 80%) fail to respond to antidepressant therapy in most clinical trials (Kirsch, Moore et al. 2002; Kirsch, Scoboria et al. 2002; Moncrieff and Kirsch 2005; Moncrieff, Wessely et al. 2010), and that the reported significant superiority of antidepressants over placebos does not reach a clinically acceptable significant level (Kirsch, Moore et al. 2002; Kirsch, Scoboria et al. 2002; Moncrieff and Kirsch 2005; Kirsch 2009; Moncrieff, Wessely et al. 2010). However, antidepressant use still remains a major therapeutic option in the management of depression (RANZCPCP 2004; NIMH 2010; Muskens, Eveleigh et al. 2013).

By extension, the arguments against the efficacy of antidepressants also affect the validity of the monoamine hypothesis, questioning the role of monoamines in the

development of depression, particularly because deprivation of neurotransmitters (serotonin, noradrenaline and dopamine) in healthy subjects does not result in decreased mood (Ruhe and Mason 2007), neither does the introduction of antidepressants in depressed individuals immediately reduce depressive symptoms, rather it takes several weeks before symptomatic relief is reported (Rang, Dale et al. 2007; NIMH 2010). Thus, it may be that, rather than being a direct causal factor of depression, neurotransmitters are contributory factors to the causal chain of depression (others being genes and environmental stressors, all of which are probably linked by the HPA axis) (Kato and Serretti 2010; Keers, Uher et al. 2010; Shyn and Hamilton 2010).

2.6.2 Psychotherapy

Psychotherapy or "talk therapy" is a specific intervention which is aimed at alleviating psychological distress through communication or talking, rather than the use of medications (NIMH 2010). Well-established psychotherapies which have been used in the treatment of mild, moderate and severe forms of depression include Cognitive Behaviour Therapy (CBT), Interpersonal Psychotherapy (IPT), Behavioural Activation Therapy (BAT), Problem-Solving Therapy (PST), Social Skills Training (SST) and Psychodynamic Therapy (PDT) (Cuijpers, van Straten et al. 2007; Cuijpers, van Straten et al. 2008; Shedler 2010; Dimidjian, Barrere et al. 2011; Cuijpers, Reynolds et al. 2012).

For most forms of psychotherapy that are used in depression management, the effectiveness of therapy appears to be the same irrespective of the different therapeutic approaches (Ahn and Wampold 2001; Cuijpers, van Straten et al. 2008; Cuijpers, van Straten et al. 2008), which is contrary to previous claims suggesting that CBT is a more effective therapeutic approach (Andrews 1991). While some authors argued that the increase in the number, duration and frequency of treatment sessions influences the effectiveness of psychotherapy for treating depression (Hansen, Lambert et al. 2002), others have indicated that effectiveness of psychotherapy is not affected by these factors (Dekker, Molenaar et al. 2005; Molenaar, Boom et al. 2011), and some other authors have shown that the intensity rather than the quantity of psychotherapy determines therapeutic effectiveness (Cuijpers, Huibers et al. 2013).

However, the "*Therapist-Patient Therapeutic Alliance*" remains a major factor which has been identified as an important contributor to the observed differences in the effectiveness of psychotherapy approaches (Andrews 2000; Martin, Garske et al. 2000). This factor is believed to be the most important aspect of the therapy process and it has been shown to influence the achievement of a positive outcome in psychotherapies (Andrews 2000; Sharpley 2010).

Overall, rather than a "one-size fits all approach" (which presumes one psychotherapy approach is better than the rest, and can be applied in most cases of depression), the choice of the best approach for any patient should be made on an "ideographic basis" by which the psychotherapy that best suits the patient (depending on the presenting problems and associated stressors) is adopted for treatment purposes. This process allows psychotherapy to be individualized rather than generalized (Parker, Roy et al. 2003; Parker and Parker 2006).

Apart from psychological/behavioural changes which contribute to the relief of depression symptoms, psychotherapies have been shown to have positive effects on brain structure and function with accompanying reduction in depression symptoms (Goldapple, Segal et al. 2004; Siegle, Carter et al. 2006; Kennedy, Konarski et al. 2007; Lehto, Tolmunen et al. 2008). Specifically, following psychotherapy sessions (e.g., CBT, psychoanalysis, IPT), increase in the performance of brain regions (such as amygdala activity, hippocampal blood flow, prefrontal cortex-limbic connectivity and enhanced serotonin transporter) have been reported, and these increased functionalities were associated with alleviation of depression (Goldapple, Segal et al. 2004; Siegle, Carter et al. 2006; Kennedy, Konarski et al. 2007; Lehto, Tolmunen et al. 2008). Also, different forms of psychotherapy have been shown to significantly reduce high cortisol levels (which may imply an improvement in depression symptoms) (Euler, Schimpf et al. 2005; Mommersteeg, Heijnen et al. 2006), and also shown to reduce both cortisol levels and depression (Antoni, Cruess et al. 2000).

2.6.3 Antidepressant vs. Psychotherapy: The 'when and how'

While there is a reciprocal relationship between the use of antidepressants and psychotherapy in depression management (Kocsis and Gelenberg 2009), the major consideration in treatment of depression remains 'when and how do we use either or both methods of therapy in managing depression?' Generally, it appears that antidepressants are the treatment of choice for severe forms of depression, and are particularly beneficial for patients with melancholic depression (RANZCPCP 2004; Rang, Dale et al. 2007; NIMH 2010). Psychotherapy could be beneficial to patients for whom medication was ineffective (Schatzberg and Rush 2005), and also for patients with high cognitive and social skills (Rude and Rehm 1991; Fournier and DeRubeis 2009). A combination of both therapies has been suggested for cases where the probability for relapse is high (Friedman, Detweiler-Bedell et al. 2004; De Maat and Dekker 2007; Cuijpers, Sijbrandij et al. 2014), and also for patients with low cognitive dysfunction (Slotsky and Glass 1991). Either or a combination of both antidepressants and psychotherapy can be used for the treatment of comorbid depression with personality disorders, as the presence of personality disorders has been found not to influence the outcomes of treatment (Mulder 2002; Maddux and Riso 2008).

From the review of the guidelines for depression treatment, the use of serotonin reuptake inhibitors, psychotherapy, or a combination of pharmacotherapy and psychotherapy are recommended as first-line treatments, while switching between therapy or augmentation of current therapy (depending on patient response to the initial therapy) is the next line of treatment, and the continuation of the approach that led to remission is advocated as maintenance therapy (Gelenberg 2010).

But it appears that future direction in the use of antidepressants and psychotherapy is in favour of the combination of both as Castren (2013) suggested in his recent review on the neuronal network plasticity and recovery from depression (Castren 2013). Castren noted that antidepressants reactivate a juvenile-like neuroplasticity which provides an avenue for the positive effects of rehabilitation and psychological therapy to bring about effective resolution of mood disorders (Castren 2013). He explained that if the gained neuro-plasticity is not followed by an appropriate positive learning environment (which can be provided by psychotherapy), the induced neuro-plasticity

will be lost, and antidepressant use will be ineffective in treating depression (Castren 2013). Thus, the best model of depression therapy will be to institute antidepressant therapy first, and then follow this by psychotherapy (Castren 2013) in cases of severe depression. If this explanation holds true, it may partly explain why either of both therapies has not been shown to be 100% effective when singly applied in most cases, and it may then imply that most forms of depression will require a combination of both therapies for appropriate treatment (Castren 2013). Treatment of less severe depression may be satisfactory with psychotherapy alone.

2.6.4 Other interventions that produce changes in brain structure and function

2.6.4.1 Electroconvulsive therapy (ECT)

ECT involves the passage of an electrical current through the brain using two electrodes placed on the scalp, usually under general anaesthesia. It is believed to be the most potent and rapidly acting antidepressant intervention by some authors (Eranti and Mogg 2007; Weiner, Lisanby et al. 2013). It is indicated for the treatment of very severe forms of depression and treatment-resistant melancholic depression (Sackeim, Dillingham et al. 2009; Weiner, Lisanby et al. 2013). ECT is believed to produce decreased frontal cortical connectivity (Perrin, Merz et al. 2012) and leads to decreased activity in the prefrontal cortex (Nobler and Oquendo 2001), although neurogenesis in the hippocampus following ECT has also been reported (Madsen and Treschow 2000), thus the precise explanation for its mode of action is still unclear. However, ECT remains a highly effective treatment for the management of very severe depression and for depressions that are resistant to multiple treatment interventions (Weiner, Lisanby et al. 2013).

2.6.4.2 Trans-cranial magnetic stimulation (TMS)

TMS has been used effectively in the treatment of MDD (O'Reardon and Solvason 2007; Carpenter, Janicak et al. 2012; Janicak, Dunner et al. 2013), in the management of treatment resistant depression (Schlaepfer, Cohen et al. 2008; Malone and Dougherty 2009) and in reducing depression relapse (Richieri, Guedj et al. 2013). It involves the application of a strong pulsed magnetic field close to a region of the cranium, which generates an electrical current that produces depolarization of brain neurons (Barker, Jalinous et al. 1985; Blumberger, Silverstein et al. 2013). Following the application of TMS to brain regions such as prefrontal cortex, cingulate gyrus,

ventral tegmental area and hippocampus, depressed patients showed significant remission of depression (Stern, Tormos et al. 2007; Lozano and Mayberg 2008; Friedman and Frankel 2009). Potential neurobiological mechanisms of TMS include: alterations in brain blood flow and increased metabolism (Lozano and Mayberg 2008; Blumberger, Silverstein et al. 2013), alterations in neuroendocrine and neurotransmitter levels (Lozano and Mayberg 2008), neurogenesis and decreased brain cortisol levels (Czeh and Welt 2002), electrophysiology (Lozano and Mayberg 2008) and enhanced neuroplasticity (Leuchter, Cook et al. 2013).

2.6.4.3 Functional magnetic resonance imaging neuro-feedback (fMRINF)

fMRINF is a promising procedure which can be employed in depression management as a means of achieving symptomatic relief (Weiskopf, Veit et al. 2003; Weiskopf, Scharnowski et al. 2004). With the aid of fMRI live feedback, patients can be taught how to control blood flow to specific brain regions which are relevant to depression pathophysiology (such as limbo-thalamo-cortical pathways, amygdala, insula, hippocampus and ventral striatum) (Weiskopf, Veit et al. 2003; Weiskopf, Scharnowski et al. 2004; Yoo, Lee et al. 2008; Johnston, Boehm et al. 2010), and by doing so they are able to improve brain activity in these areas and as such reduce depressive symptoms (Yoo, Lee et al. 2008; Johnston, Boehm et al. 2010).

2.6.4.4 Adjunct therapies

Adjunct therapies that are believed to contribute to alleviation of depressive symptoms include Diet, Exercise and Resilience training. A well balanced diet which is rich in fruits, grains, meat and fish, with less fat plus reduced alcohol intake may be helpful in preventing depression (Jacka and Kremer 2010; Jacka and Pasco 2010; Sanchez-Villegas and Martínez-González 2013). This is particularly important because poor diets especially those which are described as 'junk meals', have been shown to predispose individuals to developing obesity and depression (Sánchez-Villegasa, Toledoa et al. 2012; Sanchez-Villegasa and Toledoa 2012; Sanchez-Villegas and Martínez-González 2013), and obesity increases the risk of depression (*and vice versa*) (Luppino and de Wit 2010). Exercise which is maintained at an intensity level not greater than the patient's usual level has been shown to be effective in the treatment and prevention of depression (Salmon 2000; Strohle 2009; Mead, Morley et al. 2010; Lopresti, Hood et al. 2013). Similarly, psychological resilience

which can be developed by training could serve as a protective trait and act as a 'buffer' against depression (Reivich and Seligman 2011; Sharpley, Bitsika et al. 2012; Reivich, Gillham et al. 2013; Sharpley, Wootten et al. 2013).

2.7 Comorbidity of Depression and Anxiety

Many epidemiological studies have consistently reported that both depression and anxiety co-occur commonly (Hirschfeld 2001; Lenze, Mulsant et al. 2001; Smalbrugge, Jongenelis et al. 2005; Lamers, van Oppen et al. 2011; Bitsika and Sharpley 2012), and in clinical presentation (either in primary care or specialized mental health settings), depression is more likely to co-occur with anxiety than with any other disorder (AIHW 2007). Also, the likelihood of co-morbidity of anxiety and depression increases with the increased severity of either depression or anxiety (Smalbrugge, Jongenelis et al. 2005), and the incidence of comorbidity may be higher in chronic conditions such as diabetes, inflammatory bowel diseases and malignancies (Aina and Susman 2006; Mikocka-Walus, Turnbull et al. 2007; Sharpley, Bitsika et al. 2010).

Previous cohort studies have shown that between 58% and 85% of patients with MDD have at least one anxiety disorder (Gorman 1996; Kessler, Nelson et al. 1996), while between 45% and 85% of patients with generalized anxiety disorder may have comorbid major depressive disorder (Gorman 1996; Rickels and Rynn 2002). As reported by Lamers *et al.,* (2011), the current and lifetime prevalence of comorbid anxiety in patients with MDD was 67% and 75% respectively, while the current and lifetime prevalence of comorbid depression in patients with anxiety disorders was 63% and 81%. In Australia, co-morbid depression and anxiety disorders have been found to occur in about 25% of general practice patients (Tiller 2012).

2.7.1 Symptom Overlap between Depression and Anxiety

Some symptoms are common to both depression and anxiety (e.g. sleep disturbances, change in appetite and libido) (Mineka, Watson et al. 1998; APA 2013), and this symptom overlap which occurs in the diagnosis of depression and anxiety may explain why more than 50% of patients with generalized anxiety disorder and more than 30% of those with social anxiety disorder meet the criteria for MDD (Van Ameringen, Mancini et al. 1991; Yonkers, Warshaw et al. 1996). The fact that

patients with both depression and anxiety disorders seem to respond similarly to antidepressants and psychotropic drugs may provide an explanation for the comorbidity of these two disorders (Zimmerman, McDermut et al. 2000; Nemeroff 2002). However, the precise mechanism which explains the findings of comorbid depression and anxiety is still largely unknown.

Some authors have suggested that the occurrence of anxiety disorder may predict subsequent risk of developing MDD, possibly because the initial anxiety state results in nervousness, worry, fear and inability to cope with life stressors, which then results in a low energy state, loss of drive and reduced motivation which depict a depressive state (Kessler, Nelson et al. 1996; Muris, Merckelbach et al. 2001; AIHW 2007; Lieberman 2009). However, depression has been shown to also precede anxiety just as much as anxiety precedes depression, and this may suggest that depression and anxiety are distinct diagnoses, and one may not necessarily lead to the development of the other (Merikangas, Zhang et al. 2003; Moffitt, Harrington et al. 2007).

2.7.2 Theoretical Models of Depression and Anxiety

Some authors have used theoretical models to explain the relationship between depression and anxiety disorders and to justify the findings of comorbidity of depression and anxiety (Anderson and Hope 2008; Kemp and Felmingham 2008; Mathersul, Williams et al. 2008). The models which have been used for these purposes include the tripartite model, the approach-withdrawal model and the valence-arousal model (Heller's model) (Anderson and Hope 2008; Kemp and Felmingham 2008; Mathersul, Williams et al. 2008).

Following the work of Watson and Tellegen (1985), the varying combinations of two stable and heritable broad factors of temperament (positive affectivity (PA) and negative affectivity (NA)), were identified as possible explanations for the distinct features of depression and anxiety and also the comorbid occurrence of both (Mathersul, Williams et al. 2008).

NA (which includes emotions of sadness, guilt, nervousness, fear, hostility, uneasiness and self-dissatisfaction) is related to neuroticism, and it is believed to be common to the phenotypic structures of both depression and anxiety (Watson and Clark 1984; Clark and Watson 1991 ; Mineka, Watson et al. 1998), while PA (which

includes traits such as excitement seeking, enthusiasm, energy and gregariousness) is related to extraversion (Watson and Clark 1984; Clark and Watson 1991 ; Mineka, Watson et al. 1998). The tripartite model proposed that anxiety and depression share a common component of NA, but they can be differentiated by low PA associated with depression and high physiological hyper-arousal (with symptoms such as dizziness, shortness of breath, racing heart, and shaky hands) which is specific for anxiety (Clark and Watson 1991).

The approach-withdrawal model is a bio-behavioral model which uses two separate systems of motivation and emotion (the approach and withdrawal systems), in addition to affective component (Davidson 1998). The approach system is believed to be responsible for the generation of PA (facilitated by reward) and termination of negative emotion (Henriques and Davidson 2000). The activation of the left prefrontal cortex is hypothesized to be related to the activation of the approach system (Gray 1994; Davidson 1998). On the other hand, the withdrawal system is purported to be responsible for eliciting arousal and for the generation of certain facets of NA (such as fear or disgust) in response to aversive stimulus (Henriques and Davidson 2000). The activation of the right prefrontal cortex is also hypothesized to be related to the withdrawal system (Gray 1994; Davidson 1998).

The approach-withdrawal model proposes that in depression, under-activation of the approach system (left prefrontal cortex) results in less responsiveness to rewards (rewards become less reinforcing) (Henriques and Davidson 2000), and negative emotion or aversive responses are less extinguished, thus positive affect is less generated while negative affect lasts longer (Fowles 1994; Davidson 1998; Kring and Bachorowski 1999). Anxiety disorder is viewed as over-activation of the withdrawal system (right prefrontal cortex) resulting in oversensitivity and over-reactivity to aversive stimuli the outcome of which is increased arousal and anxious apprehension associated with anxiety disorders (Davidson 1998; Tomarken and Keener 1998; Kring and Bachorowski 1999). The combination of over-activation of the withdrawal system and under-activation of the approach system results in comorbid depression and anxiety (Shankman and Klein 2003).

This valence-arousal model (Heller's model) characterizes depression as a decrease in approach behaviour and subsequent lower PA, while anxiety is described as having two dimensions of neuropsychological models of emotion (anxious apprehension and anxious arousal) (Heller, Nitschke et al. 1997; Mathersul, Williams et al. 2008). Anxious arousal is associated with ipsilateral increased activity in the right hemisphere and anxious apprehension is associated with increased activity in the left hemisphere (Heller, Nitschke et al. 1997). In addition, anxious arousal results in increased activity in the right frontal region while anxious apprehension may yield a bilateral increase in frontal activity—increase in left from the anxious apprehension (approach system) and increase in right from the withdrawal system (Heller, Nitschke et al. 1997).

The valence-arousal model proposes that individuals with depression and anxiety can be differentiated by lower and higher right parieto-temporal activity, respectively (Kemp and Felmingham 2008; Mathersul, Williams et al. 2008) and comorbid depression and anxiety result from under-activation of the approach system plus over-activation of anxious apprehension system (Shankman and Klein 2003). However, anxious apprehension is also believed to be somewhat related to approach tendencies associated with PA and to withdrawal tendencies associated with NA (Shankman and Klein 2003). The degree to which anxious apprehension yields either approach or withdrawal tendencies is dependent on factors such as the amount of stress and discomfort an individual is exposed to and the person's coping style (Heller and Nitschke 1998). Thus the dual association of anxious apprehension with both PA and NA may also explain the co-occurrence of depression and anxiety (Shankman and Klein 2003).

The summary of the theoretical models is presented in Table 8 (Adapted from Shankman and Klein, 2003).

Table 8: The three models hypotheses regarding the description and aetiology of depression, anxiety, and when they co-occur (Adapted from Shankman and Klein, 2003).

Model	Description of depression	Aetiology of depression	Description of anxiety	Aetiology of anxiety	Description of comorbid[a]	Aetiology of comorbid[a]
Tripartite	Low PA and/or high NA	Low PA and/ or high NA temperament	High PH and/or high NA	High arousal and/or high NA temperament	Low PA, high NA, and high PH	High PH, low PA, high NA temperament
Approach withdrawal	Low PA (and/or high NA)[b]	Under-activation of approach system and/or over-activation of withdrawal system	High arousal and high NA	Over-activation of withdrawal system	Low PA, high NA, high PH	High PH, low PA, high NA temperament
Valence-arousal (Heller's Model)	Low PA (and/or high NA)[b]	Under-activation of approach system and/or over-activation of withdrawal system	1. High NA, and 2. High PH, High AA, or both	Over-activated AA system or PH System, or both	1. Low PA, 2. High NA, and 3. High PH, high AA or both	1.Under-activated approach system, 2.Over-actived AA system and/or PH system

AA= Anxious apprehension; PH = Physiological hyperarousal.
a- These predictions are extrapolations as they have never fully been discussed.
b- Predictions in brackets are not integral components of the model.

2.7.3 Implications of comorbid occurrence of Depression and Anxiety

Some researchers have suggested that anxiety increases the severity, duration and recurrence of MDD symptoms and also worsens the disability associated with depression (Sartorius, Ustun et al. 1996; Zimmerman, McDermut et al. 2000; Hirschfeld 2001). Depressed patients with anxiety symptoms are more ill at presentation, they have more social, psychological and vocational impairment, they are more chronically ill, they show poorer response to treatment (both short and long term), they demonstrate low remission rates and they are more likely to have alcohol and substance abuse with higher suicidal rates (Lydiard and Brawman-Minzer 1988; Keller and Hanks 1995; Hirschfeld 2001). Also, comorbid depression and anxiety has been associated with greater incidence of prematurity in neonates of mothers with prenatal depression (Field, Diego et al. 2010).

Patients with comorbid depression and anxiety may require additional or adjunct therapies such as psychotherapy and benzodiazepines, and this makes their management more challenging and more expensive (Fava, Rush et al. 2008; Lieberman 2009; Stein 2009). More importantly, ineffective recognition and

treatment of anxiety and depression co-morbidity is associated with worse psychiatric outcomes, increased treatment costs and increased utilization of the health care system (Wittchen 2002; Marciniak, Lage et al. 2005).

In clinical practice, following appropriate history-taking and examination, the identification of comorbid anxiety with depression may be possible by symptom identification. For instance, the presence of any hyper-vigilance, agitation, dysphoria, sleep problems, concentration problems, restlessness, irritability, worry, anxiety and tension in the background of depressive symptoms may indicate a comorbid anxious state (Roy-Byrne and Katon 1997). Also, the use of combinations of acronyms and screeners such as the "SOAP" (Subjective, Objective, Assessment and Plan), the "BATHE" (Background, Affect, Trouble, Handling, Empathy), the "SIG E CAPS" (Sleep or Sexual desire, Interest, Guilt, Energy, Concentration, Appetite, Psychomotor agitation, Suicidal ideation) and the "SWICKIR" (Somatic symptoms, Worries, Irritability, Concentration, Keyed up, Initial insomnia, Relaxation difficulties) is helpful in establishing the right diagnosis of comorbid depression and anxiety (Lieberman 2009). However, most comorbid depression and anxiety go undiagnosed in clinical practice, especially in primary health care (Tiller 2012), and in order to increase clinical vigilance, clinicians are advised to always remember that co-morbidity is the rule with anxiety and depression rather than being the exception, especially when considering the presentation, course of illness and treatment options of both disorders (Aina and Susman 2006; Lieberman 2009).

2.8 Neuroimaging in Depression

The use of neuroimaging in neurophysiology and neuropsychology research on depression has made significant contributions to the understanding of depression pathophysiology (Köhler, Thomas et al. 2010; Bruder, Bansal et al. 2012; Weber, Giannakopoulos et al. 2012; Grotegerd D, Suslow et al. 2013). More importantly, neuroimaging has been a useful tool in highlighting the neuroanatomical and functional activity changes which occur in the brain under different forms of depression (Yao, Wang et al. 2009; Köhler, Thomas et al. 2010; Baeken, De Raedt et al. 2011; Gaffrey, Luby et al. 2011; Lanzenberger, Kranz et al. 2012; Marchand, Lee et al. 2013; Nugent, Bain et al. 2013; Smith, Nødskov et al. 2013). In addition, neuroimaging studies have helped scientists to investigate the effectiveness of various

treatments and therapeutic interventions in the clinical management of depression (Siegle, Carter et al. 2006; Wu, Li et al. 2011; Lanzenberger, Kranz et al. 2012; Guo, Liu et al. 2013; Nugent, Bain et al. 2013).

Commonly used neuroimaging tools for investigating cerebral changes in neurophysiology and neuropsychology of depression include: Electroencephalography (EEG), Computed Axial Tomography Scan (CT scan), Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT). Of the above listed neuroimaging methods, EEG (the most widely used neuroimaging tool in neuropsychiatry research, and in many neurophysiology and neuropsychology studies on depression) (Buzsáki, Anastassiou et al. 2012), is described below and the others are summarized in Table **9**.

2.8.1 Electroencephalography (EEG)

Electroencephalography is an important electrophysiological technique or neuro-imaging tool used in neuroscience to investigate brain electrical activity and cerebral changes that usually accompany many pathological and psychological conditions (Schlögl, Slater et al. 2002; NINDS 2011; Scomer and da Silva 2011). It involves the use of electrodes attached to the scalp for the purpose of recording the electrical activity originating from the brain. It measures the voltage fluctuations resulting from ionic current flows within the neurons of the brain (Schlögl, Slater et al. 2002; Scomer and da Silva 2011). EEG entails recording of the brain's spontaneous electrical activity over a short period of time (usually less than 40 minutes) from multiple electrodes placed on the scalp (NINDS 2011). EEG may be used in sleep studies, diagnosis of epilepsy, coma, encephalopathies, focal brain disorders (tumours and stroke) and to diagnose brain death (Abou-Khalil and Misulis 2006; NINDS 2011).

EEG has the advantage of being able to determine the relative strengths and locations of electrical activity arising from different brain regions (Schlögl, Slater et al. 2002; NINDS 2011; Scomer and da Silva 2011). Also, EEG is a painless, relatively cheap and risk-free procedure, and EEG recordings of timed brain activity are more precise, although, resolution is poor and it does not directly record interior brain activity (Schlögl, Slater et al. 2002; NINDS 2011; Scomer and da Silva 2011). As a result,

researchers often use EEG images of brain electrical activity in combination with MRI scans to better pinpoint the location of the activity in the brain (this process is termed 'high density EEG') (NINDS 2011; Buzsáki, Anastassiou et al. 2012).
The advent of other anatomical imaging techniques such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) with higher spatial resolution has led to a decline in the use of EEG in clinical practice (NINDS 2011; Buzsáki, Anastassiou et al. 2012). However, EEG continues to be a valuable tool for research, especially when millisecond-range temporal resolution (not possible with MRI) is required (NINDS 2011; Scomer and da Silva 2011; Buzsáki, Anastassiou et al. 2012).

Some of the applications of EEG in depression studies include: the investigation of regional differences in the brain electrical activities, especially in the frontal, parietal and temporal regions (Hinrikus, Suhhova et al. 2010; Steiger and Kimura 2010; Stewart, Bismark et al. 2010; Stewart, Coan et al. 2011; Feng, Forbes et al. 2012; Olbrich, Sander et al. 2012; Talati, Weissman et al. 2013; Zhang, Hu et al. 2013); as a diagnostic/prognostic marker of depression (Steiger and Kimura 2010; Stewart, Bismark et al. 2010; Stewart, Coan et al. 2011; Feng, Forbes et al. 2012; Olbrich, Sander et al. 2012; Talati, Weissman et al. 2013; Zhang, Hu et al. 2013); for measuring the antidepressant effect of interventions such as electroconvulsive therapy and slow wave sleep deprivation (Landsness, Goldstein et al. 2011; Okazaki, Takahashi et al. 2013); for investigating structural and functional changes in the brains of depressed subjects (Wei, Li et al. 2009; Leistritz, Weiss et al. 2010; Lopez-Duran, Nusslock et al. 2012; Plante, Landsness et al. 2012; Bat-Pitault, Da Fonseca et al. 2013; Bornas, Noguera et al. 2013); for measuring treatment efficacy and as a predictor of treatment response in depression (Iznak, Tiganov et al. 2013; Widge, Avery et al. 2013); for investigating functional changes during treatment of depression (Iznak, Tiganov et al. 2013); and for investigating the association between genetic factors and depression severity (Zoon, Veth et al. 2013).

Table 9: Descriptive features of other types of neuroimaging in Neuroscience (from NINDS 2011).

Neuroimaging	Principles of Image Acquisition	General Applications	Advantages	Disadvantages	Applications in Depression Studies
Computed Axial Tomography Scan (CT scan)	* CT utilizes a series of x-rays applied from different directions to produce quick and clear two-dimensional images of organs, bones, and tissues. * The X-rays which are passed through the body during a CT session are detected by a computerized scanner which has been programmed to process the data and displayed it as a cross-sectional images, or "slices," of the internal structure of the organ under investigation. * The computer program of the CT scanner uses a set of algebraic calculations to estimate how much x-ray is absorbed by an organ, and the harder a material is, the whiter it will appear on the scan, so bony structures appear whiter than soft tissues.	* CT scans are used to investigate a wide variety of abnormalities such as, identifying blood clot or intracranial bleeding in patients with stroke, detecting bone and vascular irregularities, confirming the presence of brain tumours and cysts, evaluating swelling from tissue damage in the brain, investigating brain and spinal cord damage from traumatic injuries, assessment of ventricle size in patients with hydrocephalus, and for assisting diagnosis of other disorders such as herniated discs, epilepsy, encephalitis and spinal canal stenosis.	* CT scan is a non-invasive, painless procedure which is relatively quick to carry out. A regular CT scan procedure takes about 20 minutes (CT of the brain may take up to one hour). * CT scan is usually done in a hospital or in an imaging centre as a day procedure, so no extensive pre-procedure preparation is required, and images are available for use almost immediately. * Apart from differentiating soft and hard tissues in the body, CT scan is also capable of differentiating various brain regions and as such it is very helpful in differentiating many neurological disorders which share similar characteristics.	* CT scan is relatively expensive. * Persons who are Obese or individuals who have claustrophobia may find it hard to undergo a CT scan as they will be staying in a closed space for a period of time. * Pregnant women cannot undergo CT scan because of potential harm to the foetus from exposure to high ionizing radiation. * Individuals who are restless may require a light sedative to help them stay still during the procedure. * Occasionally, a contrast dye may be injected into the veins to further highlight the different areas in the brain. The contrast dye has been known to give unwanted side effects such as allergic reactions, and patients may experience a slight metallic taste or feeling of a warm or cool sensation as the dye circulates through their bloodstream.	* CT scan has been used extensively to investigate various neurophysiological and neuropsychological factors associated with depression, some of which include neuropsychological deficits and cognitive impairment associated with depression (Köhler *et al.,* 2010), association of depressive symptoms and medical condition such as acute stroke (Kouwenhoven *et al.,* 2013) and Alzheimer's disease (Brommelhoff *et al.,* 2011), and depressive symptoms following traumatic brain injury (Rao *et al.,* 2010; Sigurdardottir *et al.,* 2013).
Magnetic Resonance Imaging (MRI)	* MRI uses a combination of powerful magnetic field and computer-generated radio waves to produce high quality two- or three-dimensional detailed images of body structures including tissues, organs, bones, and nerves. * The mechanism by which MRI scan generates images involves the temporary realignment of water	* Based on their water content and structural properties, MRI is able to differentiate between bone, soft tissues and fluid-filled spaces. * MRI is used in the diagnosis and differentiation of brain and spinal cord tumours,	* MRI is a safe procedure because, unlike CT scanning, MRI excludes the use of ionizing radiation to produce images. *The use of magnetic fields and radio waves to produce high quality images also	* MRI is more expensive than CT * Patients with surgically implanted medical devices (e.g., pacemaker, and metallic prosthesis in bones) will not be able to undergo MRI procedure. * Obese and claustrophobic patient may find it somewhat uncomfortable.	* In many depression studies, MRI has been used as: a diagnostic and prognostic marker of depression (Nouretdinov *et al.,* 2011); for measuring the antidepressant effect of interventions such as repetitive trans-cranial magnetic stimulation (Martinot *et al.,* 2010); for investigating structural abnormalities and functional changes in the brain of depressed subjects (Gunning-Dixona *et al.,* 2010; Hwang *et al.,* 2010; Marchand *et al.,* 2013; Takahashia *et al.,*

	molecules as a result of the high magnetic field created around the body. As radio waves are passed through the body, the "relaxation" of the molecules back to a random alignment is detected and resonance signal at different angles within the body are acquired with the aid of sensors which read the frequencies and a computer uses the information to construct the required image. * The computer processing of the triggered resonance is able to create either a two-dimensional "slice" or a three-dimensional picture of the tissue under investigation.	structural deficits of the eyes, inflammation, infection, and vascular irregularities in the brain which may lead to stroke and in the diagnosis and monitoring of various neuro-degenerative disorders (e.g., multiple sclerosis and Parkinson's disease).	excludes the use of radioactive tracers. * MRI is able to generate images of both surface and subsurface structures with a high degree of anatomical detail. * In addition, cross sectional images in any direction (top to bottom, side to side, or front to back) can be computer generated in an MRI study and the precision of the detection mechanisms enables MRI to detect changes in structures over time.	* MRI machines generate grating or knocking noises which may require that patients wear special earphones to block out the unwanted sounds. * The unwanted side effects of contrast dye could also occur whenever contrast dye is applied during an MRI procedure. * MRI is unable to provide information about how well the brain is working at the time of imaging.	2010a; Takahashia *et al.,* 2010b) ; for investigating treatment resistance (Duhameaua *et al.,* 2010) and treatment outcomes (Disabato *et al.,* 2013) in depression; for investigating cortical changes in individuals at risk for depression (Bruder *et al.,* 2012); for investigating the association of depressive symptoms and cortical changes in medical condition such as stroke and Alzheimer's (Lassalle-Lagadec *et al.,* 2012; Lebedev *et al.,* 2012); for investigating cognitive and personality changes in depression (Weber *et al.,*2012); and for investigating the association of anatomical changes and genetic liability for development of depression (Alemany *et al.,* 2013).
Functional Magnetic Resonance Imaging (fMRI)	* fMRI uses the blood's magnetic properties to produce real-time images of blood flow to particular areas of the brain. Increased blood flow to an area of the brain implies increased activity in that area. * During an fMRI procedure, the performance of a repetitive motion (like tapping a finger or tapping a foot) results in activation of brain regions evidenced by increased blood flow. The mapping of blood flow using fMRI allows for dynamic brain mapping to take place and scientist are able to determine which brain regions become active and for how long.	* fMRI is used to assess brain damage from head injury or degenerative disorders (e.g., Alzheimer's disease) and to identify and monitor other neurological disorders, including multiple sclerosis, stroke, and brain tumours.	* fMRI can produce images of the brain every second, and scientists can determine with great precision when brain regions become active and for how long. * fMRI has a high resolution (it can distinguish structures which are less than a millimetre apart). This allows scientists to know exactly which areas of the brain are being activated. * It can also tell if brain activity within a region occurs simultaneously or sequentially.	* It takes quite a bit of time to perform the procedure and the patient needs to be completely still for often more than twenty minutes at a time * It is also an expensive procedure * Interpretations of fMRI results may be confounded by other factors (e.g., subject's thought which may be difficult to regulate during the procedure). This can cause certain parts of the brain to become active, and it may be difficult to distinguish if the scanner had picked up real data or noise. * fMRI is unable to identify which brain receptors are being activated by neurotransmitters, drugs and potential treatment compounds.	* fMRI has been used in various depression study for the purpose of: investigating brain anatomical changes in depression (Aizenstein *et al.,* 2011; Liu *et al.,* 2010); understanding brain functional changes which accompany depression (Groenewold *et al.,* 2013; Korsnes *et al.,* 2013; Lawson *et al.,* 2013; Milne *et al.,* 2013; Olino *et al.,* 2011; Oliveira *et al.,* 2013); for differentiating unipolar and bipolar depressions (Grotegerd *et al.,* 2013); for measuring the antidepressant effect of interventions such as cognitive behaviour therapy (Siegle *et al.,* 2006); for the understanding and investigation of treatment resistance and treatment refraction in depression (Guo *et al.,* 2013:Wu *et al.,* 2010); for investigating the association between depression severity and brain functional changes in depression (Gaffrey *et al.,* 2011; Smith *et al.,* 2013); for investigating the association between depression symptoms and abnormalities in brain activities (Yao *et al.,* 2009); and for instituting neuro-feedback treatment in the management of depression (Johnston *et al.,* 2010; Yoo *et al.,* 2008),

Positron Emission Tomography (PET)	* PET measures emissions from radioactively labelled chemicals that have been injected into the bloodstream, and it uses the data to produce two or three-dimensional images of the distribution of the chemicals throughout the brain. * PET scans involve the use of a machine called a cyclotron to label chemicals with small amounts of radioactivity. The labelled compound, called radiotracer, is injected into the bloodstream and eventually makes its way to the brain, and they can be traced to their specific location even as the brain performs different functions. * Overhead sensors in the PET scanner detect the radioactivity (gamma rays) as the compound accumulates in different regions of the brain. A computer uses the data gathered by the sensors to create multi-coloured two or three-dimensional images that show where the compound acts in the brain, and the information gathered is displayed on a video monitor or on film.	* PET scans are used to highlight tumours and diseased tissue especially the brain. It measures cellular and/or tissue metabolism and it can show blood flow to an organ. * PET is used to evaluate patients who have seizure disorders that do not respond to medical therapy, and patients with certain memory disorders, and also to determine brain changes following injury or drug abuse. * PET may be ordered as a follow-up to a CT or MRI scan to give the physician a greater understanding of specific areas of the brain that may be involved with certain problems.	* PET scan is able to make different compounds show blood flow, oxygen consumption and glucose metabolism in the tissues of the working brain. These measurements reflect the amount of brain activity in the various regions of the brain and allow us to learn more about how the brain works. * PET scans have superior resolution and higher speed of completion (as little as 30 seconds). This improved resolution enables scientist to make better judgments as to the area of the brain activated by a particular task. * Also, by using different compounds in a PET scan procedure, more than one brain function can be traced simultaneously.	* The biggest drawback of PET scanning is that, the radioactive materials used in the process decay rapidly, therefore its use is limited to monitoring short tasks only. * There is the risk of exposure to radioactive materials. * It is also an expensive procedure.	* Apart from using PET scan to investigate brain structural and functional changes in depression (Monkul *et al.,* 2012; Moses-Kolko *et al.,* 2012; Nugent *et al.,* 2013; Parsey *et al.,* 2006; Shrestha *et al.,* 2012), most studies have used PET scan for the purpose of measuring the effectiveness and treatment outcomes of many anti-depressant medications (de Klerk *et al.,* 2010; Diaconescu *et al.,* 2011; Ding *et al.,* 2013; Kennedy *et al.,* 2001; Lanzenberger *et al.,* 2012; Mayberg *et al.,* 2000; Meyer *et al.,* 2001) and antidepressant interventions (Clark and Beck, 2010; Goldapple *et al.,* 2004; Lanzenberger *et al.,* 2013; Schönfeldt-Lecuona *et al.,* 2010), and also for the understanding and investigation of treatment resistance and treatment refraction in depression (Carlson *et al.,* 2013; Lan *et al.,* 2013: Lakhan and Callaway, 2010; Mayberg 2005). PET scan has also been used for studying neuro-inflammatory changes in depression (Dobos *et al.,* 2012; Hannestad *et al.,* 2013), and for investigating the association of depressive symptoms and cortical changes in medical condition such as Parkinson's and Alzheimer's disease (Joutsa *et al.,* 2013; Caroli *et al.,* 2010).
Single Photon Emission Computed Tomography (SPECT)	* Similar to PET, SPECT is a nuclear imaging test which utilizes the blood flow to tissue to evaluate certain brain functions. * It uses radioactive tracers and a scanner to record data which a computer uses to construct two- or three-dimensional images of active brain regions. * As with a PET scan, a radioactive isotope, which binds to chemicals that flow to the brain, is injected intravenously into the body. Areas of increased blood flow will collect more of the isotope. As the patient	* SPECT may be ordered as a follow-up to an MRI to diagnose tumours, infections, degenerative spinal disease, and stress fractures. * SPECT is the desired neuroimaging whenever longer lasting brain functions are to be examined.	* The tracers of SPECT are longer lasting than those of PET, which allows for different, longer lasting brain functions to be examined. * SPECT is often chosen over PET simply as a cost issue, for less equipment is involved and fewer staff is required to perform the tests.	* SPECT tracers are considered to be more limited than PET scanners in the kinds of brain activity they have the ability to monitor. * The resolution of SPECT is poor (about 1 cm) when compared to that of PET. * SPECT also requires more time for completion.	* In many depression study, SPECT has been used for: investigating brain structural and functional changes in depression (Amsterdam *et al.,* 2013; Hamilton *et al.,* 2012; Hannestad *et al.,* 2013; Hsieh *et al.,* 2010; Selvaraj *et al.,* 2009; Tsai *et al.,* 2013) or predicting the antidepressant effect of interventions such as repetitive trans-cranial magnetic stimulation and chronic vagus nerve stimulation (Kito *et al.,* 2012; Kosel *et al.,* 2011; Richieri *et al.,* 2011); for the understanding and investigation of treatment resistance and treatment refraction (Helge *et al.,* 2012; Richieri *et al.,* 2012) and treatment outcomes (Baeken *et al.,* 2011; Brockmann *et al.,*2009; Wu *et*

	lies on a table, a gamma camera (radioactive sensor) rotates around the head and records where the radioisotope has travelled. * The information gathered by the radioactive sensor is converted by the computer into cross-sectional slices that are stacked to produce a detailed three-dimensional image of blood flow and activity within the brain.				*al.,* 2013) of different therapeutic medications for depression; for investigating the association of depressive symptoms with structural and functional brain changes in medical condition such as Parkinson's and Alzheimer's (Chagas *et al.,* 2013; Di Giuda *et al.,* 2012; Kang *et al.,* 2012; Lebedev *et al.,* 2013; Staffen *et al.* 2009; Wu *et al.,* 2011), and for investigating the association of functional changes and genetic polymorphism in depression (Ho *et al.,* 2013).

CHAPTER THREE

Alpha EEG Asymmetry and Depression: a systematic analytical review of the Literature and Issues for Research

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3.1 Introduction

A characteristic finding in EEG measurements of depressed individuals is "frontal lobe hemispheric asymmetry" (FLA) (Coan and Allen 2004; Blackhart, Minnix et al. 2006; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Feng, Forbes et al. 2012). FLA is defined as the relative difference between the amounts of alpha electrical activity in the left and right frontal lobes during measurements of resting EEG (Henriques and Davidson 1990; Davidson 1998). As opposed to healthy non-depressed individuals, who demonstrate equal amounts of electrical activity in both frontal lobes, depressed individuals show relative greater electrical activity in the right frontal lobe than in the left frontal lobe (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 1998; Gotlib 1998; Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Deslandes, de Moraes et al. 2008; Carvalho, Moraes et al. 2011; Gold, Fachner et al. 2013).

FLA has been explained by the "approach withdrawal" model (Davidson 1998), in which it is hypothesized that electrical activity in the left prefrontal cortex reflects the behavioural *approach* system (responsible for *engaging* with pleasant stimuli) (Davidson 1998) and the activation of the right prefrontal cortex represents the behavioural *withdrawal* system (responsible for *disengaging from* or *avoiding* aversive stimuli) (Henriques and Davidson 2000). This model is based upon the depressed individual's desire to withdraw from aversive environmental stimuli as a behavioural strategy for reducing the sum total of negative emotional experiences they are undergoing and has a strong base in models of depression (Ferster 1973; Dougher and Hackbert 1994). This withdrawal behaviour is accompanied by less left frontal lobe activation and more right frontal lobe activation, often shown as $R_a > L_a$ cerebral activation (Gray 1994; Davidson 1998; Henriques and Davidson 2000).

3.1.1 Alpha brain waves

In general terms, EEG measurements of brain electrical activities are classified according to the frequencies of brain waves (i.e. 8 – 13 Hz (alpha waves), 3.5 – 7 Hz (theta waves), 0.5 – 3 Hz (delta waves), 13 – 30 Hz (beta waves) and 30 – 70 Hz (gamma waves) (Shaker 2007). Each of these frequency bands represents different brain activities. For example, delta waves represent deep sleep, theta waves occur during emotional stress, beta waves predominate during a state of mental

concentration and alpha waves are more rhythmic in pattern and occur in a state of wakeful quiet rest (Shaker 2007). It has been shown that EEG power in the alpha band has an inverse relation to brain electrical activation (Shagass 1972). Most EEG studies on depression measure alpha waves as an indication of brain activation during a quiet state of wakefulness (especially in the frontal lobes) (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 1998; Gotlib 1998; Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Deslandes, de Moraes et al. 2008; Carvalho, Moraes et al. 2011; Gold, Fachner et al. 2013). Using this model, electrical activity in depression is described in terms of *alpha power*, wherein a *high* alpha power is assumed to be indicative of *less* overall electrical (EEG) activation (*hypo-activation*) of the brain regions over which it is recorded, while a *low* alpha power is assumed to be indicative of *greater* overall electrical activation (*hyper-activation*) (Cook, O'Hara et al. 1998; Laufs, Krakow et al. 2003). Therefore, according to the "approach withdrawal" model, EEG asymmetry in depression is accompanied by *lesser* alpha power in the right frontal lobe and *greater* alpha power in the left frontal lobe ($L^{\alpha}>R^{\alpha}$) (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 1998; Gotlib 1998; Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Deslandes, de Moraes et al. 2008; Carvalho, Moraes et al. 2011; Gold, Fachner et al. 2013). That is, $L^{\alpha}>R^{\alpha}$ is the reverse of the $R_a>L_a$ phenomenon of FLA, but still may be used to assess the actual level of cerebral activation via an easily-quantifiable metric (alpha power).

3.1.2 Alpha asymmetry score

Generally, frontal alpha asymmetry is presented as a mathematical score (called an "asymmetry score") in most of the EEG studies on depression. This asymmetry score for an individual could have either a negative or a positive value and it is obtained by first measuring the alpha power (in volts) which is then normalized by Log transformation or Ln transformation (Ln means natural logarithm). The alpha asymmetry scores is obtained by subtracting the value of the Log or Ln transformed alpha power of the left frontal lobe from that of the right frontal lobes (Diego, Field et al. 2001). Alternatively, alpha power values from both right and left frontal lobes may be converted to power density (by dividing alpha power by frequency) before being normalized by Log or Ln transformation and the difference between these two values also provides an alpha asymmetry score (Shagass 1972; Debener, Beauducel et al. 2000). These values are referred to as Positive alpha asymmetry scores ($R^{\alpha}>L^{\alpha}$) and

negative alpha asymmetry scores ($L^{\alpha}>R^{\alpha}$). Increasing values of negative and positive alpha asymmetry scores indicate the magnitude of the asymmetry in favour of the left and right frontal lobes respectively (Figure 1).

In terms of actual electrical activation, negative alpha asymmetry scores thus represent greater relative right frontal EEG activation ($R_a>L_a$) and positive alpha asymmetry scores represent greater relative left frontal EEG activation ($L_a>R_a$) (Debener, Beauducel et al. 2000; Diego, Field et al. 2001) (Shagass 1972). Therefore, as proposed by the "approach-withdrawal" model of frontal brain activity (Davidson 1998), depressed persons with FLA are expected to have a negative asymmetry score (i.e. $L^{\alpha}>R^{\alpha}$ or $R_a>L_a$). Thus, for the purpose of clarity in this discussion, FLA will be referred to in terms of negative alpha asymmetry scores (i.e., $L^{\alpha}>R^{\alpha}$ or $R_a>L_a$, which represent greater overall electrical activity in the right frontal lobe than in the left frontal lobe, consistent with the $R_a>L_a$ model described above.

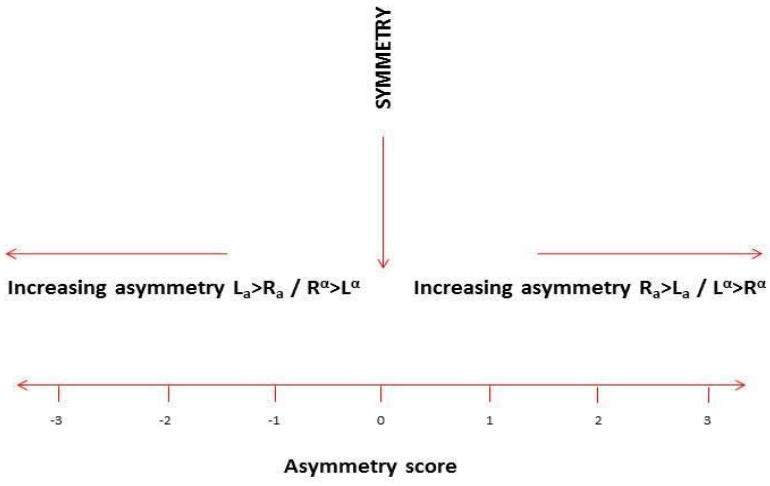

Figure 1: Scale of Alpha Asymmetry.

3.1.3 Models of frontal lobe asymmetry

Using the frontal lobe alpha power metric associated with depression (i.e., $L^{\alpha}>R^{\alpha}$), there are five possible ways in which this condition might eventuate. Firstly, when there is an *increase in left frontal lobe alpha power plus a decrease in right frontal lobe alpha power*; secondly, when there is *no change in left frontal lobe alpha power but there is a decrease in right frontal lobe alpha power*; thirdly, when there is an *increase in left frontal lobe alpha power plus no change in right frontal lobe alpha power*; fourthly, there could be a *decrease in left frontal lobe alpha power but a much greater decrease in right frontal lobe alpha power*; and fifthly, when both the left and right frontal lobes experience *increases in alpha power but the left frontal lobe undergoes a much greater increase in alpha power than the right frontal lobe*. These five possible pathways to $L^{\alpha}>R^{\alpha}$ alpha asymmetry occurring are shown in lines 2 to 6 of Table 10. The first line of Table 10 shows symmetry of alpha power across the left and right frontal lobes.

Table 10: The possible pathways of left and right frontal lobe alpha power which may lead to $L^{\alpha}>R^{\alpha}$ frontal alpha EEG asymmetry in depression

Possible pathways to $L^{\alpha}>R^{\alpha}$	Left frontal lobe change	Right frontal lobe change	Outcome
1	=	=	$L^{\alpha}= R^{\alpha}$
2	+	-	$L^{\alpha}> R^{\alpha}$
3	=	-	$L^{\alpha}> R^{\alpha}$
4	+	=	$L^{\alpha}> R^{\alpha}$
5	-	---	$L^{\alpha}> R^{\alpha}$
6	+	+++	$L^{\alpha}> R^{\alpha}$

Note: (-), (+) and (=) represent decreases, increases and no change in brain alpha power respectively.

Although these are the five possible pathways that could lead to $L^{\alpha}>R^{\alpha}$ frontal lobe alpha asymmetry, most previous studies have reported a combination of increased alpha power of the left frontal lobe plus decreased alpha power of the right frontal lobe, thus, reflecting the model shown on line 2 of Table 1) (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 1998; Gotlib 1998; Reid, Duke et al. 1998; Debener,

Beauducel et al. 2000; Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Deslandes, de Moraes et al. 2008; Kline and Allen 2008; Carvalho, Moraes et al. 2011; Shankman, Sarapas et al. 2011; Gold, Fachner et al. 2013).

3.1.4 Cerebral areas of where alpha EEG asymmetry occurs in depression

A number of EEG studies have provided evidence that depressed patients (both those with current and past depressive episodes) display $L^{\alpha}>R^{\alpha}$ *frontal* alpha asymmetry (Henriques and Davidson 1990; Henriques and Davidson 1991; Davidson 1998; Liao, Zhou et al. 2013; Gollan, Hoxha et al. 2014) and some authors have further demonstrated that *posterior* alpha power in depression exhibits an asymmetry opposite to that of frontal alpha (i.e., $L^{\alpha} < R^{\alpha}$), indicative of *greater right than left posterior alpha power* in depression (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Kentgen, Tenke et al. 2000; Shankman, Sarapas et al. 2011). However, not all studies have demonstrated this pattern of posterior lobe alpha asymmetry being the reciprocal of frontal lobe alpha asymmetry in depression (Reid, Duke et al. 1998; Kline and Allen 2008; Stewart, Coan et al. 2011). Further, one study reported that inter-hemispheric alpha asymmetry in depressed persons was evident across the entire cortex (Fingelkurts, Fingelkurts et al. 2006). However, this argument is yet to be validated as no other work has demonstrated similar EEG asymmetry across the whole cerebral cortex. One report indicated that individuals with *parietal* $L^{\alpha} < R^{\alpha}$ alpha asymmetry had a greater risk factor for developing depression (Stewart, Coan et al. 2011). The exact relationship between $L^{\alpha} < R^{\alpha}$ asymmetry across the entire cortex has yet to be determined.

3.2 Categories of previous research studies on EEG FLA in Depression

A comprehensive and exhaustive review of the literature on frontal EEG alpha asymmetry in depression revealed three categories of research that had been reported to date: (i) the relationship between resting and task-related frontal EEG asymmetry and depression, (ii) the relationship between frontal EEG asymmetry and depression with other co-morbid psychological disorders (majorly anxiety), and (iii) the influence of therapeutic interventions such as pharmacotherapy, psychotherapy, music therapy, and transcranial magnetic stimulation upon neuro-feedback frontal EEG asymmetry. The comprehensive lists of these three categories of reports are presented in Appendices 1, 2 and 3, and the summaries of their findings are presented in the

following sections. The findings from this systematic analytical review were published as "Frontal alpha asymmetry as a pathway to behavioural withdrawal in depression: Research findings and issues" in the Behavioural Brain Research journal and the published work is attached to this thesis as Appendix 7.

3.2.1 The relationship between frontal EEG asymmetry and depression

In their meta-analysis of 31 papers published between 1965 and 2006 and which examined the magnitude of the association between resting FLA and anxiety, depression and comorbid anxiety and depression for infant and adult samples, Thibodeau, Jorgensen and Kim (2006) reported significant and very similar associations for depression across the two age samples (r = .26 for adults, r = .29 for infants, both $p < .05$). There were some effects within age groups due to a number of moderator variables including length of EEG recording period (shorter periods gave larger effects for adults) and age (younger infant samples showed larger effects than older infant samples). However, overall, the associations between frontal asymmetry and depression were established via the mathematical results of that meta-analysis.

3.2.1.1 Resting- *vs* task-related frontal EEG asymmetry and depression

Working onwards from the overall results reported by Thibodeau and colleagues (2006), that depressed individuals show frontal alpha asymmetry in favour of increased alpha power (hypo-activation) in the left frontal lobe relative to the right frontal lobe with (i.e. $L^{\alpha}>R^{\alpha}$ or a negative asymmetry score), it is also noteworthy that this finding is consistent whether EEG activity is measured during a resting state (Henriques and Davidson 1990; Baehr, Rosenfeld et al. 1998; Gotlib 1998; Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Deslandes, de Moraes et al. 2008; Carvalho, Moraes et al. 2011; Gold, Fachner et al. 2013) or during an emotional or cognitive task (Schaffer, Davidson et al. 1983; Henriques and Davidson 1991; Harmon-Jones and Allen 1997; Gotlib 1998; Jones, Field et al. 2000; Jones, Field et al. 2001). While some authors have proposed that brain activity during emotional challenge is a more powerful indicator of predisposition toward psychopathology than brain activity observed at rest (Stewart, Coan et al. 2014) and they have supported this with data indicating that depressed individuals demonstrate frontal alpha EEG asymmetry during cognitive and emotion eliciting/affective tasks (Schaffer, Davidson et al. 1983; Jones, Field et al. 2000; Jones, Field et al. 2001), others have reported that frontal

asymmetry is unrelated to mood reactivity and cognitive functions (Henriques and Davidson 1991; Gotlib 1998; Stewart, Coan et al. 2011). Although these are contrasting findings, the important information from these studies is that EEG asymmetry has been demonstrated in depressed individuals under both conditions of resting and task-related frontal EEG measurements.

3.2.1.2 Stability of Frontal EEG asymmetry

Little difference has been reported between the EEG asymmetry of previously-depressed and currently-depressed individuals, which may imply that EEG asymmetry is a state-independent marker for depression (Henriques and Davidson 1990) irrespective of when an individual experienced depression, perhaps also challenging the validity of frontal asymmetry *per se* as an indicator of current depression alone. Similarly, it was demonstrated that alpha asymmetry is relatively stable (Allen, Urry et al. 2004; Vuga, Fox et al. 2006; Bruder, Sedoruk et al. 2008) and reliable (Niemiec and Lithgo 2005; Gold, Fachner et al. 2013), although the findings of Debener et al. (2000) suggested that posterior EEG asymmetry is more stable than anterior EEG asymmetry. It is not known if successful treatment of depression results in complete restoration of frontal lobe EEG symmetry, but depressed individuals who showed therapeutic response to Selective Serotonin Reuptake Inhibitors (SSRI) still had evident EEG asymmetry despite improvement in depression symptoms (Bruder, Sedoruk et al. 2008), thus suggesting that EEG asymmetry may represent a state-independent characteristic of depression.

The finding that FLA is still present when a previously-depressed subject is no longer depressed requires further research attention but one possible hypothesis for this finding could be in the behaviour of the immune system in response to pathogen invasion. That is, just as individuals develop and retain antibodies to certain microbial organisms following an episode of infection from those organisms, depressed individuals may develop FLA as an adaptive response to the psychological insult they experience and then retain the FLA, possibly as a defense mechanism against future adverse circumstances (i.e., "pathogens") in the same way that antibodies are retained following a previous episode of microbial infection. This hypothesis is congruent with models of depression as an adaptive psychological process (Sharpley and Bitsika 2010).

3.2.1.3 Behavioural traits and Frontal EEG asymmetry

Harmon-Jones and Allen (1997) investigated the relationship between frontal alpha EEG asymmetry and the behavioural activation system (BAS), demonstrating that depressed subjects exhibited lower levels of BAS, ostensibly due to reduced activation of the left frontal lobe (i.e. $L^{\alpha}>R^{\alpha}$). In a similar study, Harmon-Jones and colleagues (2002) showed that, when confronted with an anger-provoking stimulus, individuals who were prone to depression (identified with the aid of the General Behavior Inventory, GBI) demonstrated a stronger withdrawal motivation (which was evidenced by greater relative right frontal activation) as opposed to individuals with proneness towards hypomania/mania symptoms (also identified with the aid of GBI) who showed stronger approach motivation with an EEG pattern of relative left frontal activation when exposed to the same anger-provoking stimulus. Therefore, behavioural activation of either approach or withdrawal system may be hypothesized to play a significant role in depression pathophysiology.

Other behavioural traits such as high re-assurance and repressive-defensive coping style have been shown to modulate the association between frontal EEG asymmetry and depression (Tomarken and Davidson 1994; Minnix, Kline et al. 2004). More specifically, in line with the approach-withdrawal model, Tomarken and Davidson (1994) showed that individuals who demonstrated repressive-defensive coping style (termed "repressors") also demonstrated a higher left anterior lobe activation than individuals who are non- repressors. They argued that repressive-defensive behaviour may influence frontal asymmetry by regulating emotion and other goal-directed behaviours. These data suggest that apart from the known effects of self-reported negative affect on FLA, other dimensions of temperament also contribute to the overall status of FLA in depression (Tomarken and Davidson 1994; Minnix, Kline et al. 2004). This argument is somewhat supported by the findings of Tomarken and Davidson (1994) who showed that, in depressed individuals, high re-assurance seeking behaviour was accompanied by increased left activation.

Nusslock et al. (2011) investigated the role of depressogenic cognitive style measured by the Cognitive Style Questionnaire--negative events (CSQ-N) composite scores and FLA in the development of depression. They showed that individuals with greater CSQ-N scores (i.e., greater cognitive vulnerability) had decreased relative left-frontal

EEG activity at baseline. After a 3 year follow-up period, 13 of the 40 initially non-depressed participants who had greater CSQ-N scores at baseline also developed a first-ever depressive episode and that decreased relative left-frontal activity at baseline was significantly associated with a greater probability of a first prospective depressive episode during the follow-up period (Nusslock, Shackman et al. 2011). In addition, both cognitive vulnerability and asymmetric frontal cortical activity prospectively predicted the onset of a first depressive episode. These data suggest that when depressogenic cognitive style is incorporated with resting frontal EEG asymmetry, they induce a vulnerability to the development of depression. It has also been suggested that vulnerability to depression may be complicated by other factors such as temperament, defensiveness and coping styles (Reid, Duke et al. 1998; Kline and Allen 2008) and that major stress is also a predictor of depression (Mirescu and Gould 2006).

3.2.1.4 Frontal EEG asymmetry and Anatomic/Physiologic changes

In an attempt to explain the brain changes which accompany depression, some authors have described anatomical changes such as increased cortical thinness (Bruder, Bansal et al. 2012) and increased neurophysiologic connectivity which induce "a broad loss of selectivity in functional connections" that may be inculcated in major depressive disorder (Leuchter, Cook et al. 2012) (pg 7). These changes were found to significantly correlate with increased $R_a > L_a$ in depression (Bruder, Bansal et al. 2012). These findings may be interpreted as indicative of a structural basis for the measured increased right frontal activity in depression; however, it is still unclear if depression precedes these anatomical changes or these specific changes contribute to the development of depression. For example, cerebral structural changes may lead to the reduced cognitive efficiency that is experienced by depressed individuals, as demonstrated in deficits in performance of tasks such as dot localization (although these deficits were found to be more strongly correlated with hypo-activation in the posterior right hemisphere rather than in the anterior left hemisphere) (Henriques and Davidson 1997).

Physiological differences associated with FLA include pain hyper-sensitivity in depressed patients who also demonstrated $R_a > L_a$ (Pauli, Wiedemann et al. 1999). This effect was primarily due to reduced pain hyper-sensitivity in the right frontal lobe,

which may help to explain why depressed individuals have lower tolerances of noxious or unpleasant stimuli than non-depressed peers (Pauli, Wiedemann et al. 1999). Reduced left and increased right frontal activation has also been linked to reduced cardio-vagal tone (i.e. increased heart rate) in depression (Chang, Yoo et al. 2012). This may be somewhat expected as the left and right cerebral hemispheres have been previously associated with the parasympathetic and sympathetic systems respectively (Yoon, Morillo et al. 1997; Hilz, Dutsch et al. 2001) which influence heart rate.

3.2.1.5 Frontal asymmetry across different age groups of depressed subjects

Expanding upon the overall findings reported for age by Thibodeau et al (2006) in their meta-analysis, it has been found that $R_a>L_a$ frontal EEG asymmetry has been reported across different ages, ranging from elderly depressed subjects (Deslandes, de Moraes et al. 2008; Carvalho, Moraes et al. 2011) and menopausal women with depression (Saletu, Brandstatter et al. 1996), to children and adolescents with depression (Bruder, Tenke et al. 2005; Feng, Forbes et al. 2012) and adolescents at risk for depression (Tomarken, Dichter et al. 2004) and in infants and children of depressed mothers (Dawson, Klinger et al. 1992; Dawson, Frey et al. 1997; Jones, Field et al. 1997; Jones, Field et al. 1998; Field, Diego et al. 2001; Diego, Field et al. 2004; Field, Diego et al. 2004; Diego, Field et al. 2006; Jones, Field et al. 2009). The consistent finding of greater $R_a>L_a$ across different ages reinforces the argument that frontal EEG asymmetry is a state-independent trait or marker for depression and age is neither a protective nor a predisposing factor in that association.

3.2.1.6 Relative depression risk and EEG asymmetry

Depression has a heritability of about 38% (Gershon, Hamovit et al. 1982; Downey and Coyne 1990) and EEG studies in neonates have been a useful tool for explaining the different risks individuals are exposed to by the mere fact that they were born to parent(s) who have or have had depression. Specifically, when compared to healthy infants of non-depressed mothers, infants of depressed mothers exhibited significantly reduced left frontal EEG activation (i.e. $R_a>L_a$) and this finding was positively related to mothers' depressive symptoms (Dawson, Klinger et al. 1992; Field, Fox et al. 1995; Dawson, Frey et al. 1997; Jones, Field et al. 1997) and mothers' interaction style (Diego, Field et al. 2006). Neonates of depressed mothers also exhibited

abnormal physiological and cognitive development in relation to maternal frontal EEG asymmetry (Jones, Field et al. 1998; Jones, Field et al. 2009) in that maternal depression, frontal EEG asymmetry and biochemistry (higher cortisol, lower serotonin, and lower dopamine levels) were positively related to their children's frontal EEG asymmetry and biochemistry, which suggested a risk for future development of depression in these infants in addition to elevated risk for poorer physiological and developmental outcomes than their peers (Field, Diego et al. 2001; Diego, Field et al. 2004; Field, Diego et al. 2004). Interestingly and by contrast, frontal EEG asymmetry with greater relative left frontal activation (i.e. $L_a > R_a$) has been shown to moderate the effects of stressful life events on internalizing symptoms in children at familiar risk for depression. This suggestion that increased left frontal lobe activation offers protection against depression in high risk children (Lopez-Duran, Nusslock et al. 2012) represents a further affirmation of the overall association between $R_a > L_a$ EEG asymmetry and depression.

Further to these findings, Bruder and collegues reported that children with either parents or grandparents who were depressed demonstrated significantly greater $L_a > R_a$ alpha EEG asymmetry in the parietal (but not frontal) regions than children whose parents grandparents were not depressed (Bruder, Tenke et al. 2007). Although no prospective study has determined if depression at-risk children (as identified by EEG asymmetry) will eventually develop depression has been reported as yet, Talati et al., (2014) reported cross-generational data which demonstrated that the offspring of depressed parents and grandparents were at higher risk of developing depression (and anxiety) and that offspring with two generations previously experiencing depression had the greatest risk for developing depression (Talati, Weissman et al. 2013). As well as this elevated risk of depression, the offspring of depressed parents and grandparents showed greater thinning of the cortical mantle measured via MRI than offspring of non-depressed parents and grandparents (Talati, Weissman et al. 2013).

3.2.1.7 Frontal asymmetry and gender differences

The influence of gender on alpha frontal asymmetry has also been examined, with differing results. Although Flor-Henry et al., (2004) found that 25 un-medicated depressed males demonstrated significantly greater left anterior functional hypo-activation when compared to healthy controls and Knott et al. (2001), showed that

depressed men demonstrated relatively less right frontal activation than healthy control subjects, Stewart et al. (2010) reported that depressed women demonstrated relatively greater frontal alpha EEG asymmetry than healthy female controls, and that frontal alpha EEG asymmetry was linked to current depression (depressed men showed no asymmetry). In a contrary finding, Jaworska et al. (2012) reported that anterior alpha asymmetry in depression was more evident in men than in women, and Miller et al. (2002) reported that men with childhood onset depression exhibited greater relative right mid-frontal alpha suppression (or right hyper-activation) while women displayed the opposite pattern. Overall, gender differences have not been consistent (Miller, Fox et al. 2002; Jaworska, Blier et al. 2012) and there has been no valid suggestion as to why EEG asymmetry should differ as a result of gender.

3.2.2 Frontal EEG asymmetry and depression with other co-morbid psychological disorders

3.2.2.1 EEG asymmetry in Anxiety

The effects of comorbid psychological disorders on EEG measures in depression have also been investigated. Most studies have examined EEG asymmetry in depression in patients with co-morbid anxiety (Bruder, Fong et al. 1997; Kentgen, Tenke et al. 2000; Papousek and Schulter 2001; Bruder, Kayser et al. 2002a; Blackhart, Minnix et al. 2006; Lee, Odom et al. 2007; Smit, Posthuma et al. 2007; Mathersul, Williams et al. 2008) and Social Anxiety disorder (Moscovitch, Santesso et al. 2011; Schmidt, Santesso et al. 2012). Generally, most researchers have reported that EEG asymmetry in anxiety is similar to that found in depression (i.e. greater relative left than right alpha power ($L^{\alpha}>R^{\alpha}$) in frontal sites (Baving, Laucht et al. 2002; Blackhart, Minnix et al. 2006; Smit, Posthuma et al. 2007; Beaton, Schmidt et al. 2008; Crost, Pauls et al. 2008; Avram, Baltes et al. 2010), a finding that has been attributed to the withdrawal motivation (negative affect) associated with the right frontal cortex which would predict that anxious individuals would show more alpha power in the left frontal lobe than in the right frontal lobe (Wiedemann, Pauli et al. 1999; Davidson, Marshall et al. 2000). This finding of greater relative left than right alpha power ($L^{\alpha}>R^{\alpha}$) in frontal sites in anxiety and depression has been interpreted as risk for the development of both anxiety and depression (Baving, Laucht et al. 2002; Blackhart, Minnix et al. 2006; Smit, Posthuma et al. 2007; Crost, Pauls et al. 2008; Yang, Park et al. 2013).

The reported FLA in anxiety has been described as being relatively stable (Schmidt, Santesso et al. 2012), heritable (Smit, Posthuma et al. 2007) and a predictor of negative neonatal outcomes in children born to mothers affected by anxiety (Field, Diego et al. 2010). Although infants of mothers with depression only and mothers with co-morbid depression and anxiety did not differ in their EEG measures (both groups demonstrated $L^{\alpha}>R^{\alpha}$ FLA) (Field, Diego et al. 2010), the presence of co-morbid anxiety with depression in pregnancy has been reported to produce worse neonatal outcomes (increased incidence of prematurity) than depression alone (Field, Diego et al. 2010).

However, some null findings in regard to the association between FLA and anxiety have been reported. For example, no significant FLA was found in unmedicated neurotic patients suffering from chronic moderate anxiety (Sicilianmi, Schiavon et al. 1975) and no significant FLA was found in anxious apprehension individuals, although individuals with anxious arousal showed greater relative right frontal activation ($R_a>L_a$) when compared to healthy controls (Nitschke, Heller et al. 1999). In contrast, Heller et al. (1997) reported that anxious participants showed $L_a>R_a$ asymmetry (largely in the frontal lobe) compared to healthy controls. This was supported by the findings of Nelson et al. (2012), which indicated that anxious-depressed patients showed asymmetrical performance in neuropsychological tasks demonstrating poorer performance on a design task (right frontal lobe activation) relative to verbal fluency (left frontal lobe activation), thus suggesting that the abnormal frontal asymmetry in neurocognitive performance which is seen in anxious-depressed individuals is driven primarily by right frontal dysfunction or hypo-activation (Heller, Nitschke et al. 1997; Nelson, Sarapas et al. 2012).

3.2.2.2 EEG asymmetry in Co-morbid Anxiety and Depression

Contrasting findings have been reported where EEG asymmetry has been assessed in cases where anxiety is comorbid with depression. While Kentgen et al. (2000) reported that co-morbid anxiety reduced posterior alpha asymmetry, almost to the point of equal activation of the left and right posterior hemispheres in depressed patients; Bruder et al. (1997) found that anxious-depressed patients showed evidence of greater activation over their right than left anterior and posterior sites ($R_a>L_a$). In a study of depressed patients with Post-Traumatic Stress Disorder (PTSD), the presence

of anxiety in the form of PTSD explained more than twice the variance in parietal asymmetry compared to PTSD alone (Metzger, Paige et al. 2004), while Manna et al. (2010) reported that depressed patients with high anxiety exhibited greater right than left central-parietal activation than depressed patients who had low anxiety (Manna, Tenke et al. 2010) and Mathersul et al. (2008) found that patients with depression co-morbid with anxiety showed symmetrical frontal activation with bilateral increases in frontal and increased right parieto-temporal activation compared to healthy control (Mathersul, Williams et al. 2008).

Despite depressive and anxious symptomatology being each moderately correlated with relatively greater right-sided frontal EEG asymmetry (i.e. $R_a > L_a$), there are some studies which have not shown frontal EEG asymmetry in co-morbid anxiety and depression (Bruder, Fong et al. 1997; Nitschke, Heller et al. 1999; Kentgen, Tenke et al. 2000). The reasons for these contrary findings are yet to be given. As previously suggested by Nitschke et al., (1999), it may be that a distinction between anxious apprehension (worry) and anxious arousal (somatic anxiety) may be at the base of these discrepant findings.

3.2.2.3 EEG asymmetry in Depression with other co-morbid Psychological Disorders

EEG asymmetry has also been examined in some other psychological disorders such as Panic Disorder (Wiedemann, Pauli et al. 1999; Nelson, Sarapas et al. 2012; Nelson, Shankman et al. 2014; Stewart, Coan et al. 2014), Obsessive Compulsive Disorder (Ischebeck, Endrass et al. 2014), Borderline Personality Disorder (Beeney, Levy et al. 2014), PTSD and Schizophrenia (Gaebel and Ulrich 1988; Gordon, Palmer et al. 2010; Kemp, Griffiths et al. 2010), PTSD (Metzger, Paige et al. 2004; Rabe, Beauducel et al. 2006; Gordon, Palmer et al. 2010), Attention Deficit Hyperactive Disorder (ADHD) and Conduct Disorder (Gordon, Palmer et al. 2010). While individuals with Panic Disorder and PTSD have been shown to demonstrate greater relative right than left frontal lobe activation (i.e., $R_a > L_a$) (Wiedemann, Pauli et al. 1999; Metzger, Paige et al. 2004; Kemp, Griffiths et al. 2010), individuals with Schizophrenia, ADHD and Conduct Disorder did not display any frontal asymmetry (Gordon, Palmer et al. 2010). Contrasting findings were reported by Shankman et al., (2008) who showed a null finding for frontal EEG asymmetry in PTSD subjects

(Shankman, Silverstein et al. 2008). Similarly, Gaebel and Ulrich (1988) indicated that schizophrenic patients had a pattern of EEG asymmetry only over their posterior brain regions. Overall, there seems to be no consistent asymmetry pattern for each of the identified psychological disorders as yet, and the evident contradictions in research findings on this topic call for further investigations in these areas.

3.2.3 The influence of therapeutic interventions on frontal EEG asymmetry in depression

The influence of therapeutic interventions such as pharmacotherapy, psychotherapy, music therapy and transcranial magnetic stimulation on frontal EEG asymmetry has also been investigated (Rosenfeld, Baehr et al. 1996; Earnest 1999; Bruder, Stewart et al. 2001; Bruder, Sedoruk et al. 2008; Barnhofer, Chittka et al. 2010; Saletu, Anderer et al. 2010; Choi, Chi et al. 2011; Valiulis, Gerulskis et al. 2012; Fachner, Gold et al. 2013; Gollan, Hoxha et al. 2014). Firstly, frontal alpha EEG asymmetry has been shown to differentiate between responders and non-responders to antidepressant medications (SSRIs and TCA), with responders showing greater alpha activation over right than left hemisphere, while non-responders showed the opposite asymmetry (Bruder, Sedoruk et al. 2008). Following anti-depressant treatment, responders did not show any significant change in FLA (Bruder, Sedoruk et al. 2008; Saletu, Anderer et al. 2010), although some reports showed a decrease in absolute alpha power (i.e. generalized increased cerebral activity)(Saletu, Anderer et al. 2010) while others did not show any change in alpha power (Bruder, Sedoruk et al. 2008). Consequently, it has been suggested that EEG asymmetry could be a predictor of response to antidepressant therapy (Bruder, Stewart et al. 2001; Bruder, Sedoruk et al. 2008; Khodayari-Rostamabad, Reilly et al. 2010; Saletu, Anderer et al. 2010).

Similarly, neurofeedback interventions in which depressed subjects are trained to increase the difference in activation levels between right and left frontal cortices (Rosenfeld, Baehr et al. 1996; Earnest 1999; Peeters, Oehlen et al. 2014), and Repetitive Transcranial Magnetic Stimulation (rTMS) (Deslandes, Moraes et al. 2010; Choi, Chi et al. 2011; Valiulis, Gerulskis et al. 2012; Mantovani, Aly et al. 2013; Noda, Nakamura et al. 2013; Sutin, Terraccino et al. 2013) have been shown to produce significant reductions in depression symptoms and an improvement (but not reversal) in frontal EEG asymmetry. Other forms of therapy such as Meditation

therapy (Barnhofer, Chittka et al. 2010), Mindfulness-based interventions (Keune, Bostanov et al. 2013; Moynihan, Chapman et al. 2013), Cognitive therapy (Deldin and Chiu 2005), Music therapy (Fachner, Gold et al. 2013), Choir therapy (Petchkovsky, Robertson-Gillam et al. 2013), Aerobic training (Deslandes, Moraes et al. 2010) and Deep brain stimulation surgery (Quraan, Protzner et al. 2014) have all been shown to be effective in alleviating depressive symptoms and to significantly improve overall cerebral activity, mostly in favor of increased left frontal activation.

The effects of other factors such as toxins, hormones, breastfeeding and genetics have also been investigated for their influence upon FLA. For instance, nicotine (Jaworska, McIntosh et al. 2011) and environmental chemicals (Bell, Schwartz et al. 1998) have been shown to have deleterious effects on brain activation, resulting in an overall increase in alpha power (less activation) and a worsening of EEG asymmetry in depressed subjects (Bell, Schwartz et al. 1998; Jaworska, McIntosh et al. 2011). In a group of 11 healthy adult males, the exogenous administration of cortisol produced an EEG pattern of frontal asymmetry similar to that in depression, further outlining the role of cortisol and the hypothalamus-pituitary-adrenal (HPA) axis in the pathogenesis of depression. Breastfed infants of depressed mothers show less frontal EEG asymmetry, less reactive temperament and more positive dyadic interactions than bottle fed infants of depressed mothers (Jones, McFall et al. 2004). Genetic influences have been demonstrated via the HTR1a gene, with subjects having the homozygous HTR1A gene also showing significantly greater left frontal alpha power than subjects with the non-risk allele, thus implying that variation in the HTR1a can be indicative of increased risk for depression (Bismark, Moreno et al. 2010).

3.3 Issues for Research

From this review of the literature in the asymmetry-depression field, several issues for research may be identified.

3.3.1 Cerebral sites of alpha asymmetry in depression

EEG studies described above have provided convincing evidence that previously and currently depressed patients display $L^{\alpha}>R^{\alpha}$ *frontal* alpha asymmetry (Henriques and Davidson 1990; Henriques and Davidson 1991; Davidson 1998; Thibodeau, Jorgensen et al. 2006; Liao, Zhou et al. 2013; Gollan, Hoxha et al. 2014) while several

studies have reported posterior alpha asymmetry opposite to that of frontal alpha asymmetry (i.e., $R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) in depressed patients (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Kentgen, Tenke et al. 2000; Shankman, Sarapas et al. 2011). In other words, parietal asymmetry in depression (without anxiety) is associated with impaired right parietal cortex function i.e., impaired processing of emotional stimuli (e.g., Bruder, 2003; Heller, 1993; Heller & Nitschke, 1997) which manifests as right parietal hypoactivity or greater right parietal alpha activity (i.e., $R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) when compared with healthy controls (Allen, Coan, & Nazarian, 2004, Blackhart, Minnix, & Kline, 2006; Bruder et al., 1997; Henriques & Davidson, 1990). It is also the case that some studies showed null findings in frontal and posterior sites (Reid, Duke et al. 1998; Kline and Allen 2008; Stewart, Towers et al. 2011). Stewart et al. (2011) reported that alpha asymmetry ($L^{\alpha}>R^{\alpha}$) is also displayed by depressed subjects in the *parietal* regions. Furthermore, only one study reported that inter-hemispheric alpha asymmetry in depressed persons was measurable across the entire cerebral cortex (Fingelkurts et al., 2006), and this finding is yet to be validated by further investigations. Thus, the exact relationship between left and right alpha asymmetry across the entire cerebral cortex is currently unknown, and is a field for further investigation.

3.3.2 Gender differences in alpha asymmetry in depression

Although there has been no valid suggestion made in the literature as to why EEG asymmetry might differ on the basis of gender, most EEG studies on alpha asymmetry in depression have been carried out on female samples. This may be partly attributed to the fact that depression affects more women than men (WHO 2012; WHO 2012), although men are more likely to suicide than women (APA 2013).

From the few studies that did examine gender differences in alpha asymmetry among depressed persons, Stewart et al. (2010) reported that depressed women demonstrated relatively greater *frontal* alpha EEG asymmetry ($L^{\alpha}>R^{\alpha}$) than healthy female controls but that there was no significant difference in frontal alpha asymmetry among depressed men than among non-depressed men, but Jaworska et al. (2012) reported that *anterior* alpha asymmetry in depression was significantly more pronounced in men than in women. Some reports showed that depressed men demonstrated the commonly reported EEG alpha asymmetry of ($L^{\alpha}>R^{\alpha}$) (Miller, Fox et al. 2002; Flor-Henry, Lind et al. 2004) and others have also shown that opposite pattern of frontal

alpha asymmetry is obtainable in depressed men (Knott, Mahoney et al. 2001) and depressed women (Miller, Fox et al. 2002). Overall, gender differences have not been consistently examined and this remains a potential topic for research in itself. The relative lack of data on gender differences also argues for inclusion of cortex asymmetry mapping procedures that incorporate the kinds of research suggested by the summary in 3.8.1 (i.e., site differences in asymmetry among depressed persons) into studies of gender differences.

3.3.3 What is the relationship between depression severity and frontal EEG asymmetry?

Surprisingly little work has been reported on the relationship between depression severity and EEG frontal alpha asymmetry, leaving the status of frontal alpha asymmetry across a full spectrum of depression severity (mild, moderate and severe) yet to be fully described. Apart from a single study which demonstrated a linear relationship between CES-D scores and frontal EEG alpha asymmetry in women suffering from post natal depression (not MDD) (Diego, Field et al. 2001), all other EEG asymmetry studies used dichotomous measures of depression, i.e., between severe *vs* no depression and frontal EEG asymmetry (Coan and Allen 2004; Blackhart, Minnix et al. 2006; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Feng, Forbes et al. 2012). The findings from these studies have indicated that individuals who are deemed as "not depressed" showed no frontal EEG asymmetry but individuals with higher scores on the rating scales (who were categorized as having "severe depression") demonstrated significant frontal EEG asymmetry.

A closer examination of the studies which investigated the relationship between depression and frontal EEG asymmetry suggests that there seems to be a restriction in the definition of what constitutes a depressive state so that only the severe forms of depression have been reported as demonstrating frontal EEG asymmetry. For instance, the study by Diego et al. (2001), which showed that women with maternal depression as defined by high scores on the Center for Epidemiological Studies scale (CES-D) (the "depressed" group) had significantly greater frontal EEG asymmetry than women with low CES-D scores (the "non-depressed" group), did not report any difference in the asymmetry patterns between individuals with moderate scores

("borderline" group) and "depressed" individuals (Diego, Field et al. 2001). This use of a dichotomous classification of depression has been the most common method of defining depressive state (Coan and Allen 2004; Blackhart, Minnix et al. 2006; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Feng, Forbes et al. 2012), and potentially obscures the presence of asymmetry differences that may occur due to minor or moderate levels of depression.

The only report which made an attempt to specify depression severity was Stewart et al. (2010). By classifying the combined sample of both depressed and non-depressed individuals using Beck Depression Inventory-II (BDI-II), groups were identified as: low, moderate and high depression (corresponding to BDI scores of 0-10, 11-20 and >21 respectively) (Stewart, Bismark et al. 2010). The authors reported that, following a full factorial mixed model analysis, no main effect or group differences emerged. The issue of depression severity remains relatively uninvestigated, and no study has combined severity of depression as a variable with gender and site.

3.3.4 Thesis focus and Research Questions

Therefore, this research study was designed to investigate the presence and nature of alpha EEG asymmetry across sites, genders and severity levels of depression. As an exploratory study (in the absence of consistent data regarding site, gender or severity of depression), no directional hypotheses could be raised for testing. Instead, three ***research questions*** were formulated for investigation. These were:

1. (a) ***Does EEG alpha asymmetry occur at the frontal lobe in the sample, irrespective of depression status and gender?***

(b) ***Does EEG alpha asymmetry occur at other cerebral sites apart from the frontal lobes, irrespective of depression status and gender? Specifically, temporal, parietal and occipital sites were to be examined.***

(c) ***If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites in the sample, irrespective of depression status and gender?***

2. (a) ***Is there any gender difference in alpha asymmetry across different cerebral sites (i.e., frontal, temporal, parietal and occipital sites) in the sample, irrespective***

of depression status?

(b) ***If so, what is the nature of those differences?***

3. ***(a) Do depressed and non-depressed individuals show different patterns of EEG alpha asymmetry at frontal, temporal, parietal and occipital sites, irrespective of their gender?***

(b) If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites according to depression status?

4. (a) ***Is there any gender difference in alpha asymmetry across frontal, temporal, parietal and occipital sites according to depression status?***

(b) ***If so, do males and females show different patterns of alpha asymmetry across these sites according to the status of their depression?***

Severity will be defined in terms of subgroups of depression and also by the complete range of scores on a measure of depression.

Part B: The Investigation of the Roles of Depression Severity, Gender and Cerebral Sites in the occurence of Alpha EEG asymmetry in Depression.

CHAPTER FOUR
METHODS

4.1 Participants

4.2 Participant recruitment

4.3 Instruments

4.4 Laboratory Session/EEG Measurements

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- 4.5.1 Participants information and consent.
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4.6 EEG recording

4.7 EEG Signal Processing, Data Reduction and Data Extraction

4.8 Data Analysis

4.1 Participants

As mentioned in the previous chapter, this research was designed as an exploratory study to investigate the presence and nature of alpha EEG asymmetry across cerebral sites, genders and severity levels of depression. To do this, members of the Armidale and the University of New England (UNE) communities with or without a history or current diagnosis of depression were invited to participate in a single-session EEG measurement in the Behavioural Neuroscience Laboratory at the UNE campus in Armidale, NSW, Australia. Only adult individuals (age > 18years) were allowed to take part in this study, and individuals with a previous medical history that would have potentially confounded their results (see below) were excluded from this study. Participants were classified into depressed and non-depressed groups via scores on the Zung Self Rating Depression Scale (SDS) (Zung 1965). EEG data were collected from the sample of depressed and non-depressed adult individuals drawn from the normal population to ensure that a wide range of depression severity was available.

Participants were included in the study irrespective of their gender (Henriques and Davidson 1991; Debener, Beauducel et al. 2000; Miller, Fox et al. 2002; Vuga, Fox et al. 2006) because we intended to investigate the presence of gender differences in the occurrence of FLA in depression. Also, as in some previous studies (Dawson, Klinger et al. 1992; Miller, Fox et al. 2002; Quinn, Rennie et al. 2014), participation in this study was not limited to individuals with right handedness (i.e., individuals with left brain language dominance) because there is no certainty that left hemispheric brain dominance is determined entirely by right handedness, as evidenced by the finding that 61% to 70% of left handed people also have left hemispheric dominance (Segalowitz and Bryden 1983; Clarke, Howard et al. 2009).

4.2 Participant recruitment

Following ethics approval by the Human Research Ethics Committee of the University of New England, Armidale (APPROVAL NUMBER: HE14-051), participants for this study were invited from the Armidale/UNE communities via publicity materials (print media, information sheet and the UNE website) and by word of mouth. Prior to participation in the laboratory phase of the study, potential participants completed a background questionnaire **(Appendix 4)** from which

information on age, gender, previous depression history, past medical history, medication and occupation were obtained. This was designed to address the inclusion and exclusion criteria. Individuals who had previous history of severe physical brain injury, previous brain surgery, past or current history of Epilepsy or Seizure disorder and individuals who were claustrophobic were excluded from the study. A total of 101 volunteering individuals were eligible to participate in the study. One participant discontinued the study during the EEG laboratory session due to sudden onset of dizziness, leaving a total of 100 participants who completed the study (54 women and 46 men). Further details of the sample are reported in the Results chapter.

4.3 Instruments

Following written informed consent **(Appendix 5),** participants filled out the Zung Self-Rating Depression Scale (SDS) (Zung 1965)**,** a 20-item self-rating depression scale used for diagnosis of depression and for quantifying the severity of depression. The SDS is a standardised test of depression and includes ten positively-worded and ten negatively-worded questions which have been developed on the basis of data obtained from factor analytic studies of the depression syndrome as defined by the DSM series (APA 2000). The SDS includes items for all of the current DSM V criteria for diagnosis of MDD (APA 2013). The SDS askes respondents to indicate the frequency of each of the depressive symptoms contained in those 20 items by answering in one of four possible ways: "None or a little of the time", "Some of the time", "Good part of the time", or "Most or all of the time" during the last two weeks. The response to each question is scored on a scale of 1 to 4, with the minimum and maximum possible scores being 20 and 80 respectively; higher scores indicate more severe depression (Zung 1965; Zung 1973).

According to the SDS' author, SDS scores of 40 or above indicate the presence of "clinically significant depression" (Zung 1973, p. 335), while individuals with scores less than 40 are classified as non-depressed. Re-classification of the depressed group may also be carried out by the SDS scores (i.e., individuals with SDS scores less than 50 *vs* individuals with SDS scores of 50+) into "severe" *vs* "not-severe" depression respectively (Zung 1973). Although a procedure is provided for changing the raw scores on the SDS to "index" scores (Zung 1965; Zung 1973), there is no obvious advantage in using that process and so SDS raw scores were used in this study.

Apart from being superior to the Minnesota Multiphasic Personality Inventory (MMPI) Depression Scale and the Beck Depression Inventory (BDI) for assessing depression (Schaefer, Brown et al. 1985), the SDS is a useful and easy-to-use depression diagnostic tool and has been shown to be reliable and consistent. It has split-half reliability of .81, (Zung 1965), .79 (DeJonge and Baneke 1989) and .94 (Gabrys and Peters 1985), with an internal consistency (alpha) of .88 for depressed patients and .93 for non-depressed patients (Schaefer, Brown et al. 1985), and an internal consistency of .84 has been reported in a previous Australian sample (Sharpley and Christie 2007). Of the , 100 adult individuals who completed the study, 67 were classified as non-depressed and 33 as depressed using the 40-point raw score cut-off recommended by Zung (Zung 1965; Zung 1973).

4.4 Laboratory Session/EEG Measurements

4.4.1 Laboratory Protocol and setting.

The experiment consisted of a single session of Resting EEG measurement (i.e., participants undertook no activity during EEG measurements). Each participant underwent resting EEG measurement for 6 minutes, during which they were instructed to keep their eyes opened for 3 minutes, followed by 3 minutes with their eyes closed. The laboratory session took place in the Behavioural Neuroscience Laboratory of the School of Science and Technology, University of New England (UNE), Armidale. This research study was partly funded by a grant from the Collaborative Research Network for Rural and Regional Mental Health (UNE) and partly by the School of Science and Technology, UNE.

4.4.2 EEG measurement and placement.

EEG measurement was carried out using a 40-channel Digital EEG Amplifier (NuAmps) connected to a *Quick Cap* (containing EEG electrodes). EEG signals were acquired and recorded on a desktop computer using the *Curry 7* software. The EEG amplifier, *Quick Cap* and *Curry 7* software were supplied by *Compumedics Limited, Australia*.

The number of active electrodes commonly used in previous studies investigating FLA in depression ranged from between 2 active electrodes (Baehr, Rosenfeld et al. 1998) to 22 active electrodes (Harmon-Jones, Abramson et al. 2002; Allen, Urry et al. 2004). To adequately enable direct comparison with all of those previous studies,

twenty-four active homologous channels were used in this study, activated through a standardized laboratory protocol **(Appendix 6)** derived from a series of pilot studies. The EEG Amplifier Configuration was: Frontal lobe electrodes (FP1, FP2, F3, F4, F7, F8, FT7, FT8, FC3, FC4), Temporal lobe electrodes (T7, T8, TP7, TP8, C3, C4), Parietal lobe electrodes (P3, P4, P7, P8, CP3, CP4) and Occipital lobe electrodes (O1, O2).

All electrodes with odd numbers were located or placed on the left cerebral hemisphere and even numbered electrodes were placed on the corresponding right cerebral hemisphere. Standard electrode placement also requires additional electrodes which are generally applied for referencing purposes and for monitoring the EEG recording process. Such electrodes include the ground electrode (GND), the Central electrodes (Fz, FCz, Cz, CPz, Oz), Ear (Auricle) electrodes (A1, A2), and the Horizontal Electro-Occulographic electrodes (X2, X4) and Vertical Electro-Occulographic electrodes (X1, X3). The Electro-Occulographic electrodes are used for monitoring horizontal and vertical eye movements, and for off-line eye-movement artefact reduction of the EEG data. In this study, only the twenty-four active homologous electrodes were used for the purpose of comparison between the electrical activity measured on the right and left cerebral hemispheres. Figure 2 shows the locations of all the electrodes on the cerebral hemispheres.

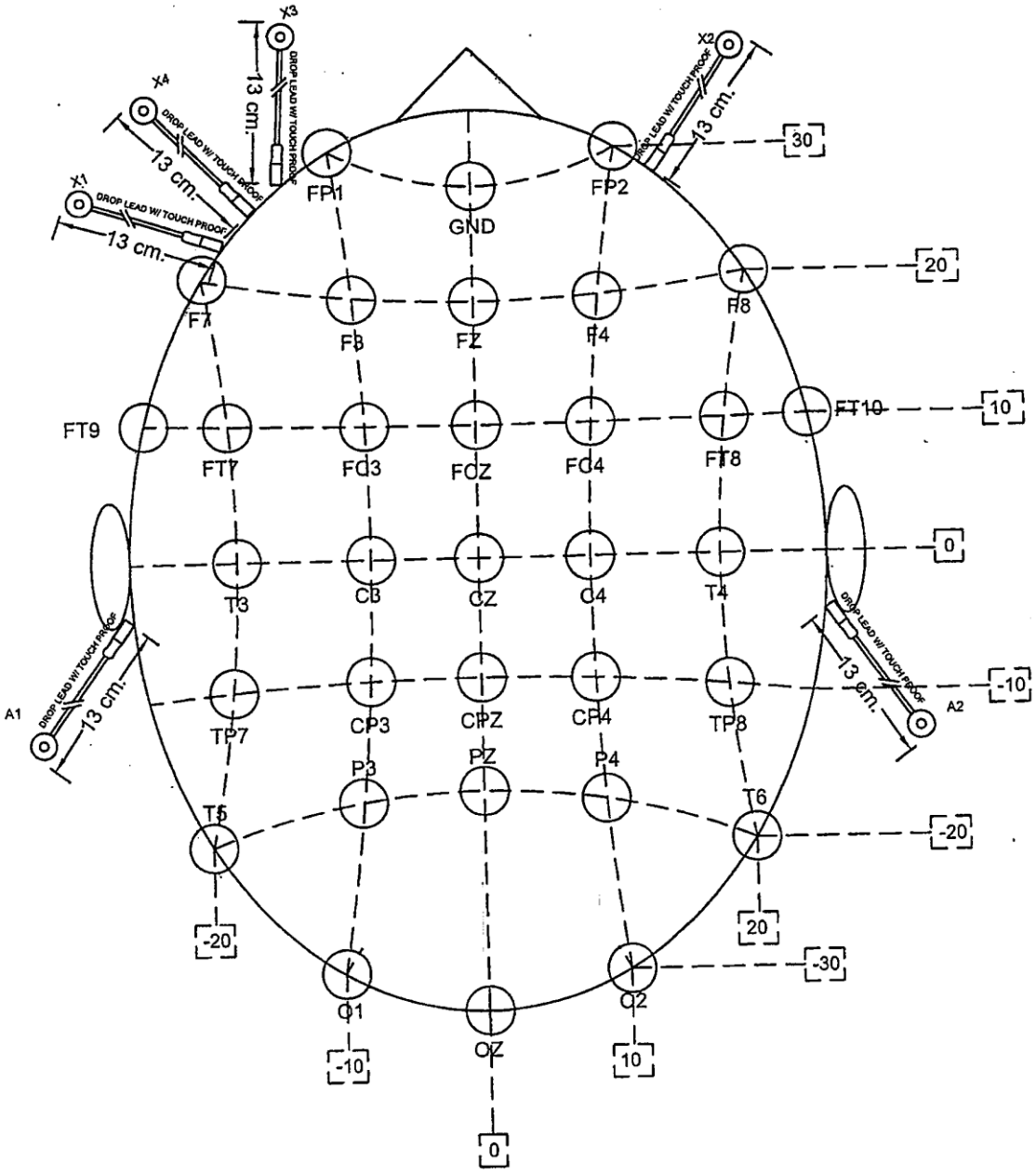

Figure 2: Electrode placement for EEG measurement.

4.4.3 Data collection.

The EEG measurement was carried out at a sampling rate of 1 KHz and the frequency band was set to collect alpha wave activity (using low and high filters of 8Hz and 13 Hz respectively). The allowable impedance level in each electrode was set as < 5K Ω. The electrode placement system used was the 10–10 system and the CAR (Common Average Referencing) referencing style was used. The CAR referencing style is

commonly used in EEG research because it facilitates the identification of small signal sources in a very noisy EEG recording (Offner 1950; Osselton 1965; Cooper R 2003). The CAR style uses the average of all the recordings on every electrode site as a reference for all other electrodes (Offner 1950; Osselton 1965; Cooper R 2003). The use of CAR referencing reduces the effects of uncorrelated noise sources while providing an accurate representation of correlated noise at electrode sites (Ludwig, Miriani et al. 2009). This is achieved by using an averaging process which ensures that only the signal/noise that is common to all sites is allowed to remain in the CAR while single-unit activity (i.e., isolated signals from one active site) is excluded from the CAR unless it is a very large signal that is capable of dominating the average (Offner 1950; Osselton 1965; Cooper R 2003). The CAR reference style has been shown to be the best referencing style because it improves the quality of neural recording (Ludwig, Miriani et al. 2009; Alhaddad 2012).

4.4.4 Experimenter and materials.

Following the pilot studies, it was concluded that both skin/scalp preparations and EEG acquisition/measurement on participants should be carried out by the same person (the student researcher) using the laboratory protocol designed for that purpose, so as to maintain treatment consistency for all participants. To facilitate this consistency, all required materials were identified and supplied, including: EEG acquisition software (i.e., Curry 7) and Digital EEG Amplifier (NuAmps) by the same company (*Compumedics Limited, Australia*.).

The list of equipment and materials used included:

- 1 desktop computer hard drive (Dell, OptiPlex 9020 Small Form Factor) for checking and processing EEG acquisition
- 1 high-resolution desktop computer monitor (Dell (TM) UltraSharp U2713H 27" Monitor with PremierColor)
- EEG Cubicle (an electrically sheltered room/chamber)
- *Quick cap* (Cap containing EEG electrodes)
- Adhesive tapes
- Nuroprep gel *(Quick gel)*
- 10-ml customary syringes

- 16 G Blunt needles
- Cotton swabs with a free wooden end
- Alcohol or Acetone swabs
- Earphones
- Non-stretched tape measure
- Sterile gauze
- Towel or cape to cover participants' clothes

4.5 Procedure

4.5.1 Participants information and consent.

Before commencing the laboratory session, the purpose of the study was verbally explained to each participant to ensure that they understood it and their written consent was obtained. Participants were assured that, apart from a little discomfort which might occur during scalp preparation, EEG recording is a very safe procedure with no major risks and that all equipment had been standardized and was functioning efficiently. Participants were also reminded that they were free to withdraw from the study at any time if they so wished and that they did not have to provide any reasons for doing so. Aseptic procedures (e.g., hand washing before and after each laboratory session and the use of disposable gloves and swabs) were adhered to throughout the laboratory sessions.

4.5.2 Scalp/Skin Preparations

Prior to presenting to the lab for the EEG measurement session, participants were instructed to wash their hair the night or morning before the EEG session with a normal shampoo that did not contain any conditioner. This is because conditioner coats the scalp and makes it much more difficult to obtain a low impedance connection but ordinary shampoo facilitates the removal of dead skin and any other hair products which might increase impedance level.

The following scalp/skin preparations were carried out on all participants in the laboratory setting:

1. Brushing the scalp with a bristle hairbrush for about 3-5mins for the purpose of exfoliating dead skin from the scalp surface (dead skin generates impedance between skin surface and electrodes).

2. Cleaning the skin sites for the frontal pole electrodes and the external or drop electrodes (below the right and left eyes, and on each mastoid prominence at the back of the ears) by gentle application of the 'Nuprep gel' (a gritty gel which removes any dead and dry skin from the scalp) with the aid of a cotton swab with a free wooden end. The 'Nuprep gel' was scrubbed onto these electrode sites and then the sites were cleansed with alcohol or acetone swab immediately after the gel application.
3. Alcohol or acetone swabs were used to clean the electrode sites in order to ensure that these areas were clear of makeup and foundation.

4.5.3 Electrode and gel application

According to the manufacturer's specifications, the *Quick Cap* has been designed in three different sizes (small, medium and large, representing a head circumference of 50-53cm, 55-59cm and 60-65cm respectively) to accommodate all adult individuals. Each participant's head circumference was measured with the aid of a non-stretch measuring tape wrapped snugly around the widest circumference of the skull, usually from the most prominent part of the forehead (usually 1-2 finger diameters above the eyebrow) around to the widest part of the back of the head. The value obtained from this measurement (in cm) was used to determine which cap size was selected for use in each participant.

The *Quick Cap* containing the EEG electrodes was then applied to the participant's head, making sure that the Cz electrode was located at a site half way between the glabella in front and the inion at the back of the head. After this, the cap was then firmly attached to the scalp by applying the cap fastening (Velcro tape) at the chin. In some cases, a wound gauze mesh of about 10-15cm length was cut and applied over the top of the EEG cap. Adequate electrode contact with the scalp was established by pulling the mesh over the cap. The drop or external electrodes were then applied with the aid of adhesive tape to make sure the electrodes were in secure contact with the skin.

Following skin preparation, with the aid of a blunt needle and 10mL syringe, all EEG electrodes were loaded with *Quick gel*, which is a conductive gel that facilitates electrical contact between the electrodes and the scalp. First, the ground electrode

(located in the cap on the midline between the Fz and FP1/FP2) was filled, and then the Cz, the ear and eye electrodes, followed by frontal, temporal, central, parietal and occipital electrodes. The gel was gently applied in an adequate amount to prevent the spread of gel beyond the proximity of the electrode reservoir (which can result in a salt bridge with other electrode locations). If too little gel is loaded, the conductive column between the scalp and the electrode may contain gaps and this may result in intermittent contact between the electrode and the scalp. The gel was allowed to soak into the scalp before checking and adjusting the impedances. *Quick gel* also has the advantage of being able to significantly lower the impedance level without further abrading the scalp. Participants were asked if they had any known allergies to gel before the *Quick gel* was applied but no participant reported such allergic reactions to the applied gel. All electrodes (active channels and reference channels) were filled with gel to facilitate EEG recording from these sites.

After the application of the gel into all the EEG electrodes as described above, the participants were comfortably seated in the EEG cubicle located in the laboratory with the EEG cap already connected to the Neuroscan amplifier, shown in Figure 3. The amplifier was connected to the desktop computer (located behind the cubicle) on which the Curry 7 software (for EEG acquisition from Neuroscan devices) was already installed.

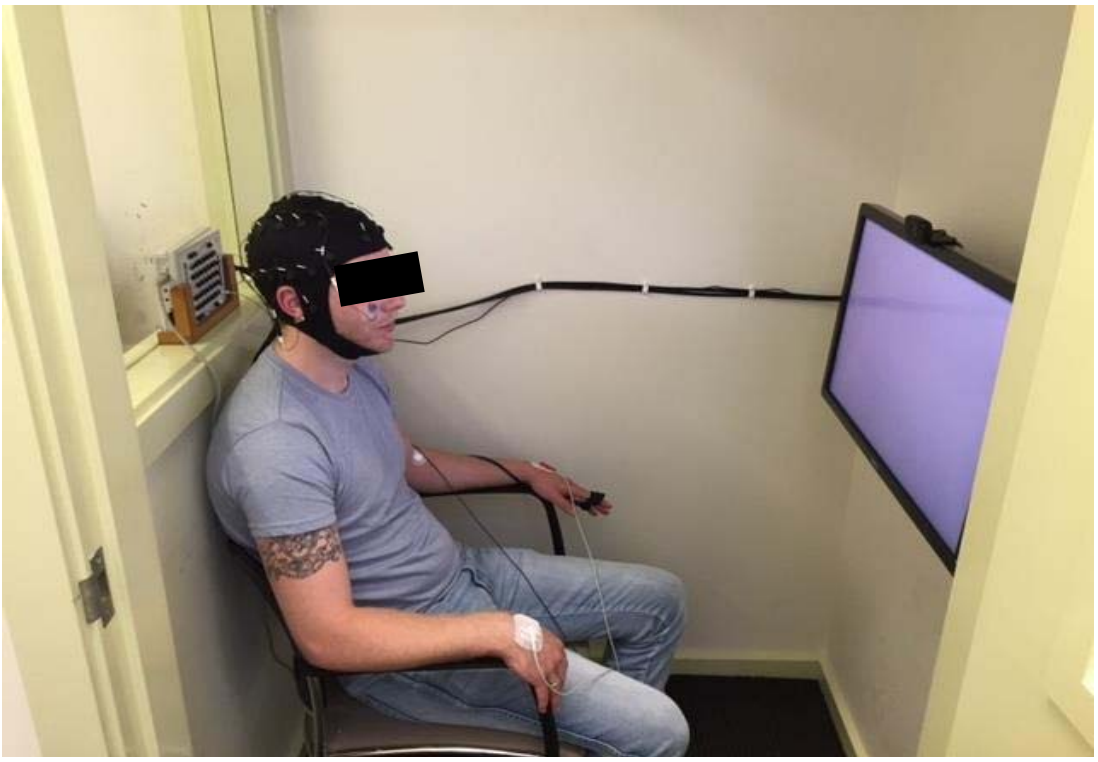

Figure 3: A participant wearing the *Quick Cap* filled with gel seated in the cubicle in the Behavioural Neuroscience Laboratory, UNE.

4.5.4 Impedance check.

Before EEG acquisition, impedance checks were performed for all electrodes to ensure that impedance was < 5K Ω. Any electrode with an impedance of >5K Ω was readjusted until impedance was < 5K Ω. The process of adjusting electrode connections to reduce impedance followed the manufacturer's instructions by inserting a blunt needle into the ground electrode and introducing additional gel. The needle was moved in and out of the electrode or rotated gently to ensure adequate contact was obtained between the gel and the scalp.

4.5.5 Ear pieces for instructions.

Once all the electrode impedances were below 5K Ω and the participant was comfortably seated in the cubicle, ear pieces were applied to the participant's ears for the purpose of providing pre-recorded audio instructions to ensure procedural conformity. The audio instructions informed the participant about the commencement of EEG recording, when to open their eyes, when to close their eyes and also when the EEG recording was finished. The application of the ear pieces marked the end of

the participant preparation. The participants were then informed that the recording was about to start.

4.6 EEG recording

Baseline EEG recording was undertaken for 6mins (3mins each of eyes opened and eyes closed) and the student researcher monitored the experimental process by listening to the audio instructions to follow the timeline whilst viewing the desktop computer screen to monitor the EEG signal acquired on the Curry 7 software.

A continuous EEG measurement of 3mins eyes opened and 3mins eyes closed was chosen instead of the common method of alternating between 1min of eyes opened and 1min of eyes closed for the whole duration of baseline EEG measurement (Reid, Duke et al. 1998; Harmon-Jones, Abramson et al. 2002). This was because the introduction of more frequent changes in instructions (i.e., "Please close your eyes for the next 1min" or "Please open your eyes for the next 1min") in an alternating manner might have interfered with participants' resting cerebral activity as the participants would have had to process these instructions for 5 different times during the 6mins EEG baseline recording as opposed to 2 times if a continuous EEG measurement was used. Therefore, the continuous EEG measurement provided a simple experimental procedure which was relatively easy for participants to follow. In addition, there is no identified study which has demonstrated that alternating between the two conditions of eyes opened and eyes closed provided a more accurate or reliable dataset than a simple continuous EEG measurement.

At the completion of the EEG measurement, EEG tracings acquired through the Curry 7 software were saved on the pc with the participant's identification by numbers only as required by Ethics approval so that the participants were de-identified. The *Quick Cap* was then disconnected from the amplifier and the ear pieces were removed from participants' ears. The drop or external electrodes and the *Quick Cap* were also gently detached from the participants, and with the aid of antimicrobial wipes, the *Quick gel* was cleaned up from the scalp/skin of the participant, ensuring that no gel was left on the scalp. Participants were instructed to wash their hair, head and scalp with water as soon as they got home. Participants were thanked for giving their time and for their cooperation in the study. All re-usable devices (*Quick Cap* and EEG external

electrodes) were properly rinsed with clean tap water to remove the electrode gel and then allowed to dry to make them ready for the next participant. All disposable materials such as swabs, gauze, gloves, tapes, blunt needles and syringes were properly disposed of.

4.7 EEG Signal Processing, Data Reduction and Data Extraction

EEG signals were recorded in microvolts (μV) at a sampling rate of 1000 Hz and stored on the desktop computer hard drive. EEG data were reduced by using the CAR reference such that the data recordings for any active electrode of interest represented the difference (in μV) between the average of all the recordings from all electrode sites and the recordings from the scalp site of the active electrode of interest (Cooper R 2003; Alhaddad 2012).

The Curry software (Curry Neuroimaging Suite 7.0.9 XS) was used to process EEG signals. Recorded EEG data were processed by applying the following filter parameters: a Band pass filter with a low filter (high pass), frequency of 1Hz and a slope of 2 Hz; a high filter (low pass) with frequency of 30 Hz and a slope of 8 Hz; a Notch filter of 50 Hz (Harmonics) with a slope of 1.5 Hz; and a Band stop filter of frequency of 50Hz (Harmonics) with of width of 10 Hz and slope of 5Hz. Data tapering was done using a Hann with a 10% width to prevent data loss.

The EEG signals were visually examined on the high-resolution desktop computer monitor. By this process, those portions of the EEG data which contained artefacts (eye movements, muscle movements, spontaneous discharges or electrode pops and any other sources of artefacts) were identified and removed from the recorded EEG (this is the usual process for this task reported in the wider literature). Further artefact detection was carried out by automatic bad block detection and eye blink detection (using the magnitude of eye blink deflections as a set threshold criteria to detect artefacts). Artefact reduction was done by three automated methods (i.e., Subtraction, Covariance and Principal Component Analysis) to produce clean EEG data.

Back-to-back epochs of 4 secs duration were then created from the clean EEG data. This duration was chosen as a number of studies have used it (Deslandes 2008; Shankman, Silverstein et al. 2008; Kemp 2010; Iznak, Tiganov et al. 2013; Quinn,

Rennie et al. 2014). Epochs which contained identified bad blocks were rejected and excluded from averaged data. Most participants had over 90% usable artefact-free epochs for both conditions of eyes opened and eyes closed, with the lowest frequencies of such epochs being 87% and 49% for eyes opened and eyes closed conditions respectively. The EEG data were then digitally filtered for alpha-band frequencies (8-13 Hz). Spectral analysis was performed on the generated epochs (for both conditions for each participant) by using a Fast Fourier Transformation (FFT) to calculate the power spectra. The power values obtained from FFT were averaged across the 4-second EEG epochs. From this process, the total power within the alpha (8–13 Hz) frequency range was obtained for each condition for each participant. The values of the total power within the alpha (8–13 Hz) frequency range were then extracted and transferred to an SPSS file for statistical analysis.

4.8 Data Analysis

Raw data from participants' EEG and SDS were examined for the means, standard deviations and ranges, and also to test for normality by use of the Kolgomorov-Smirnov statistic and examination of the histograms of distributions and the normal Q-Q plots. In the EEG literature, it is the common and accepted procedure to normalise the EEG signal data via log transformations (Debener, Beauducel et al. 2000; Diego, Field et al. 2001; Deslandes, de Moraes et al. 2008; Kemp, Griffiths et al. 2010; Quinn, Rennie et al. 2014) regardless of whether non-normality has been demonstrated via the statistical analyses described above. Therefore, in order to make the results from this study directly comparable to those from other studies reviewed in Chapter 3, that procedure was also followed here.

In regards to the SDS data, normality was also tested via the procedures described above. However, there is some conjecture in the literature regarding the need to transform non-normal data if they are found in studies such as these. That is, Tabachnik and Fidell (2007) comment that skewness in the distribution of a variable does not make a substantive difference to the results of MANOVA statistical processes in samples of 100 or more. Further, regression processes may be used with similar data because "non-normality does not lead to serious problems with the interpretation of significance tests" (Cohen, Cohen et al. 2003), p. 120, and skewed

data do not significantly alter the outcomes of Pearson correlational analyses, as demonstrated by Norris and Aroian (2004).

Bearing these caveats regarding non-normality in mind, it was decided to transform the EEG data in the same way as is the norm in the wider literature (i.e., via log transformation) and do the same for the SDS data but to analyse the data using the log transformed EEG data twice: once with the log transformed SDS data and once with the raw SDS data. The SDS data were tests for non-normality and results appear in the next chapter.

CHAPTER FIVE

RESULTS

5.1 Overview of Data

5.1.1 Participants

5.1.2 Depression (SDS) Scores

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5.2 Research Questions

5.2.1 Research Question 1: EEG asymmetry and cerebral sites

5.2.2 Research Question 2: EEG asymmetry, gender difference and cerebral sites

5.2.3 Research Question 3: EEG asymmetry, depression status and cerebral sites

5.2.4 Research Question 4: EEG asymmetry, gender difference, depression status and cerebral sites

5.2.5 Full scale SDS analysis

5.2.5.1 Data analysis

5.3 Summary of Significant findings/results

5.1 Overview of Data

The following section describes the participants, the SDS raw scores, gender distribution, alpha power values, normality testing of alpha power values and SDS scores and the log transformation of alpha power values.

5.1.1 Participants

The sample of 100 adult individuals had a mean *age* of 32.53 years (SD = 14.13 years, range = 18 to 75 years), and included 54 females and 46 males. There was no statistical difference between the ages of the males (M = 33.09, SD = 13.85) and females (M = 32.06, SD =14.47: $F(1,99) = 0.131$, $p = .718$, $\eta^2 = .001$), nor any significant correlation between age and SDS total score ($r = .006$, $p = .954$).

5.1.2 Depression (SDS) Scores

The distribution of the SDS scores for the 100 participants is presented in Figure 4. The mean SDS score for the entire sample was 36.7 (SD = 11.26), with the minimum and maximum SDS scores being 21 and 66 respectively. Internal consistency for the 20 SDS items (Cronbach's alpha) was .905, which meets the accepted criteria for this index of reliability (DeVellis 2003).

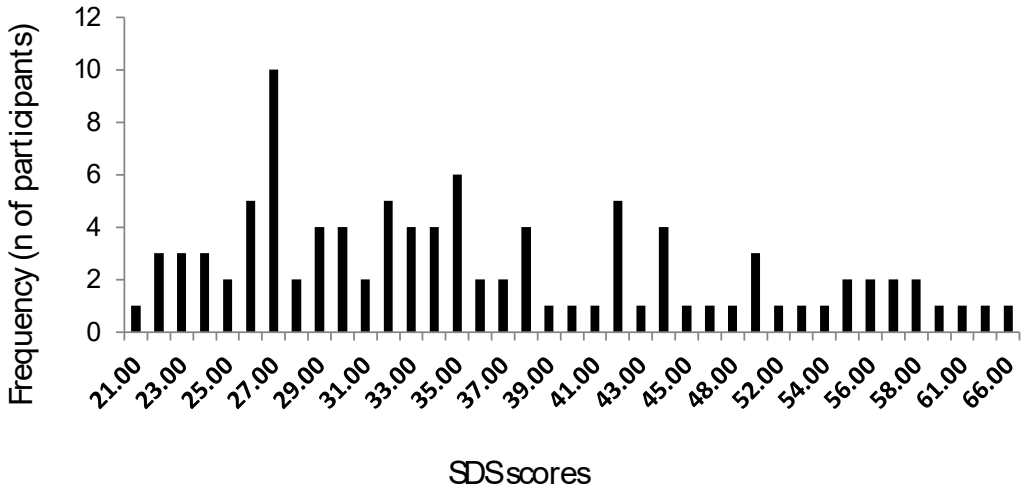

Figure 4: Sample Distribution of SDS Scores (N=100).

Two categorisations of SDS status were undertaken. First, based on the SDS scores and Zung's classification (Zung 1965; Zung 1973), the entire group was reclassified into two subgroups, designated as "clinically significant depression" (i.e., SDS raw scores 40+) and "Non-clinically significant depression" (i.e., SDS raw scores < 40). The gender and total breakdown of these two subgroups of SDS score is presented in Table 11.

Table 11: Gender distribution for the non-clinically significant depression and clinically significant depression groups.

SDS score categories	Males		Females		Total percent
	N	%	N	%	
Non-clinically significant depression (SDS < 40)	32	32	35	35	67
Clinically significant depression (SDS 40+)	14	14	19	19	33
Total	46	46	54	54	100

Second, the entire participant cohort was re-categorized as "severe depression" and "not-severe depression" based on SDS scores and Zung's criteria (Zung 1965; Zung 1973), with the severe depression category having SDS scores of 50 and above (i.e., SDS 50+) and the not-severe depression category having SDS scores of less than 50. The gender and total breakdown of these two categories of depression severity is presented in Table 12.

Table 12: Gender distribution for the not-severe and severe depression categories.

SDS score categories	Males		Females		Total percent
	N	%	N	%	
Not-severe depression (SDS < 50)	38	38	44	44	82
Severe depression (SDS 50+)	8	8	10	10	18
Total	46	46	54	54	100

5.1.3 Alpha EEG Data

5.1.3.1 Alpha power values

The mean alpha power values (μV^2) for the 100 participants obtained from the twenty-four active electrode sites under the two experimental conditions (i.e., eyes opened and eyes closed) are presented in Tables 13 and 14.

Table 13: Mean values of raw alpha power (μV^2) for each cerebral site (Eyes opened condition), N=100.

Sites	Fp1	Fp2	F3	F4	F7	F8	FT7	FT8	FC3	FC4	T7	T8
Mean	.0153	.0156	.0116	.0120	.0135	.0142	.0141	.0135	.0105	.0105	.0154	.0151
SD	.0151	.0160	.0111	.0125	.0115	.0135	.0137	.0123	.0107	.0111	.0161	.0140
Min	.0020	.0020	.0010	.0020	.0020	.0020	.0020	.0020	.0010	.0020	.0020	.0020
Max	.0710	.0800	.0530	.0660	.0520	.0660	.0780	.0640	.0570	.0650	.0970	.0910
Sites	**C3**	**C4**	**TP7**	**TP8**	**CP3**	**CP4**	**P7**	**P8**	**P3**	**P4**	**O1**	**O2**
Mean	.0123	.0127	.0146	.0169	.0141	.0143	.0168	.0239	.0200	.0209	.0167	.0166
SD	.0154	.0146	.0158	.0176	.0171	.0164	.0163	.0250	.0277	.0260	.0177	.0179
Min	.0010	.0010	.0020	.0020	.0010	.0010	.0020	.0020	.0020	.0010	.0030	.0020
Max	.0900	.0910	.1010	.1030	.0900	.0860	.0830	.1170	.1530	.1720	.1050	.1210

Table 14: Mean values of raw alpha power (μV^2) values for each cerebral site (Eyes closed Condition), N=100.

Sites	Fp1	Fp2	F3	F4	F7	F8	FT7	FT8	FC3	FC4	T7	T8
Mean	.0500	.0501	.0427	.0443	.0383	.0402	.0327	.0343	.0331	.0335	.0299	.0315
SD	.0666	.0701	.0525	.0620	.0452	.0534	.0360	.0388	.0420	.0408	.0320	.0277
Min	.0020	.0020	.0010	.0010	.0020	.0030	.0020	.0040	.0010	.0010	.0020	.0030
Max	.5000	.5370	.3650	.4710	.3340	.4120	.2790	.2830	.3360	.2400	.2400	.1450
Sites	**C3**	**C4**	**TP7**	**TP8**	**CP3**	**CP4**	**P7**	**P8**	**P3**	**P4**	**O1**	**O2**
Mean	.0284	.0268	.0383	.0466	.0370	.0344	.0760	.1036	.0872	.0921	.1014	.0953
SD	.0363	.0261	.0472	.0401	.0378	.0342	.1131	.0962	.1224	.1307	.1347	.1088
Min	.0010	.0010	.0020	.0030	.0010	.0010	.0050	.0040	.0020	.0010	.0040	.0030
Max	.2980	.1170	.2980	.1880	.1780	.2090	.8550	.4210	.6320	.6860	.8230	.6940

5.1.3.2 Normality testing and log transformation of alpha power values

The normality values for the SDS raw scores and EEG alpha power values were explored. Although there was some (non-significant) evidence for skewness towards the lower end of the scale for the SDS total scores, this is to be expected in a community sample, and the spread of scores across the range from 21 to 66 (shown in Figure 4) represents 75% of the possible range (i.e., from 20 to 80) that is possible on the SDS and argues for the representativeness of these data. Further, inspection of the Normal Q-Q plots for the SDS revealed an almost completely straight line, suggestive of normality. In addition, each of the statistical procedures used with the SDS raw scores is reasonably robust to the effects of non-normality with samples of the size used in this study (e.g., males = 46, females = 54). For instance, Pallant (2011) commented that "with large enough sample sizes (e.g., 30+), the violation of (normality) should not cause any major problems" (p. 206). Further, and as noted by Tabacknik and Fidell (2007), skewness does not make a substantial difference to the outcomes of parametric statistical analyses in reasonably large samples, and ANOVA is "robust to moderate violations of normality", particularly when the cell sizes are at least 20 (p. 251). Previous Monte Carlo studies (Seo, Kanda et al. 1995) have demonstrated robustness to non-normality in MANOVA with an overall N of 40 , which the present study more than doubled. As noted in the Methods Chapter, section 4.7, Pearson correlation coefficients may also be legitimately applied to skewed data (Norris & Aroian, 2004).

Therefore, these parametric procedures were used with the EEG and SDS data collected in this study. As also mentioned in the Methods chapter, section 4.8, the SDS raw scores (i.e. untransformed) were used in these analyses but all analyses were repeated with SDS log transformed values to check if there were any variations in the results for the statistical tests that were conducted on the SDS raw scores. There were no variations in the results of any of these tests, providing some support for the comments made by Tabacknik and Fidell (2007) regarding the effects of skewness and confirming that the amount of skewness present in the SDS raw scores did not invalidate the use of parametric tests with these data.

As mentioned in the Methods chapter, section 4.8, it is traditional in EEG studies to log transform the raw data, even though almost none of those studies actually tested

for normality. Therefore, this procedure was followed in this study so as to make the data analysis procedures consistent with those from previous studies reviewed in Chapter 3. The Kolmogorov-Smirnov statistics for all sites were significant ($p < .05$), and therefore all raw EEG values were transformed by log transformation**.** The means of the log transformed alpha power values for all 100 participants are presented in Tables 15 and 16, and they were used in the statistical analyses reported below.

Table 15: Mean values for transformed alpha power values (log alpha power score under eyes opened condition) N=100.

Site	LogFP1	LogFP2	LogF7	LogF8	LogF3	LogF4	LogFT7	LogFT8
Mean	-1.9785	-1.9763	-2.0043	-1.9926	-2.0997	-2.0872	-2.0120	-2.0024
SD	0.3721	0.3753	0.3474	0.3476	0.3846	0.3686	0.3774	0.3304
Min	-2.6990	-2.6990	-2.6990	-2.6990	-3.0000	-2.6990	-2.6990	-2.6990
Max	-1.1487	-1.0969	-1.2840	-1.1805	-1.2757	-1.1805	-1.1079	-1.1938
Site	**LogFC3**	**LogFC4**	**LogT7**	**LogT8**	**LogC3**	**LogC4**	**LogTP7**	**LogTP8**
Mean	-2.1640	-2.1495	-1.9658	-1.9633	-2.1455	-2.0994	-1.9854	-1.9370
SD	0.4089	0.3729	0.3552	0.3486	0.4588	0.4241	0.3481	0.3745
Min	-3.0000	-2.6990	-2.6990	-2.6990	-3.0000	-3.0000	-2.6990	-2.6990
Max	-1.2441	-1.1871	-1.0132	-1.0410	-1.0458	-1.0410	-0.9957	-0.9872
Site	**LogCP3**	**LogCP4**	**LogP7**	**LogP8**	**LogP3**	**LogP4**	**LogO1**	**LogO2**
Mean	-2.0804	-2.0662	-1.9171	-1.8202	-1.9678	-1.9392	-1.9427	-1.9536
SD	0.4506	0.4538	0.3434	0.4188	0.4732	0.4892	0.3657	0.3837
Min	-3.0000	-3.0000	-2.6990	-2.6990	-2.6990	-3.0000	-2.5229	-2.6990
Max	-1.0458	-1.0655	-1.0809	-0.9318	-0.8153	-0.7645	-0.9788	-0.9172

Table 16: Mean values for transformed alpha power values (log alpha power score under eyes closed condition) N=100.

Site	LogFP1	LogFP2	LogF7	LogF8	LogF3	LogF4	LogFT7	LogFT8
Mean	-1.5338	-1.5405	-1.6098	-1.6065	-1.5998	-1.6013	-1.6630	-1.6457
SD	0.4442	0.4456	0.4084	0.4122	0.4607	0.4630	0.3997	0.3921
Min	-2.6990	-2.6990	-2.6990	-2.5229	-3.0000	-3.0000	-2.6990	-2.3979
Max	-0.3010	-0.2700	-0.4763	-0.3851	-0.4377	-0.3270	-0.5544	-0.5482
Site	**LogFC3**	**LogFC4**	**LogT7**	**LogT8**	**LogC3**	**LogC4**	**LogTP7**	**LogTP8**
Mean	-1.7091	-1.7083	-1.6905	-1.6549	-1.7640	-1.7646	-1.6009	-1.4990
SD	0.4603	0.4590	0.3790	0.3800	0.4506	0.4322	0.3862	0.4149
Min	-3.0000	-3.0000	-2.6990	-2.5229	-3.0000	-3.0000	-2.6990	-2.5229
Max	-0.4737	-0.6198	-0.6198	-0.8386	-0.5258	-0.9318	-0.5258	-0.7258
Site	**LogCP3**	**LogCP4**	**LogP7**	**LogP8**	**LogP3**	**LogP4**	**LogO1**	**LogO2**
Mean	-1.6575	-1.6655	-1.3654	-1.1844	-1.3760	-1.3553	-1.2544	-1.2574
SD	0.4787	0.4483	0.4465	0.4618	0.5378	0.5458	0.4831	0.4810
Min	-3.0000	-3.0000	-2.3010	-2.3979	-2.6990	-3.0000	-2.3979	-2.5229
Max	-0.7496	-0.6799	-0.0680	-0.3757	-0.1993	-0.1637	-0.0846	-0.1586

5.2 Research Questions

Each of the four Research Questions may be broken down into three separate parts for the purposes of data analysis. These are shown below as (a), (b) and (c), and each is addressed separately.

5.2.1 Research Question 1:

EEG asymmetry and cerebral sites

(a) ***Does EEG alpha asymmetry occur at the frontal lobe in the sample, irrespective of depression status and gender?***

(b) ***Does EEG alpha asymmetry occur at other cerebral sites apart from the frontal lobes, irrespective of depression status and gender? Specifically, temporal, parietal and occipital sites were to be examined.***

(c) ***If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites in the sample, irrespective of depression status and gender?***

As described above in Chapter 3, alpha EEG asymmetry is defined in the literature as the difference between the log transformed alpha power values obtained from corresponding cerebral sites: i.e., LogRight minus LogLeft (Diego, Field et al. 2001; Shankman, Silverstein et al. 2008; Kemp, Griffiths et al. 2010; Lopez-Duran, Nusslock et al. 2012; Quinn, Rennie et al. 2014). According to that literature, a negative value from that subtraction is indicative of a negative alpha asymmetry score. This is taken as indicative of the presence of EEG "asymmetry" with greater cerebral activation on the right hemispheric site (Henriques and Davidson 1990; Henriques and Davidson 1991; Henriques and Davidson 1997; Kentgen, Tenke et al. 2000; Kemp, Griffiths et al. 2010; Shankman, Sarapas et al. 2011; Quinn, Rennie et al. 2014). Similarly, a positive value from that subtraction is indicative of a positive alpha asymmetry score, which is used in the literature as indicative of EEG "symmetry" or "no asymmetry" (i.e., the absence of asymmetry), with greater cerebral activation on the left hemispheric site (Henriques and Davidson 1990;

Henriques and Davidson 1991; Henriques and Davidson 1997; Kentgen, Tenke et al. 2000; Kemp, Griffiths et al. 2010; Shankman, Sarapas et al. 2011; Quinn, Rennie et al. 2014). The mean alpha asymmetry scores for each site were obtained for all 100 participants under both experimental conditions (i.e., eyes opened and eyes closed) and these values were used to answer the specified research questions that were generated from the Literature Review (Chapter 3).

(a) ***Does EEG alpha asymmetry occur at the frontal lobe in the sample, irrespective of depression status and gender?***

A series of paired *t*-tests was conducted to test for the presence of significant differences in frontal alpha activity from left to right hemispheres for each of the sites where EEG data were collected, irrespective of the effects of gender and/or depression severity. The results of those paired *t*-tests are shown below in Table 17. Considering that five *t*-tests were undertaken within each experimental condition, the traditional level of significance ($p < .05$) was corrected by dividing it by the number of tests conducted in each experimental condition (i.e., a Bonferroni correction). Therefore the required level of significance was $p < .01$ (i.e., .05/5 = .01).

As shown in Table 17, the results of the paired *t*-tests indicated that, irrespective of gender and depression, EEG alpha asymmetry (as defined in the literature as $L^{\alpha}>R^{\alpha}$ or $R_a>L_a$ which is represented by a negative asymmetry score) was not present at the frontal sites under the two experimental conditions (i.e., eyes opened, eyes closed). Although two of the comparisons in the eyes closed condition at frontal sites FP2/FP1 and F4/F3 showed negative asymmetry scores, neither of these comparisons was statistically significant at the corrected level of $p < .01$. Thus, irrespective of gender and depression, EEG asymmetry was not observed at the frontal sites under either of the two experimental conditions (i.e., eyes opened, eyes closed).

Table 17: Mean values and paired *t*-tests of the alpha asymmetry scores for Frontal sites (N=100).

Site	Mean (SD)	Difference	*t*	*p*
Eyes opened condition				
LogFP2	-1.9763 (0.3753)			
LogFP1	-1.9785 (0.3721)	0.0022	0.214	.831
LogF8	-1.9926 (0.3476)			
LogF7	-2.0043 (0.3474)	0.0117	0.643	.522
LogF4	-2.0872 (0.3686)			
LogF3	-2.0997 (0.3846)	0.0124	0.755	.452
LogFT8	-2.0024 (0.3304)			
LogFT7	-2.0120 (0.3774)	0.0096	0.513	.609
LogFC4	-2.1495 (0.3729)			
LogFC3	-2.1640 (0.4089)	0.0146	0.798	.427
Eyes closed condition				
LogFP2	-1.5405 (0.4456)			
LogFP1	-1.5338 (0.4442)	-0.0068	-1.132	.260
LogF8	-1.6065 (0.4122)			
LogF7	-1.6098 (0.4084)	0.0032	0.242	.809
LogF4	-1.6013 (0.4630)			
LogF3	-1.5998 (0.4607)	-0.0015	-0.124	.902
LogFT8	-1.6457 (0.3921)			
LogFT7	-1.6630 (0.3997)	0.0173	1.032	.305
LogFC4	-1.7083 (0.4590)			
LogFC3	-1.7091 (0.4603)	0.0008	0.046	.963

(b) ***Does EEG alpha asymmetry occur at other cerebral sites apart from the frontal lobes? Specifically, temporal, parietal and occipital sites were to be examined.***

As was done for the frontal areas, and irrespective of the effects of gender and/or depression status, a series of paired *t*-tests was conducted to test for the presence of significant differences in alpha activity from left to right hemispheres for each of the temporal, parietal and occipital sites where EEG data were collected. The results of those paired *t*-tests are shown below in Table 18. Those results indicate that only one of the comparisons in the eyes opened condition (at occipital site O2/O1) and three of the comparisons in the eyes closed conditions (each at temporal, parietal and occipital sites C4/C3, CP4/CP3 and O2/O1) showed negative asymmetry scores (i.e., presence of alpha asymmetry). However, none of these were statistically significant at the corrected level of $p < .007$ (i.e., .05/7 = .007). Thus, irrespective of gender and depression, EEG asymmetry was not present at the temporal, parietal or occipital sites under either of the two experimental conditions (i.e., eyes opened, eyes closed).

Table 18: Mean values and paired *t*-tests of the alpha asymmetry scores for temporal, parietal and occipital sites (N=100).

Site	Mean (SD)	Difference	*t*	*p*
Eyes opened condition				
LogT8	-1.9633 (0.3486)			
LogT7	-1.9658 (0.3552)	0.0025	0.103	.919
LogC4	-2.0994 (0.4241)			
LogC3	-2.1455 (0.4588)	0.0461	2.586	.011
LogTP8	-1.9370 (0.3745)			
LogTP7	-1.9854 (0.3481)	0.0484	2.368	.020
LogCP4	-2.0662 (0.4538)			
LogCP3	-2.0804 (0.4506)	0.0143	0.738	.462
LogP8	-1.8202 (0.4188)			
LogP7	-1.9171 (0.3434)	0.0968	4.156	.000
LogP4	-1.9392 (0.4892)			
LogP3	-1.9678 (0.4732)	0.0286	1.381	.170
LogO2	-1.9536 (0.3837)			
LogO1	-1.9427(0.3657)	-0.0109	-.585	.560
Eyes closed condition				
LogT8	-1.6549 (0.3800)			
LogT7	-1.6905 (0.3790)	0.0356	1.747	.084
LogC4	-1.7646 (0.4322)			
LogC3	-1.7640 (0.4506)	-0.0007	-0.030	.976
LogTP8	-1.4990 (0.4149)			
LogTP7	-1.6009 (0.3862)	0.1019	4.406	.000
LogCP4	-1.6575 (0.4483)			
LogCP3	-1.6655 (0.4787)	-0.0080	-0.337	.737
LogP8	-1.1844 (0.4618)			
LogP7	-1.3654 (0.4465)	0.1811	7.157	.000
LogP4	-1.3553 (0.5458)			
LogP3	-1.3760 (0.5378)	0.0207	0.877	.382
LogO2	-1.2574 (0.4810)			
LogO1	-1.2544 (0.4831)	-0.0030	-0.151	.880

However, of the twelve comparisons made within each experimental condition across frontal, temporal, parietal and occipital sites as shown in Tables 17 and 18, there were some instances of significant difference in the alpha activity from left to right hemispheres at the corrected level of .05/12 (i.e, p values < .004). These were, respectively: P8/P7 in the eyes opened condition and TP8/TP7 and P8/P7 for the eyes closed condition (all had p = 000). In terms of the nature of the asymmetry on these three sites, all three sites showed positive asymmetry scores indicating the absence of alpha asymmetry. All were in the direction indicating that the three right hemisphere

sites showed greater alpha activity (lesser cerebral electrical activation) than the corresponding three left hemisphere sites. Thus, ignoring gender and depressive state, only three of the twenty-four sites (12.5%) were characterised by significant differences in the alpha activity of the right and left hemispheres in the total sample of 100 participants. However, there were some inconsistencies between the two experimental conditions. For the eyes opened condition, only P8/P7 was significantly different, but for the eyes closed condition, TP8/TP7 and P8/P7 were significantly different. Thus, condition appeared to have some interactive effect upon alpha asymmetry.

Overall, of the twelve comparisons made within each experimental condition (i.e., eyes opened, eyes closed) across the frontal, temporal, parietal and occipital sites, only one of the comparisons in the eyes opened condition and five of the comparisons in the eyes closed conditions showed negative asymmetry scores (i.e., presence of alpha asymmetry) (see Tables 17 and 18). However, none of these comparisons were statistically significant at the traditional level. Therefore, ignoring gender and depression status, the sample did not show significant EEG asymmetry at any of the cerebral sites.

NB: Research question 1(c) was not considered because there was no significant asymmetry in the sample irrespective of gender and depression status.

5.2.2 Research Question 2:

EEG asymmetry, gender difference and cerebral sites

(a) ***Is there any gender difference in alpha asymmetry across different cerebral sites (i.e., frontal, temporal, parietal and occipital sites) in the sample, irrespective of depression status?***

(b) ***If so, what is the nature of those differences?***

(a) ***Is there any gender difference in alpha asymmetry across different cerebral sites in the sample, irrespective of depression status?***

As noted in the Literature Review (Chapter 3), to examine if there was significant alpha asymmetry at the frontal site, some previous studies used data obtained from the average of the mean alpha asymmetry scores at frontal, temporal and parietal sites (e.g., [(LogFP2-LogFP1) + (LogF4-LogF3) + (LogF8-LogF87) + (LogFC4-LogFC3) + LogFT8-LogFT7)]/5) (Harmon-Jones, Abramson et al. 2002; Blackhart, Minnix et al. 2006; Quinn, Rennie et al. 2014). However, using the average value does not reflect the total alpha activity recorded over these sites. Therefore, in this analysis, the data obtained from the sum of the alpha asymmetry scores at the five frontal sites (i.e., (LogFP2-LogFP1) + (LogF4-LogF3) + (LogF8-LogF87) + (LogFC4-LogFC3) + LogFT8-LogFT7)) were used because they represent the total magnitude of alpha activity measured across these sites.

In addition, some previous studies compared each pair of the frontal sites separately (Henriques and Davidson 1990; Henriques and Davidson 1997; Tomarken, Dichter et al. 2004; Diego, Field et al. 2006; Deslandes, de Moraes et al. 2008; Kemp, Griffiths et al. 2010).To replicate that methodology in this study, five frontal sites were compared separately (i.e., FP1/FP2, F3/F4, F7/F8, FC3/FC4, FT7/FT8). These two methods of testing for FLA were followed here in order to compare the data from this investigation with those from previous studies.

First, an ANOVA on the sum of the differences across the five frontal sites was conducted and results are shown in Table 19. There was no statistically significant difference between the alpha asymmetry scores for males *vs* females for the sum of five frontal sites under both experimental conditions (see Table 19).

Table 19: Sum of Mean alpha asymmetry scores for five frontal sites for males *vs* females.

Site	**Mean (SD) alpha asymmetry scores**		***F***	***p***	**Partial eta square**
	Males (n=46)	**Females (n=54)**			
Eyes opened condition					
Sum of five frontal site differences	0.0986 (0.5334)	0.0096 (0.5759)	0.635	.427	0.006
Eyes closed condition					
Sum of five frontal site differences	0.0762 (0.4918)	-0.0406 (0.5703)	1.181	.280	0.012

Second, the testing for significant differences across each of the five frontal sites was undertaken. In order to reduce the possibility of a Type I error, testing for the presence of gender differences in alpha asymmetry (excluding any effects due to depression) was conducted on all twenty-four sites (including the five frontal sites described above) in one MANOVA. Ignoring depressive state, there was a significant main effect for Gender ($F(24,74) = 2.060$, $p = .010$ (Wilks Lambda), $\eta^2 = .400$) which was a large effect size (Cohen 1988). Means and Standard Deviations for males and females at each site, plus the univariate effects, are shown in Table 20. From these comparisons, the five sites that showed significant differences between the alpha asymmetry scores of males and females were CP4/CP3 and P4/P3 (for eyes opened condition) and C4/C3, CP4/CP3 and O2/O1 (for the eyes closed condition) (MANOVA automatically corrects for multiple comparisons).

Table 20: Mean alpha asymmetry scores for male and female participants for all 24 sites.

Sites	Mean alpha asymmetry scores		*F*	*p*	Partial Eta Squared
	Males (*n*=46)	Females (*n*=54)			
Eyes Opened condition					
LogFP2 - LogFP1	0.0169 (0.09421)	-0.0104 (0.10725)	1.748	.189	.018
LogF8 - LogF7	0.0316 (0.18531)	-0.0052 (0.17973)	1.076	.302	.011
LogF4 - LogF3	-0.0005 (0.15041)	0.0235 (0.17797)	.581	.448	.006
LogFT8 - LogFT7	0.0333 (0.19154)	-0.0106 (0.18259)	1.366	.245	.014
LogFC4 - LogFC3	0.0173 (0.18269)	0.0122 (0.18460)	.007	.932	.000
LogT8 - LogT7	0.0208 (0.25253)	-0.0131 (0.23174)	.571	.452	.006
LogC4 - LogC3	0.0424 (0.18695)	0.0492 (0.17190)	.032	.858	.000
LogTP8 - LogTP7	0.0779 (0.20069)	0.0232 (0.20577)	1.942	.167	.020
LogCP4 - LogCP3	0.0633 (0.21901)	-0.0276 (0.15844)	5.635	.020	.055
LogP8 - LogP7	0.1255 (0.23438)	0.0724 (0.23129)	1.360	.246	.014
LogP4 - LogP3	0.0754 (0.21622)	-0.0113 (0.19182)	4.648	.034	.046
LogO2 - LogO1	-0.0272 (0.16236)	0.0030 (0.20480)	.622	.432	.006
Eyes closed condition					
LogFP2 - LogFP1	0.0047 (0.05343)	-0.0165 (0.06351)	3.210	.076	.032
LogF8 - LogF7	0.0081 (0.12788)	-0.0009 (0.13927)	.113	.738	.001
LogF4 - LogF3	0.0114 (0.10223)	-0.0124 (0.13263)	.950	.332	.010
LogFT8 - LogFT7	0.0249 (0.15672)	0.0108 (0.17797)	.146	.703	.002
LogFC4 - LogFC3	0.0271 (0.17881)	-0.0216 (0.17669)	1.844	.178	.019
LogT8 - LogT7	0.0678 (0.18104)	0.0082 (0.21974)	2.047	.156	.021
LogC4 - LogC3	0.0522 (0.23499)	-0.0457 (0.20103)	5.067	.027	.050
LogTP8 - LogTP7	0.1431 (0.20554)	0.0668 (0.24765)	2.736	.101	.027
LogCP4 - LogCP3	0.0483 (0.21896)	-0.0560 (0.24296)	4.886	.029	.048
LogP8 - LogP7	0.1662 (0.23858)	0.1937 (0.26619)	.260	.611	.003
LogP4 - LogP3	0.0238 (0.22381)	0.0181 (0.24810)	.021	.884	.000
LogO2 - LogO1	-0.0675 (0.18286)	0.0520 (0.19311)	9.959	.002	.093

(b) ***If so, what is the nature of those differences?***

As shown in Table 20, females showed negative asymmetry scores (indicative of the presence of alpha asymmetry) at twelve sites (50% of all compared paired sites, six sites each for eyes opened and eyes closed condition), but only on four of these sites were there significant differences with male asymmetry scores ($p < .05$). This is in contrast to males, who showed negative asymmetry scores (presence of alpha asymmetry) at three sites (12.5% of all compared paired sites, two sites for eyes opened condition and one site for eyes closed condition); however, only on one of these sites was there a significant difference with female asymmetry scores ($p < .05$). Of note, none of the significant differences between males and females alpha asymmetry across right *vs* left cerebral hemispheres occurred in the frontal regions and there was no common cerebral site where both males and females showed negative asymmetry scores.

When perused in terms of the type of difference present across sites, there were two statistically significant differences in males' *vs* females' alpha asymmetry across right *vs* left sites for the eyes opened condition and three for the eyes closed condition. These sites are displayed in Figures 5 and 6. Each of these differences had effect sizes that were either approaching medium strength or were between a medium and large effect (Cohen 1988). One of these differences was common across both the eyes opened and eyes closed condition (i.e., CP4/CP3) and the remaining four sites with significant differences were isolated to separate locations on the cerebral hemispheres.

Of the two sites under eyes opened condition with statistically significant gender differences, males exhibited a positive value (indicative of no significant alpha asymmetry) but females exhibited a negative score (indicative of significant alpha asymmetry) (See Figure 5). For the eyes closed condition, two of the three sites with significant differences in EEG asymmetry scores across gender also reflected no significant male alpha asymmetry and the presence of significant female alpha asymmetry. However, for a single site (O2-O1), males exhibited alpha asymmetry but females did not (See Figure 6). Thus, ignoring depressive status, females tended to show more EEG asymmetry than males at cerebral sites other than frontal sites.

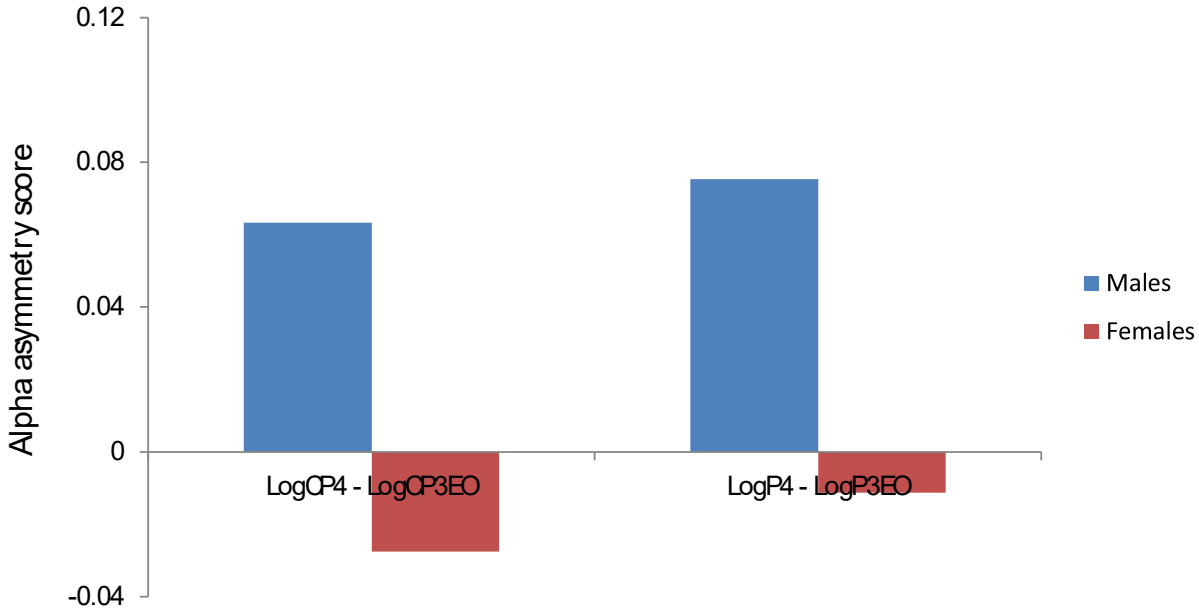

Figure 5: Direction of alpha asymmetry of males *vs* females at CP4/CP3 and P4/P3 sites (eyes opened condition).

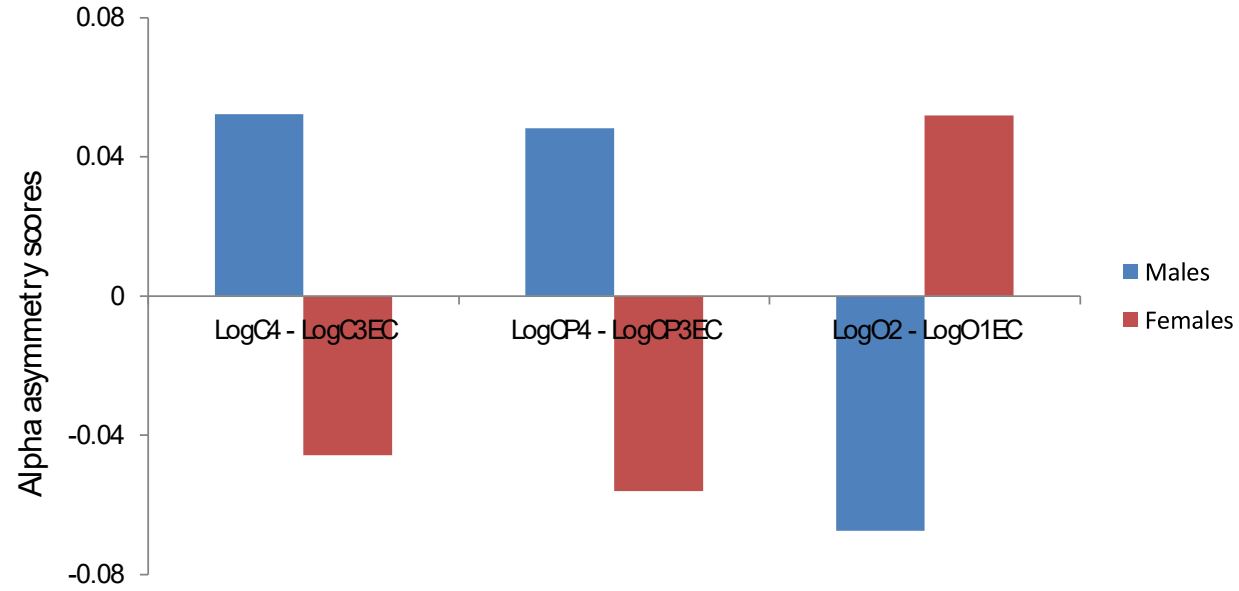

Figure 6: Direction of alpha asymmetry of males *vs* females at C4/C3, CP4/CP3 and O2/O1 sites (eyes closed condition).

5.2.3 Research Question 3:

EEG asymmetry, depression status and cerebral sites

(a) Do depressed and non-depressed individuals show different pattern of EEG alpha asymmetry at frontal, temporal, parietal and occipital sites, irrespective of their gender?

(b) If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites according to depression severity?

(a) Do depressed and non-depressed individuals show different pattern of EEG alpha asymmetry at frontal, temporal, parietal and occipital sites, irrespective of their gender?

This step of the data analysis was performed in the same sequence as in section 5.2.2. That is, the sum of the five frontal sites was compared across depressed *vs* non-depressed participants, and then each of the twenty-four sites was similarly compared across depressed *vs* non-depressed participants. To compare the effects of depression severity in terms of subgroups of SDS scores, the participant sample was divided according to the criteria set out by Zung for clinically significant depression (Zung 1965; Zung 1973), so that participants with SDS scores of < 40 were classified as "non-clinically depressed" and those with SDS scores of 40+ were classified as having "clinically significant depression". In addition, a similar subgrouping was performed for SDS scores of < 50 *vs* 50+, as this is the cut-off point defined by Zung (Zung 1965; Zung 1973) for "severe depression" and "not-severe depression". Tables 21 and 22 present the results for the ANOVAs on the sum of the five frontal sites for the two diagnostic criteria of severity derived from Zung's comments about SDS scores.

Table 21: Mean alpha asymmetry scores for sum of five frontal sites for clinically depressed *vs* non-clinically depressed participants (using SDS cut-off score of 40).

Site	Mean (SD) alpha asymmetry scores		*F*	*p*	Partial eta square
	SDS < 40	SDS 40+			
Eyes opened condition					
Sum of five frontal site differences	0.0653 (0.5424)	0.0206 (0.5893)	0.142	.707	.001
Eyes closed condition					
Sum of five frontal site differences	-0.0358 (0.5605)	0.1125 (0.4757)	1.703	.195	.017

Table 22: Mean alpha asymmetry scores for sum of five frontal sites for participants with severe depression *vs* participants with not-severe depression (using SDS cut-off score of 50).

Site	Mean (SD) alpha asymmetry scores		*F*	*p*	Partial eta square
	SDS < 50	SDS 50+			
Eyes opened condition					
Sum of five frontal site differences	0.0821 (0.5481)	-0.093 (0.5837)	1.472	.228	.015
Eyes closed condition					
Sum of five frontal site differences	0.0329 (0.5567)	-0.0770 (0.4324)	.099	.753	.001

As shown in Tables 21 and 22, there was no statistically significant difference between the alpha asymmetry scores for depressed *vs* non-depressed participants either using the SDS cut-off score of 40 or 50 for the sum of five frontal sites under both experimental conditions.

The second step in this stage of the analysis was to perform another MANOVA on all the twenty-four sites (including the five frontal sites as described above). For the SDS cut-off of 40, there was no significant main effect for depression status (F (24,75) = 0.568, p = .940 (Wilks Lambda), η^2 = .154). Means and Standard Deviations for participants with SDS scores < 40 *vs* those with SDS scores of 40+, plus the univariate effects, are shown in Table 23. None of the EEG sites showed significant differences in alpha activity between participants with SDS scores < 40 *vs* 40+.

Table 23: Mean alpha asymmetry scores for participants with SDS scores < 40 *vs* those with SDS scores 40+.

Sites	Mean (SD) alpha asymmetry scores		*F*	*p*	Partial Eta Squared
	SDS < 40 (n = 67)	**SDS > 40 (n=33)**			
Eyes opened condition					
LogFP2 - LogFP1	0.0151 (0.0900)	-0.0240 (0.1197)	3.335	.071	.033
LogF8 - LogF7	0.0177 (0.1820)	-0.0005 (0.1851)	.219	.641	.002
LogF4 - LogF3	0.0135 (0.1661)	0.0105 (0.1668)	.007	.933	.000
LogFT8 - LogFT7	0.0167 (0.1945)	-0.0048 (0.1731)	.289	.592	.003
LogFC4 - LogFC3	0.0023 (0.18510	0.0394 (0.1783)	.909	.343	.009
LogT8 - LogT7	0.0157 (0.2645)	-0.0243 (0.1847)	.608	.437	.006
LogC4 - LogC3	0.0418 (0.1782)	0.0546 (0.1804)	.114	.737	.001
LogTP8 - LogTP7	0.0479 (0.2121)	0.0493 (0.1904)	.001	.974	.000
LogCP4 - LogCP3	0.0110 (0.2144)	0.0209 (0.1434)	.057	.812	.001
LogP8 - LogP7	0.0999 (0.2373)	0.0906 (0.2276)	.035	.851	.000
LogP4 - LogP3	0.0387 (0.2300)	0.0081 (0.1510)	.482	.489	.005
LogO2 - LogO1	0.0001 (0.1890)	-0.0332 (0.1812)	.702	.404	.007
Eyes closed condition					
LogFP2 - LogFP1	-0.0077 (0.0525)	-0.0049 (0.0732)	.049	.826	.000
LogF8 - LogF7	-0.0122 (0.1399)	0.0347 (0.1154)	2.777	.099	.028
LogF4 - LogF3	-0.0046 (0.1159)	0.0048 (0.1285)	.136	.713	.001
LogFT8 - LogFT7	-0.0001 (0.1777)	0.0527 (0.1418)	2.215	.140	.022
LogFC4 - LogFC3	-0.0112 (0.1870)	0.0252 (0.1596)	.917	.341	.009
LogT8 - LogT7	0.0277 (0.2217)	0.0517 (0.1644)	.304	.583	.003
LogC4 - LogC3	-0.0005 (0.2205)	-0.0010 (0.2275)	.000	.993	.000
LogTP8 - LogTP7	0.1191 (0.2467)	0.0670 (0.1951)	1.125	.291	.011
LogCP4 - LogCP3	-0.0042 (0.2420)	-0.0156 (0.2297)	.051	.822	.001
LogP8 - LogP7	0.2028 (0.2651)	0.1369 (0.2236)	1.511	.222	.015
LogP4 - LogP3	0.0253 (0.2398)	0.0115 (0.2317)	.075	.785	.001
LogO2 - LogO1	0.0027 (0.1914)	-0.0145 (0.2100)	.168	.683	.002

For the SDS cut-off of 50, there was no significant main effect for depression status ($F(24,75) = 0.584$, $p = .930$ (Wilks Lambda), $\eta^2 = .157$). Means and Standard Deviations for participants with SDS scores < 50 *vs* those with SDS scores of 50+, plus the univariate effects, are shown in Table 24. Of the twenty-four sites of comparison under both experimental conditions, only one of the EEG sites showed significant differences in alpha activity between participants with SDS scores < 50 *vs* 50+, and that was for FP2/FP1 in the eyes opened condition, with participants with SDS score of 50+ (severe depression) showing negative asymmetry scores indicating the presence of EEG alpha asymmetry at this site. Therefore, ignoring the effect of gender, the presence of EEG alpha asymmetry at one frontal site differentiated individuals with severe depression from individuals with not-severe depression. Figure 7 displays the direction of alpha asymmetry at this site with a significant difference between the not-severe depression group (SDS scores < 50) *vs* severe depression (SDS scores 50+).

Table 24: Mean alpha asymmetry scores for participants with SDS scores < 50 *vs* those with SDS scores 50+.

Sites	Mean (SD) alpha asymmetry scores		*F*	*p*	Partial Eta Squared
	SDS < 50 (*n*=82)	SDS 50 + (*n*=18)			
Eyes Opened condition					
LogFP2 - LogFP1	0.0118 (0.0944)	-0.0419 (0.1245)	4.237	.042	.041
LogF8 - LogF7	0.0212 (0.1769)	-0.0315 (0.2051)	1.234	.269	.012
LogF4 - LogF3	0.0169 (0.1718	-0.0076 (0.1352)	.322	.572	.003
LogFT8 - LogFT7	0.0236 (0.1890)	-0.0541 (0.1688)	2.582	.111	.026
LogFC4 - LogFC3	0.0086 (0.1916)	0.0420 (0.1372)	.491	.485	.005
LogT8 - LogT7	0.0116 (0.2553)	-0.0391 (0.1583)	.652	.421	.007
LogC4 - LogC3	0.0369 (0.1832)	0.0879 (0.1498)	1.217	.273	.012
LogTP8 - LogTP7	0.0432 (0.2035)	0.0717 (0.2119)	.285	.595	.003
LogCP4 - LogCP3	0.0183 (0.2015)	-0.0040 (0.1532)	.195	.660	.002
LogP8 - LogP7	0.0962 (0.2377)	0.1000 (0.2169)	.004	.950	.000
LogP4 - LogP3	0.0322 (0.2212)	0.0120 (0.1266)	.140	.709	.001
LogO2 - LogO1	-0.0083 (0.1852)	-0.0228 (0.1957)	.089	.766	.001
Eyes closed condition					
LogFP2 - LogFP1	-0.0029 (0.0532)	-0.0242 (0.0831)	1.897	.172	.019
LogF8 - LogF7	0.0053 (0.1381)	-0.0063 (0.1137)	.112	.739	.001
LogF4 - LogF3	0.0060 (0.1188)	-0.0354 (0.1209)	1.780	.185	.018
LogFT8 - LogFT7	0.0208 (0.1774)	0.0016 (0.1173)	.192	.662	.002
LogFC4 - LogFC3	0.0038 (0.1856)	-0.0126 (0.1450)	.123	.727	.001
LogT8 - LogT7	0.0395 (0.2151)	0.0179 (0.1473)	.164	.686	.002
LogC4 - LogC3	-0.0009 (0.2111)	0.0006 (0.2719)	.001	.979	.000
LogTP8 - LogTP7	0.1045 (0.2444)	0.0901 (0.1633)	.056	.813	.001
LogCP4 - LogCP3	-0.0088 (0.2347)	-0.0045 (0.2535)	.005	.945	.000
LogP8 - LogP7	0.1798 (0.2675)	0.1867 (0.1783)	.011	.918	.000
LogP4 - LogP3	0.0140 (0.2389)	0.0515 (0.2268)	.371	.544	.004
LogO2 - LogO1	-0.0094 (0.1898)	0.0263 (0.2301)	.482	.489	.005

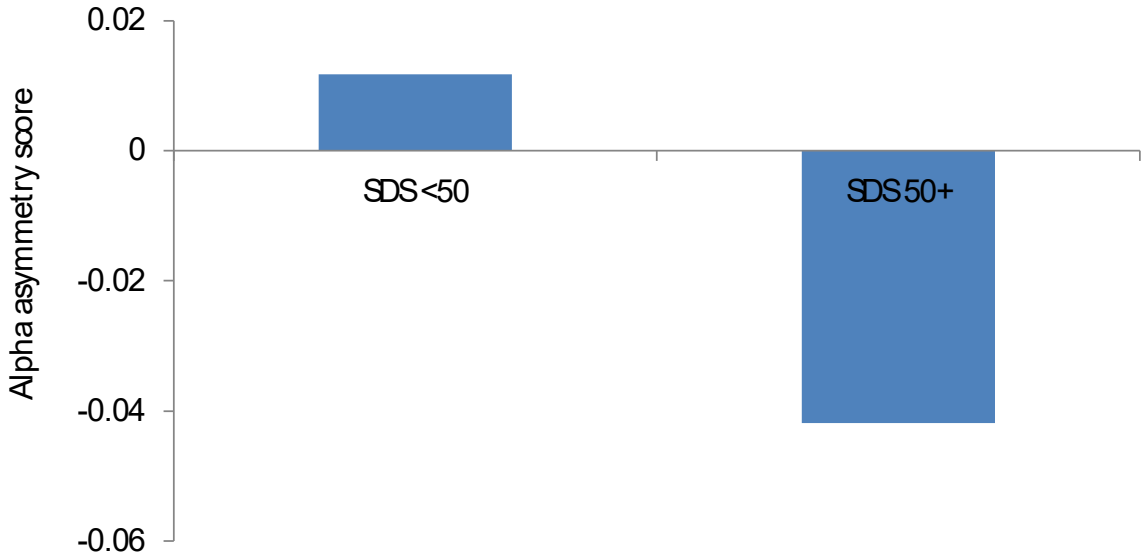

Figure 7: Direction of alpha asymmetry of not-severe depression group (SDS scores < 50) *vs* severe depression (SDS scores 50+) at FP2/FP1 site (eyes opened condition).

(b) If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites according to depression status?

As shown in Table 23, there was no significant difference in the asymmetry scores of the individuals with SDS scores of < 40 *vs* individuals with SDS scores of 40+. When further exploring these data beyond significance testing, individuals with SDS scores of 40+ showed negative asymmetry scores (indicative of the presence of alpha asymmetry) at nine sites (37.5% of all compared paired sites, five sites for the eyes opened condition and four sites for the eyes closed condition). In contrast, individuals with SDS scores of < 40 showed negative asymmetry scores at seven sites (25.9% of all compared paired sites, all of which occurred during the eyes closed condition). Thus, the occurrence of EEG alpha asymmetry was common in individuals with SDS scores of 40+ (clinically significant depression). Of note, nine out of the sixteen sites which showed negative asymmetry scores were obtained at the frontal regions (representing 37.5 % of all compared sites).

Only one of the EEG sites (FP2/FP1 in the eyes opened condition) showed significant differences in alpha activity between participants with SDS scores < 50 *vs* 50+. Further exploration of the data presented in Table 24 beyond significance testing

showed that the occurrence of alpha asymmetry was more common for participants with SDS scores of < 50 than for participants with SDS scores of 50+. Individuals with SDS scores of 50+ showed negative asymmetry scores (indicative of the presence of alpha asymmetry) at twelve sites (50% of all compared paired sites, seven sites for the eyes opened condition and five sites for the eyes closed condition) as opposed to individuals with SDS scores of < 50 who showed negative asymmetry scores at five sites (20.8% of all compared paired sites, one site for the eyes opened condition and six sites for the eyes closed condition). Thus, individuals with SDS scores of 50+ (severe depression) were more likely to demonstrate alpha asymmetry than individuals with SDS scores of < 50 (not-severe depression). Again, nine out of the seventeen sites which showed negative asymmetry scores were from the frontal regions (representing 37.5 % of all compared sites).

As stated above, for individuals with SDS scores of 40+ or 50+, the negative asymmetry scores occurred almost evenly under both experimental conditions of eyes opened and eyes closed. However, most of the negative asymmetry scores obtained for individuals with asymmetry scores of < 40 or < 50 occurred almost entirely under the eyes closed condition. Experimental conditions of eyes opened and eyes closed influenced the findings of alpha asymmetry in depressed *vs* non-depressed groups of individuals. It must be kept in mind that these differences were not statistically significant and therefore are exploratory only.

5.2.4 Research Question 4:

EEG asymmetry, gender difference, depression status and cerebral sites

(a) ***Is there any gender difference in alpha asymmetry across frontal, temporal, parietal and occipital sites according to depression status?***

(b) ***If so, do males and females show different patterns of alpha asymmetry across these sites according to the status of their depression?***

(a) ***Is there any gender difference in alpha asymmetry across frontal, temporal, parietal and occipital sites according to depression status?***

These research questions were addressed by considering the interaction between gender and depression status across cerebral sites.

To identify any significant effects due to the interaction of gender and depressive status, ANOVA and MANOVA were performed on all the combined frontal EEG sites and also on the twenty-four EEG sites, as in the two previous sections described above. The mean and SD values for males *vs* females, for SDS < 40 *vs* SDS 40+ and for SDS < 50 *vs* SDS 50+ are presented above in Tables 20, 23 and 24 respectively. First, the sum of the five frontal EEG sites was examined via ANOVA and results are shown in Tables 25 and 26 for SDS < 40 *vs* SDS 40+ and for SDS < 50 *vs* SDS 50+ respectively (for both the eyes opened and eyes closed conditions). The only significant interaction between depressive status and gender was for the SDS < 50 *vs* 50+ category of "not-severe" *vs* "severe" depression on the SDS under the eyes opened condition. This interaction is displayed in Figure 8.

Table 25: Univariate effects for the interaction between gender and depressive status, SDS < 40 *vs* SDS 40+ at the five frontal sites.

Site	*F*	*p*	Partial eta square
Eyes opened condition			
Sum of five frontal site differences	.123	.727	.001
Eyes closed condition			
Sum of five frontal site differences	3.568	.062	.036

Table 26: Univariate effects for the interaction between gender and depressive status, SDS < 50 *vs* 50+ at the five frontal sites.

Site	*F*	*p*	Partial eta square
Eyes opened condition			
Sum of five frontal site differences	4.325	.040	.043
Eyes closed condition			
Sum of five frontal site differences	1.737	.191	.018

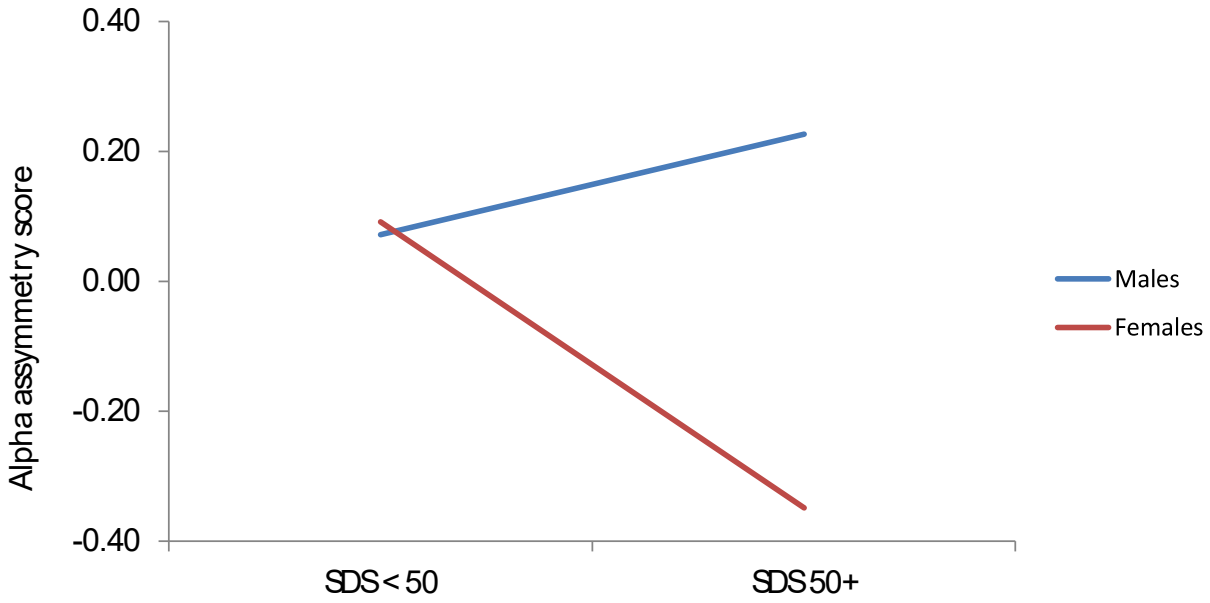

Figure 8: Interaction between gender and depressive status, SDS < 50 *vs* 50+ at the five frontal sites (eyes opened condition).

This interaction (Figure 8) indicates that, at the combined five frontal sites (under eyes opened condition), whereas males' and females' EEG alpha asymmetry scores were very similar for participants with SDS scores of < 50 (both showed positive asymmetry scores), for participants with SDS scores of 50+, there was a significant difference between males' and females' EEG alpha asymmetry scores, and that this difference emerged from (a) an *increase* in males' alpha asymmetry score and (b) a *decrease* in females' alpha asymmetry scores. That is, while severely depressed females (with SDS scores of 50+) showed more alpha asymmetry (i.e., greater alpha activity on the right hemisphere) than non-severely depressed females (or non-severely depressed males), severely depressed males (with SDS scores of 50+) showed more of the opposite kind of asymmetry (i.e., positive asymmetry scores or less alpha asymmetry, which indicates greater alpha activity on the left hemisphere).

Second, all twenty-four EEG sites were examined via MANOVA for any interactions between gender and depressive status for the eyes opened and eyes closed conditions, using both of the SDS severity indices (i.e., < 40 *vs* 40+ and < 50 *vs* 50+).

Table 27: Univariate effects for the interaction between gender and depressive status, SDS < 40 *vs* 40+ at all sites.

Site	*F*	*p*	Partial eta squared
Eyes opened condition			
LogFP2 - LogFP1	1.866	.175	.019
LogF8 - LogF7	.222	.638	.002
LogF4 - LogF3	.014	.906	.000
LogFT8 - LogFT7	.154	.695	.002
LogFC4 - LogFC3	.023	.881	.000
LogT8 - LogT7	.234	.630	.002
LogC4 - LogC3	.268	.606	.003
LogTP8 - LogTP7	.042	.838	.000
LogCP4 - LogCP3	2.421	.123	.025
LogP8 - LogP7	1.876	.174	.019
LogP4 - LogP3	4.825	.030	.048
LogO2 - LogO1	.376	.541	.004
Eyes closed condition			
LogFP2 - LogFP1	.073	.787	.001
LogF8 - LogF7	3.934	.050	.039
LogF4 - LogF3	3.108	.081	.031
LogFT8 - LogFT7	1.776	.186	.018
LogFC4 - LogFC3	2.649	.107	.027
LogT8 - LogT7	.503	.480	.005
LogC4 - LogC3	.769	.383	.008
LogTP8 - LogTP7	.050	.824	.001
LogCP4 - LogCP3	.616	.434	.006
LogP8 - LogP7	.131	.718	.001
LogP4 - LogP3	.248	.619	.003
LogO2 - LogO1	.569	.452	.006

For the cut-off using SDS raw score of 40, there was no significant interaction between gender and depressive status for the eyes opened and eyes closed conditions ($F(24,73) = 1.176$ (Wilks Lambda) $p = .292$, $\eta = .279$). Univariate effects for all the twenty-four sites are shown in Table 27, and indicated only one significant interaction between gender and depressive status for the eyes opened condition at the EEG site P4/P3 (shown in Figure 9). Of note, there was no significant interaction at the frontal sites under both experimental conditions although a trend towards significance occurred at EEG site F8/F7 for the eyes closed condition.

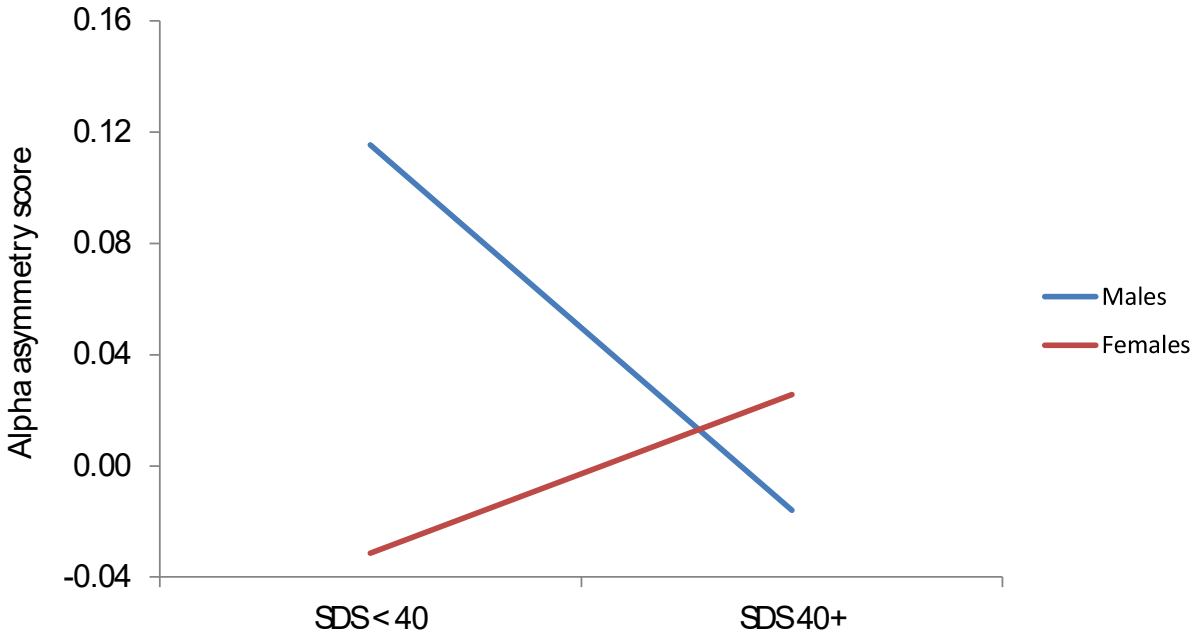

Figure 9: Interaction between gender and depressive status, SDS < 40 *vs* 40+ at EEG site P4/P3 (eyes opened condition).

This interaction (Figure 9) indicates that, at EEG site P4/P3 (under eyes opened condition), there was a significant difference between males' and females' EEG alpha asymmetry scores for participants with SDS scores of < 40 and participants with SDS scores of 40+. That is, for participants with SDS scores of < 40, males' showed positive alpha asymmetry scores (i.e., greater alpha activity on the left hemisphere) while females showed negative asymmetry scores (i.e., greater alpha activity on the right hemisphere). With increasing depression severity (i.e., SDS score of 40+), the reverse was true for both groups, i.e., males' showed more alpha asymmetry (negative asymmetry scores which indicate greater alpha activity on the right hemisphere) while females showed less alpha asymmetry (positive asymmetry scores which indicates greater alpha activity on the left hemisphere).

For the cut-off using SDS raw score of 50, there was no significant interaction between gender and depressive status for the eyes opened and eyes closed conditions ($F(24,73) = 1.188$ (Wilks Lambda) $p = .281$, $\eta = .281$). Univariate effects for all the twenty-four sites are shown in Table 28, and indicated only one significant interaction for the eyes opened condition for the EEG site FP2/FP1. This interaction is shown in Figures 10. There was no significant interaction for the eyes closed condition.

Table 28: Univariate effects for the interaction between gender and depressive status SDS < 50 *vs* 50+ at all sites.

Site	***F***	***p***	**Partial eta squared**
Eyes opened condition			
LogFP2 - LogFP1	8.405	.005	.081
LogF8 - LogF7	1.670	.199	.017
LogF4 - LogF3	3.374	.069	.034
LogFT8 - LogFT7	.092	.762	.001
LogFC4 - LogFC3	2.076	.153	.021
LogT8 - LogT7	.109	.742	.001
LogC4 - LogC3	.013	.909	.000
LogTP8 - LogTP7	.518	.474	.005
LogCP4 - LogCP3	1.766	.187	.018
LogP8 - LogP7	1.166	.283	.012
LogP4 - LogP3	3.266	.074	.033
LogO2 - LogO1	.000	.992	.000
Eyes closed condition			
LogFP2 - LogFP1	.004	.947	.000
LogF8 - LogF7	2.693	.104	.027
LogF4 - LogF3	1.549	.216	.016
LogFT8 - LogFT7	.981	.324	.010
LogFC4 - LogFC3	.949	.332	.010
LogT8 - LogT7	.710	.402	.007
LogC4 - LogC3	.406	.525	.004
LogTP8 - LogTP7	.050	.823	.001
LogCP4 - LogCP3	.120	.730	.001
LogP8 - LogP7	.025	.874	.000
LogP4 - LogP3	.039	.845	.000
LogO2 - LogO1	.491	.485	.005

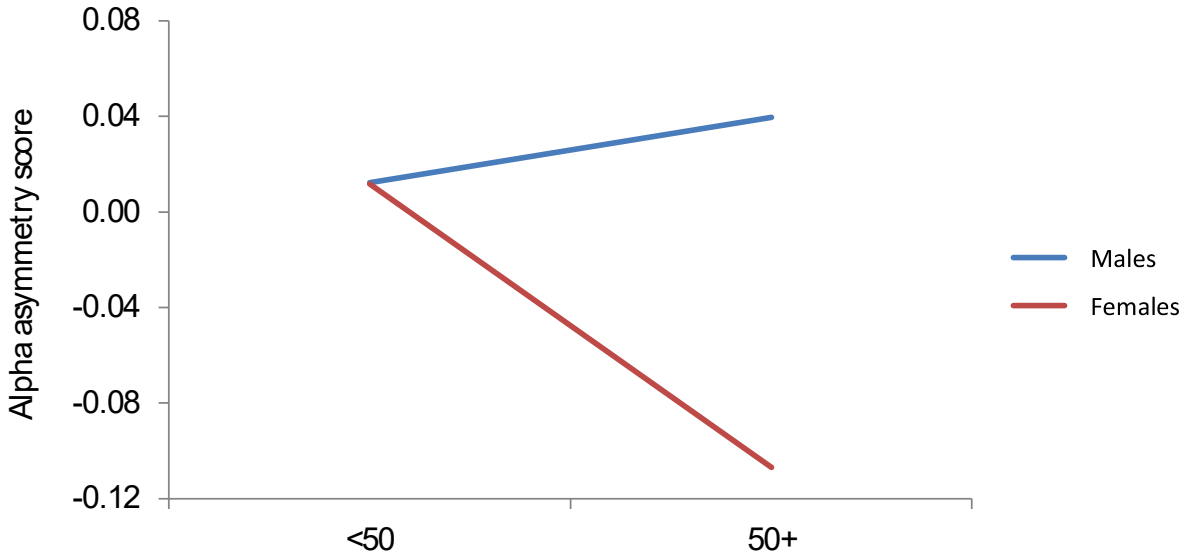

Figure 10: Interaction between gender and depressive status, SDS < 50 *vs* 50+ at EEG site FP2/FP1 (eyes opened condition).

This interaction (Figure 10) indicates that, at EEG site FP2/FP1 (eyes opened condition), whereas males' and females' EEG alpha asymmetry scores were very similar for participants with SDS scores of < 50 (both showed positive asymmetry scores), for participants with SDS scores of 50+, there was a significant difference between males' and females' EEG alpha asymmetry scores. This difference emerged from (a) an *increase* in males' alpha asymmetry score and (b) a *decrease* in females' alpha asymmetry scores. That is, while severely depressed females (with SDS scores of 50+) showed more alpha asymmetry (i.e., negative asymmetry scores which indicate greater alpha activity on the right hemisphere) than non-severely depressed females (or non-severely depressed males), severely depressed males (with SDS scores of 50+), showed more of the opposite kind of asymmetry (i.e., positive asymmetry scores or less alpha asymmetry, which indicates greater alpha activity on the left hemisphere).

(b) ***If so, do males and females show different patterns of alpha asymmetry across these sites according to the severity of their depression?***

As stated above in section 5.2.4 (a), significant interactions between gender and depression severity occurred at frontal and parietal sites but not at temporal nor occipital sites. The two sites with significant interactions between gender and depression severity were P4/P3 for SDS scores < 40 vs 40+ and FP2/FP1 for SDS scores < 50 vs 50+ (both under eyes opened condition), representing only 4.2% of all possible comparisons. Also, significant interactions between gender and depression severity occurred for the sum of all five frontal sites (under eyes opened condition) for SDS scores of < 50 vs 50+. The patterns of asymmetry for these sites with significant interactions between gender and depression severity under eyes opened condition have been described above in section 5.2.4 (a).

Overall, at the frontal and parietal sites, distinct patterns of alpha asymmetry were observed in the males and females group according to the severity of their depression. That is, at the frontal sites (FP2/FP1 and the five frontal sites combined), while severely depressed females showed more alpha asymmetry (i.e., negative asymmetry scores which indicate greater alpha activity on the right hemisphere) than non-severely depressed females, severely depressed males, showed less alpha symmetry than non-severely depressed males (i.e., positive asymmetry scores which indicate greater alpha activity on the left hemisphere) (Figures 8 and 10). By contrats, at the parietal site (i.e., P4/P3), depressed females showed less alpha asymmetry (i.e., positive asymmetry scores which indicate greater alpha activity on the left hemisphere) than non-depressed females, while severely depressed males, showed more alpha asymmetry than non-depressed males (i.e., negative asymmetry scores which indicate greater alpha activity on the right hemisphere) (Figure 9).

Therefore, with increasing depression severity, severely depressed females tended to show more alpha asymmetry at frontal sites but not at the parietal site, while severely depressed males tended to show more alpha asymmetry at the parietal site but not at frontal sites (Figures 8, 9 and 10).

The only frontal site at which a significant interaction for gender and depressive status occurred (i.e., FP2/FP1 for eyes opened condition) was the same site at which significant differences occurred in the alpha activity of participants with SDS < 50 *vs* participants with SDS scores of 50+. This warranted further exploration of the relationship between individual SDS scores and EEG alpha asymmetry scores of the male and female cohorts at this frontal site. As shown in Figure 11, excluding participants with zero EEG alpha asymmetry scores, the SDS scores of female participants were directly related to the EEG alpha asymmetry scores (i.e., female participants with higher SDS scores generally demonstrated more negative asymmetry scores). However, the male cohort tended to show a trend in the opposite direction (Figure 12).

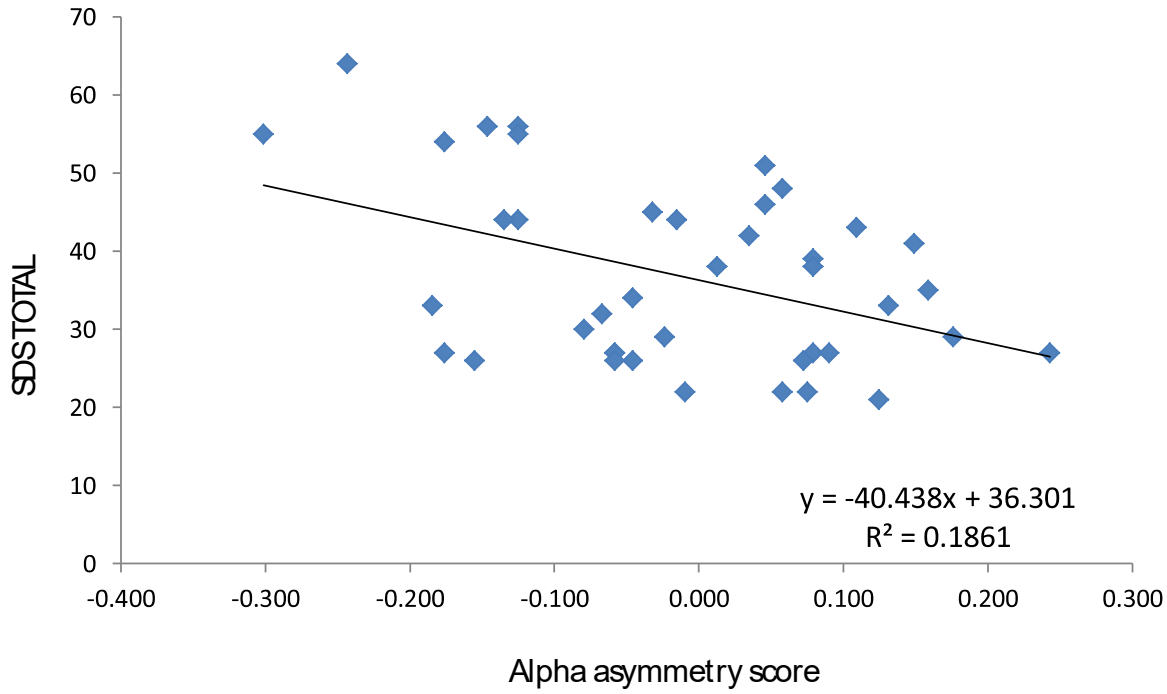

Figure 11: Graph of SDS scores vs mean alpha asymmetry scores for FP2/FP1 site for female participants (Eyes opened condition). Participants with zero alpha asymmetry scores excluded.

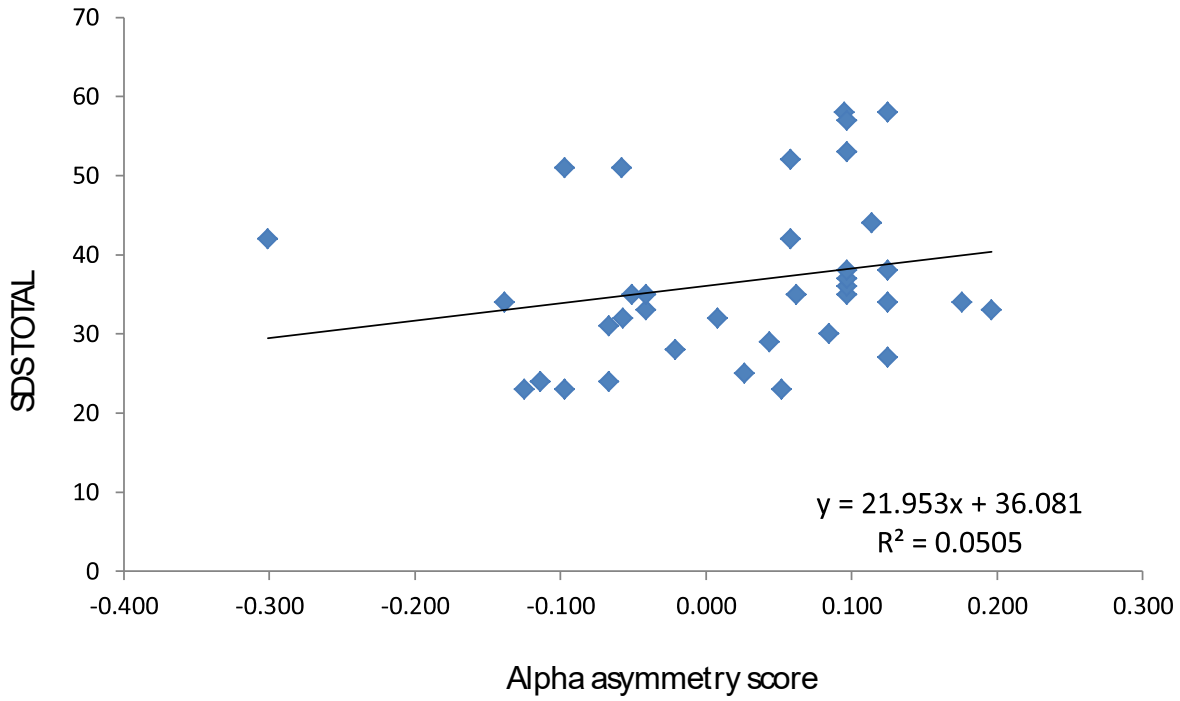

Figure 12: Graph of SDS scores vs mean alpha asymmetry scores for FP2/FP1 site for male participants (Eyes opened condition). Participants with zero alpha asymmetry scores excluded.

5.2.5 Full scale SDS analysis

5.2.5.1 Data analysis

The above analyses were based upon categorisation of the SDS scores into two subgroups according to the cut-offs recommended by Zung (Zung 1965; Zung 1973). However, although this kind of dichotomisation allows for relatively powerful statistical tests to be conducted, there is a cost to dichotomisation (Cohen 1983) that can lead to an artefactual increase in Type II errors. To overcome that possible source of error, Pearson correlation coefficients allow for the analysis of the entire range of SDS scores as potential correlates of EEG alpha asymmetry, and these were conducted for the frontal sum and all twenty-four EEG sites against SDS raw scores for males and females separately. Results of the frontal sum analyses are shown in Tables 29 and 30 for males and females respectively, but there were no significant associations between the frontal sum differences and SDS raw scores for either gender.

Table 29: Pearson correlation **coefficients for male participants for sum of five frontal site differences.**

Site	*r*	*p*
Eyes opened		
Sum of five frontal site differences	.164	.276
Eyes closed		
Sum of five frontal site differences	-.165	.274

Table 30: Pearson correlation coefficients for female participants for sum of five frontal site differences.

Site	*r*	*p*
Eyes opened		
Sum of five frontal site differences	-.096	.491
Eyes closed		
Sum of five frontal site differences	.250	.068

Tables 31 and 32 show the results of these correlation analyses for male and female participants for the twenty-four EEG sites against SDS raw scores. Although there was one significant correlation for the males' data (i.e., for P4/P3 for the eyes opened condition), when the appropriate Bonferroni correction was applied for each experimental condition (i.e., .05/12), this coefficient did not reach the required level of $p = .004$ For the females, there were two significant correlations at the traditional level (FP2/FP1 under the eyes opened condition and F8/F7 under the eyes closed condition) but neither of these reached the required corrected level of statistical significance, although the FP2/FP1 difference approached significance.

Table 31: Pearson correlation coefficients for male participants for all 24 EEG sites against SDS raw scores.

Eyes opened condition						
Site	**LogFP2 - LogFP1**	**LogF8 - LogF7**	**LogF4 - LogF3**	**LogFT8 - LogFT7**	**LogFC4 - LogFC3**	**LogT8 - LogT7**
r	.201	.160	.100	.081	.046	.019
p	.181	.288	.510	.595	.760	.901
Site	**LogC4 - LogC3**	**LogTP8 - LogTP7**	**LogCP4 - LogCP3**	**LogP8 - LogP7**	**LogP4 - LogP3**	**LogO2 - LogO1**
r	-.036	.164	-.191	-.121	-.306*	-.036
p	.814	.275	.203	.422	.039	.810
Eyes closed condition						
Site	**LogFP2 - LogFP1**	**LogF8 - LogF7**	**LogF4 - LogF3**	**LogFT8 - LogFT7**	**LogFC4 - LogFC3**	**LogT8 - LogT7**
r	-.082	-.119	-.264	-.045	-.153	-.021
p	.589	.432	.076	.768	.309	.888
Site	**LogC4 - LogC3**	**LogTP8 - LogTP7**	**LogCP4 - LogCP3**	**LogP8 - LogP7**	**LogP4 - LogP3**	**LogO2 - LogO1**
r	-.159	.056	-.103	.002	.038	.079
p	.293	.709	.496	.988	.801	.602

Table 32: Pearson correlation coefficients for female participants for all 24 EEG sites against SDS raw scores.

Eyes opened condition						
Site	**LogFP2 - LogFP1**	**LogF8 - LogF7**	**LogF4 - LogF3**	**LogFT8 - LogFT7**	**LogFC4 - LogFC3**	**LogT8 - LogT7**
r	-.357	-.119	-.019	-.069	.111	-.105
p	.008	.393	.891	.621	.426	.449
Site	**LogC4 - LogC3**	**LogTP8 - LogTP7**	**LogCP4 - LogCP3**	**LogP8 - LogP7**	**LogP4 - LogP3**	**LogO2 - LogO1**
r	.078	-.093	.157	.003	.125	-.121
p	.575	.504	.256	.980	.368	.382
Eyes closed condition						
Site	**LogFP2 - LogFP1**	**LogF8 - LogF7**	**LogF4 - LogF3**	**LogFT8 - LogFT7**	**LogFC4 - LogFC3**	**LogT8 - LogT7**
r	-.012	.305	.166	.191	.254	.033
p	.929	.025	.229	.167	.064	.814
Site	**LogC4 - LogC3**	**LogTP8 - LogTP7**	**LogCP4 - LogCP3**	**LogP8 - LogP7**	**LogP4 - LogP3**	**LogO2 - LogO1**
r	.170	-.204	.088	-.166	.054	-.088
p	.218	.139	.529	.230	.701	.528

5.3 Summary of Significant findings/results

A summary of the significant findings from the laboratory investigations that are directly relevant to the research questions generated from the literature review (Chapter 3) is presented below in Table 33.

Table 33: Research questions and corresponding significant findings

Research questions	Findings
Question 1	
Does EEG alpha asymmetry occur at the frontal lobe, irrespective of depression status and gender?	EEG alpha asymmetry (represented by $R_a > L_a$ or $R^{\alpha} < L^{\alpha}$) did not occur at the frontal sites under the two experimental conditions (i.e., eyes opened, eyes closed).
Does EEG alpha asymmetry occur at other cerebral sites apart from the frontal lobes, irrespective of depression status and gender? Specifically, temporal, parietal and occipital sites were to be examined.	EEG asymmetry (represented by $R_a > L_a$ or $R^{\alpha} < L^{\alpha}$) did not occur at the temporal, parietal and occipital sites under the two experimental conditions. However, the opposite kind of asymmetry (represented by $R^{\alpha} > L^{\alpha}$ or $R_a < L_a$) occurred at three sites (12.5%) of the 24 sites that were compared. These sites were the parietal site P8/P7 (eyes opened condition) and temporal and parietal sites TP8/TP7 and P8/P7 respectively (eyes closed condition). In terms of the nature of the asymmetry at these three sites, all showed positive asymmetry scores, indicating greater alpha activity (or lesser cerebral electrical activation) on the right cerebral sites than the corresponding left cerebral sites ($R^{\alpha} > L^{\alpha}$ or $R_a < L_a$).
If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites in the sample, irrespective of depression status and gender?	This question was not considered because there was no significant alpha EEG asymmetry in the expected direction at frontal, temporal, parietal and occipital sites.
Question 2	
Is there any gender difference in alpha asymmetry across different cerebral sites (i.e., frontal, temporal, parietal and occipital sites) in the sample, irrespective of depression status?	EEG alpha asymmetry scores of males and females did not differ at the individual frontal sites. This was also true for the combined five frontal sites. However, for the other cerebral sites (temporal, parietal and occipital sites), there were five

	individual sites with statistically significant differences between the alpha asymmetry scores of males and females. These were the parietal sites CP4/CP3 and P4/P3 (eyes opened condition), temporal site C4/C3 (eyes closed condition), parietal site CP4/CP3 (eyes closed condition) and occipital site O2/O1 (eyes closed condition).
If so, what is the nature of those differences?	Of the five sites with statistically significant differences in males' *vs* females' alpha asymmetry, at four sites (i.e., CP4/CP3, P4/P3, C4/C3 and CP4/CP3) males exhibited positive asymmetry values (indicative of no significant alpha asymmetry) but females exhibited negative scores (indicative of significant alpha asymmetry). However, for a single site (O2-O1), males exhibited alpha asymmetry but females did not.
Question 3	
Do depressed and non-depressed individuals show different pattern of EEG alpha asymmetry at frontal, temporal, parietal and occipital sites, irrespective of their gender?	For the individual frontal sites and for the combined five frontal sites under both experimental conditions, irrespective of gender, there was no statistically significant difference between the alpha asymmetry scores for depressed *vs* non-depressed participants (using the SDS cut-off score of 40). Irrespective of gender, using the SDS 50 cut off, one of the EEG sites (FP2/FP1 under the eyes opened condition) showed a significant difference in alpha activity between participants with SDS scores < 50 *vs* 50+. For the temporal, parietal and occipital sites, irrespective of their gender, there was no statistically significant difference between the alpha asymmetry scores for depressed *vs* non-depressed participants (using the SDS cut-off scores of 40 and 50).
If so, what is the nature of that asymmetry and are there any differences in asymmetry across these sites according to depression status?	For the FP2/FP1 site under the eyes opened condition, there was a significant difference in alpha activity between participants with SDS scores < 50 *vs* 50+. Participants with SDS score of 50+ (severe depression) showed negative asymmetry scores indicating the presence of EEG alpha asymmetry, while participants with SDS score of < 50 (not-severe depression) showed positive asymmetry scores indicating the absence of the hypothesised alpha asymmetry.

Question 4	
Is there any gender difference in alpha asymmetry across frontal, temporal, parietal and occipital sites according to depression status?	For the five individual frontal EEG sites and using the SDS cut-off scores of 40 and 50 for depression severity, the only significant interaction between depressive status and gender occurred at the EEG site FP2/FP1 under the eyes opened condition for the SDS < 50 *vs* 50+ category of "not-severe" *vs* "severe" depression. There was no significant interaction between depressive status and gender for the SDS < 40 *vs* 40+ category of depression severity at the five individual frontal sites. Significant interactions occurred between depressive status and gender at the combined five frontal sites (using the SDS < 50 *vs* 50+ category) under the eyes opened condition. There was no significant interaction between depressive status and gender for the combined five frontal sites using the SDS < 40 *vs* 40+ category. For the temporal, parietal and occipital sites and using the SDS cut-off scores of 40 and 50 for depression severity, the only site with a significant interaction between gender and depressive status was the parietal site, P4/P3 under eyes opened condition, using the SDS cut off score of 40. Other temporal, parietal and occipital sites did not show significant interactions between depressive status and gender, whether the SDS cut-off scores of 40 or 50 were used.
If so, do males and females show different patterns of alpha asymmetry across these sites according to the status of their depression?	For the EEG site FP2/FP1 under the eyes opened condition for the SDS < 50 *vs* 50+ category which showed significant interaction between depressive status and gender, the pattern of asymmetry was such that, while both the male and female groups with not-severe depression (SDS score of < 50) showed positive asymmetry scores (absence of asymmetry), males with severe depression (SDS score of 50+) showed positive asymmetry scores while females with severe depression showed negative asymmetry scores indicating the presence of alpha asymmetry.

	For the sum of the five frontal EEG sites with significant interactions between depressive status and gender (using the SDS cut-off score of 50), the nature of asymmetry was such that both the male and female groups with not-severe depression (SDS score of < 50) showed positive asymmetry scores, but with increasing depression severity (SDS 50+), the female group showed negative asymmetry scores while the male group showed positive asymmetry scores. For the parietal site, P4/P3 (under eyes opened condition, using the SDS cut-off score of 40) which showed significant interaction between depressive status and gender, the pattern of EEG asymmetry was that clinically depressed males showed negative asymmetry score (presence of alpha asymmetry) while clinically depressed females showed positive asymmetry score (absence of alpha asymmetry). The reverse was true for males and females with no clinically significant depression (SDS score of < 40). The only site where a significant interaction for gender and depressive status occurred was the FP2/FP1 (under eyes opened condition). Examination of the individual SDS scores of the male and female groups as against their alpha asymmetry scores at this site revealed that the SDS scores of female participants (but not male participants) were directly correlated with their EEG alpha asymmetry scores (i.e., female participants with higher SDS scores generally demonstrated more negative asymmetry scores). The male cohort showed a similar trend but in the opposite direction.

CHAPTER SIX

DISCUSSION

6.1 Summary of the outcomes of the systematic literature review regarding the areas of controversy regarding alpha asymmetry in depression

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6.1 Summary of the outcomes of the systematic literature review regarding the areas of controversy regarding alpha asymmetry in depression

6.1.1 Sites at which alpha asymmetry occurs in depression

A number of EEG studies provided evidence that depressed patients display $L^{\alpha}>R^{\alpha}$ alpha asymmetry at the frontal site (Henriques and Davidson 1990; Henriques and Davidson 1991; Davidson 1998; Thibodeau, Jorgensen et al. 2006; Liao, Zhou et al. 2013; Gollan, Hoxha et al. 2014), whereas other studies reported that posterior alpha asymmetry was opposite to that of frontal alpha asymmetry (i.e., $L^{\alpha} < R^{\alpha}$) in depressed patients (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Kentgen, Tenke et al. 2000; Shankman, Sarapas et al. 2011). However, some studies showed null findings in frontal and posterior sites (Reid, Duke et al. 1998; Kline and Allen 2008; Stewart, Towers et al. 2011). Only one study demonstrated that inter-hemispheric alpha asymmetry in depressed persons was measurable across the entire cerebral cortex (Fingelkurts, Fingelkurts et al. 2006), and this finding is yet to be replicated or validated by further investigations. Therefore, the exact relationship between left and right alpha asymmetry across the entire cerebral cortex was not described in the previous literature.

6.1.2 Gender differences in alpha asymmetry in depression

Only a few studies examined gender differences in alpha asymmetry among depressed persons and the findings from those studies vary considerably. For instance, Jaworska et al. (2012) reported that *anterior* alpha asymmetry in depression was significantly more pronounced in men than in women. Whereas, Stewart et al. (2010) reported that depressed women demonstrated relatively greater *frontal* alpha EEG asymmetry ($L^{\alpha}>R^{\alpha}$) than healthy female controls but that there was no significant difference in frontal alpha asymmetry of depressed men *vs* non-depressed men. Also, some reports showed that depressed men demonstrated the commonly reported EEG alpha asymmetry of ($L^{\alpha}>R^{\alpha}$) (Miller, Fox et al. 2002; Flor-Henry, Lind et al. 2004) and others also showed that the opposite pattern of frontal alpha asymmetry was found in depressed men (Knott, Mahoney et al. 2001) and depressed women (Miller, Fox et al. 2002). Overall, the reports on gender differences were not congruent and this issue required further investigation.

6.1.3 The relationship between depression severity and frontal EEG asymmetry

Most previous EEG asymmetry studies used dichotomous measures of depression (i.e., severe depression *vs* no depression) to examine the relationship between depression severity and frontal EEG asymmetry (Coan and Allen 2004; Blackhart, Minnix et al. 2006; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Feng, Forbes et al. 2012). The findings from these studies showed that individuals who were classified as "not depressed" showed no frontal EEG asymmetry but individuals with high enough scores on the rating scales to be categorized as having "severe depression" demonstrated significant frontal EEG asymmetry. However, one study made an attempt to describe depression severity in greater detail by classifying the combined sample of both depressed and non-depressed individuals into low, moderate and high depression (corresponding to BDI scores of 0-10, 11-20 and >21 respectively) (Stewart, Bismark et al. 2010), but the results did not show significant main effects or group differences between the three categories of depression. Diego et al. (2001) demonstrated a linear relationship between CES-D scores and frontal EEG alpha asymmetry in women suffering from post-natal depression (not MDD) but they failed to report any difference in the asymmetry patterns between individuals with moderate depression scores ("borderline" group) and "depressed" individuals (Diego, Field et al. 2001). In all, the "severe" form of depression was the only depression category reported as demonstrating frontal EEG asymmetry. Thus, the issue of depression severity remained relatively uninvestigated from the previous literature.

6.2 Summary of the significant findings from the experimental investigation of the issues of controversy regarding alpha EEG asymmetry in depression

The results of the experimental investigation of the relationship between depression severity, gender and cerebral sites and frontal alpha asymmetry in depression carried out in this thesis revealed the following:

(a) disregarding depression status, significant alpha EEG asymmetry was not observed in the community sample (across all cerebral sites);

(b) disregarding depression status, men and women did not exhibit significantly different patterns of alpha asymmetry at the frontal site. However, the presence of the opposite kind of alpha asymmetry (represented by 'positive' asymmetry scores)

significantly differentiated men and women at some temporal, parietal and occipital sites in the absence of depression;

(c) the presence of frontal alpha asymmetry significantly differentiated severely depressed individuals from not-severely depressed individuals (the latter showed a lack of alpha asymmetry). Alpha asymmetry did not differentiate severely depressed and not-severely depressed individuals at any of the other cerebral sites (i.e., temporal, parietal and occipital sites); and

(d) a significant interaction effect was observed between depression severity and frontal alpha asymmetry as a result of gender (i.e., significant frontal alpha asymmetry differentiated severely depressed females from not-severely depressed females, but severely depressed males did not differ from not-severely depressed males in frontal asymmetry). At the other cerebral sites (i.e., temporal, parietal and occipital sites), there was no significant interaction between depression severity and alpha asymmetry as a result of gender (although some interaction was observed between depression severity and alpha asymmetry at the parietal site based on gender, but this finding was deemed negligible because, in the sample population, alpha asymmetry was shown to occur even in the absence of depression, and thus this observation was independent of depression status).

6.3 Synthesis of the outcomes of the systematic review of the literature on alpha EEG asymmetry in depression and the findings of the investigation of alpha EEG asymmetry in depression undertaken in this study

Recall that, according to the "approach withdrawal" model of MDD (Davidson 1998), which hypothesized that electrical activity in the left prefrontal cortex reflects the behavioural *approach* system (responsible for *engaging* with pleasant stimuli) (Davidson 1998) and the activation of the right prefrontal cortex represents the behavioural *withdrawal* system (responsible for *disengaging from* or *avoiding* aversive stimuli) (Henriques and Davidson 2000), the withdrawal behaviour in depression is accompanied by less left frontal lobe activation and more right frontal lobe activation (i.e., $R_a > L_a$). Thus depressed individuals should demonstrate negative alpha asymmetry scores (Gray 1994; Davidson 1998; Henriques and Davidson 2000).

From the review of the literature (Chapter 3), certain issues which required further clarification as regards the occurrence of alpha EEG asymmetry in depression were identified. These were: (a) what is the relationship between depression severity and frontal EEG asymmetry; (b) are there any gender differences in alpha asymmetry in depression; and, (c) at what cerebral sites does alpha asymmetry occur in depression? In an attempt to provide some clarification on these issues, this research study was designed as an exploratory study, so that, in a community sample of 100 participants, the alpha EEG activity across frontal, temporal, parietal and occipital sites was examined to investigate (a) if alpha EEG asymmetry was present independently of depression status in the whole sample; (b) if alpha EEG asymmetry was present regardless of depression status in male *vs* female participants; (c) if alpha EEG asymmetry varied in depressed *vs* non-depressed individuals as a result of their depression status; and (d) if alpha asymmetry differed in depressed and non-depressed males and females based on their depression status and gender.

6.3.1 Irrespective of depression and gender, does alpha EEG asymmetry occur in the general population across frontal, temporal, parietal and occipital sites?

Firstly, it was found that there was no significant alpha EEG asymmetry in the community sample irrespective of depression status and gender. That is, alpha EEG asymmetry was not found to be pre-existing in this community sample when gender and depression were excluded from the analysis. This finding is particularly important because, if alpha EEG asymmetry had been found to be a common phenomenon in the community sample, then its association with depression would be challenged. That finding would also challenge the approach-withdrawal model of depression that was (at least partially) based upon this hypothesis. From the comprehensive review of the literature, virtually all the identified previous studies did not consider the possibility of alpha EEG asymmetry occurring in the general population, irrespective of gender and depression status. In fact, most studies examined alpha EEG asymmetry in depressed individuals (study group) *vs* non-depressed individuals (control group). This research study is the first identified attempt to examine this issue, and the findings suggest that the assumption that significant alpha EEG asymmetry is absent in the community irrespective of depression status and gender, holds true.

The activation of the left frontal lobe reflects interaction with positive stimuli, and the activation of the right frontal lobe reflects withdrawal from negative stimuli.

Therefore, the finding of no significant alpha EEG asymmetry in the community sample (irrespective of depression status and gender) underlies and reinforces the concept that mentally healthy individuals use both frontal cortices and both set of cognitive strategies equally, i.e., within "a balanced system". This balanced system serves as a baseline for the hypothesis that asymmetry might be associated with disordered thinking and the disordered neurological processes which are associated with major depression.

6.3.2 Irrespective of depression, are there gender differences in the occurrence of alpha EEG asymmetry in the general population across frontal, temporal, parietal and occipital sites?

From the comprehensive review of the literature, virtually all the identified studies did not consider the possibility of gender differences in alpha EEG asymmetry occurring in the general population. For example, does alpha asymmetry occur in males and not in females (and *vice versa*) irrespective of depression status? From this study, it was found that there was no significant difference in the alpha EEG asymmetry of males and females at frontal sites irrespective of depression status. This finding opens the possibility for testing the hypothesis of frontal alpha asymmetry in depression.

However, it was also found that males and females showed significant differences in alpha asymmetry at some specific temporal, parietal and occipital sites, irrespective of depression status. That is, the parietal sites CP4/CP3 and P4/P3 (for the eyes opened condition) and temporal site C4/C3, parietal site CP4/CP3 and occipital site O2/O1 (for the eyes closed condition) were sites where the expected directional asymmetry occurred in this study sample. Therefore, any findings of significant alpha asymmetry at these sites may be influenced by the fact that men and women showed significantly different alpha EEG asymmetry at these sites, even in the absence of depression.

6.3.3 Irrespective of gender, are there depression severity differences in alpha EEG asymmetry in the general population, across frontal, temporal, parietal and occipital sites?

When considering depression severity and ignoring gender, the depressed and non-depressed individuals from the community sample were able to be significantly differentiated based on their EEG asymmetry scores only at the frontal site (i.e., FP2/FP1). In other words, severely depressed individuals showed alpha asymmetry

(represented by negative asymmetry scores) while non-severely depressed individuals demonstrated an absence of alpha asymmetry (represented by positive asymmetry scores) only at the frontal site, and this finding was statistically significant. As shown in the review of the literature, some previous studies have also reported similar findings at the frontal sites using the dichotomous measures of "severe" *vs* "not-severe" depression (Coan and Allen 2004; Blackhart, Minnix et al. 2006; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Feng, Forbes et al. 2012).

More importantly, the frontal lobe has been associated with logical thinking and decision-making and it is the most likely site where cognitive activity is undertaken (Damasio 1995). Depressed individuals generally show altered logical thinking and poor decision-making, plus reduced cognitive functioning (Murphy, Rubinsztein et al. 2001; Paulus and Angela 2012). Therefore, the most likely site where alpha asymmetry is to be expected is the frontal lobe, and the finding from this study supports that proposition.

In addition, the results from this study did not show that alpha asymmetry at temporal, parietal and occipital sites was opposite to that of frontal alpha asymmetry (i.e., $R^{\alpha}>L^{\alpha}$) in depressed patients. This is in contrast to some previous reports which demonstrated that posterior alpha asymmetry was opposite to that of frontal alpha asymmetry in depressed patients (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Kentgen, Tenke et al. 2000; Shankman, Sarapas et al. 2011). A few studies argued that the parietal cortex (not temporal and occipital cortices) also plays a role in depression-related attention/executive function deficits during cognitive and emotional tasks (Mayberg 1997; Liotti and Mayberg 2001), and that depression is associated with impaired right parietal cortex function, i.e., impaired processing of emotional stimuli (Heller 1993; Heller, Nitschke et al. 1997; Bruder 2003) which manifests as right parietal hypoactivity or greater right parietal alpha activity (i.e., $R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) in depressed individuals when compared with healthy controls (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Allen, Coan et al. 2004; Blackhart, Minnix et al. 2006). On the other hand, several resting EEG studies have failed to confirm an association between right parietal hypoactivity and depression (Henriques and Davidson 1991; Nitschke, Heller et al. 1999; Debener, Beauducel et al. 2000; Deslandes, de Moraes et al. 2008; Mathersul, Williams et al. 2008; Stewart,

Towers et al. 2011). The findings from this current study which indicate that significant alpha asymmetry only occurred in the frontal lobes (but not parietal, temporal and occipital lobes) are congruent with those results.

This discrepancy might be partly due to the fact that, in the hierarchy of decision-making, the logical understanding of the outside world is done via the activation of the frontal lobe, whereas the parietal and the temporal lobes is more likely to be associated with memory and mobility functions. Although, some symptoms of MDD such as memory deficit and psychomotor retardation may suggest that depression may be accompanied by temporal and parietal lobes altered functions, the result from this study suggests that the strongest neurological marker of MDD is associated with decision-making and logical understanding of the outside world; hence frontal alpha asymmetry is a more appropriate indicator of depression than parietal asymmetry.

Furthermore, using the mild, moderate and severe depression categorization recommended by the author of the SDS, it was not possible to describe any difference in the asymmetry patterns of the participant sample because these did not occur during baseline measurements of alpha EEG activity. While previous studies have suggested a dose-response relationship between depression severity and frontal alpha asymmetry (Diego, Field et al. 2001; Mathersul, Williams et al. 2008), it follows that the more severe forms of depression will be largely differentiated from less severe forms of depression by the presence of greater alpha asymmetry on baseline EEG measurements. However, it is plausible that task-related asymmetry measurements during cognitive and emotion-eliciting or affective activities might differentiate mild to moderate forms of depression from no depression (Schaffer, Davidson et al. 1983; Jones, Field et al. 2000; Jones, Field et al. 2001). This current investigation was unable to identify asymmetry differences that may occur due to mild or moderate levels of depression but the findings from this study suggest that the approach-withdrawal model of depression may be only applicable in frontal sites in cases of severe depression (i.e., > 50 on the SDS).

6.3.4 Does alpha asymmetry differ in depressed and non-depressed males and females based on their depression status, across frontal, temporal, parietal and occipital sites?

The findings from this research study also showed that males and females demonstrated significantly differing patterns of alpha EEG asymmetry according to their depression status at the frontal site FP2/FP1 (eyes opened condition), at the combined frontal sites (eyes opened condition), and at the parietal site P4/P3 (eyes opened condition).

At the frontal sites (either FP2/FP1 or the five frontal sites combined), the pattern of asymmetry was such that, while both the male and female groups with not-severe depression showed positive asymmetry scores, males with severe depression showed significantly greater positive asymmetry scores while females with severe depression showed significantly greater negative asymmetry scores, indicating the presence of alpha asymmetry with greater cerebral activation on the right than on the left frontal site. Therefore, alpha asymmetry ($R_a > L_a$ or $R^{\alpha} < L^{\alpha}$) occurred in this study concurrently with increasing depression severity at the frontal site only in female (but not in male) participants. From the review of the literature, similar findings have been separately reported for females (Stewart, Bismark et al. 2010) and for males (Knott, Mahoney et al. 2001; Flor-Henry, Lind et al. 2004), although the findings of Jaworska et al. (2012) and Miller et al. (2012) suggest the opposite direction of gender-based differences.

The findings of Stewart et al., (2011) showed that women with current MDD exhibited higher relative right parietal activity than women with past or no MDD (although this effect was partially moderated by caffeine intake), whereas men with current and past MDD displayed higher relative right parietal activity than men without MDD (again, recent caffeine consumption moderated the relationship between MDD status and parietal asymmetry). In other words, depressed men and women generally showed alpha EEG asymmetry ($R^{\alpha} < L^{\alpha}$) in the parietal lobe, and those authors advocated for gender difference consideration in EEG studies of depression. However, this current study showed gender difference in the frontal lobes only, with women showing greater right frontal lobe activation as opposed to men who showed greater left frontal lobe activation. While there is no valid explanation as to why depressed men and women should differ in their baseline EEG activation, it may be that, in an attempt to hide their depressive illness, depressed men consciously

make continuous efforts to appear not to be depressed (Cochran and Rabinowitz 1999; Addis and Mahalik 2003), and this exaggerated behavioural response was reflected as greater left frontal lobe activation in their EEG measurements.

In addition, on examination of the individual SDS scores of the male and female groups across their alpha asymmetry scores at the frontal site FP2/FP1 (this site showed a significant interaction for gender and depressive status), it was found that the SDS scores of female participants (but not males) were directly proportional to their EEG alpha asymmetry scores (i.e., female participants with higher SDS scores generally demonstrated more negative asymmetry scores in a linear relationship). The male cohort showed a similar trend but in the opposite direction. A similar linear relationship was previously reported between the CES-D scores of women suffering from post-natal depression (not MDD) and their individual asymmetry scores (Diego, Field et al. 2001). Therefore, it may be that not only do females show significantly different patterns of alpha EEG asymmetry to males, but that they do so in a linear relationship according to the severity of their depression status (measured by SDS scores in this case). In other words, frontal alpha EEG asymmetry may demonstrate the true depressive status of depressed female participants. This finding suggests that, rather than obscuring their true emotional and cognitive state, depressed women may show behavioural responses which are commensurate with their depressive illness, and this may provide some explanations as to why depressed women seek more help with managing their depression (as opposed to men) (Padesky and Hammen 1981; Good and Wood 1995; Galdas, Cheater et al. 2005). As a result of this, women may be more likely to receive early treatment for their depression which may imply better outcomes, and this may also partly provide some explanation as to why worse outcomes such as suicide are more common in depressed men than in depressed women (Oquendo, Barrera et al. 2004; Tondo, Lepri et al. 2007; APA 2013).

6.4 Non-hypothesized findings

6.4.1 Significant positive asymmetry scores at non-frontal sites

Traditionally, EEG alpha asymmetry is defined by greater cerebral activation (or lesser alpha activity) on the right than on the left cerebral hemisphere (i.e., $R_a > L_a$ or $R^{\alpha} < L^{\alpha}$), represented by a negative alpha asymmetry score (Debener, Beauducel et al.

2000; Diego, Field et al. 2001). However, the findings from this study showed that there were some instances where significant differences in the alpha activity from left to right hemispheres was of the "opposite" kind of asymmetry represented by positive asymmetry scores, i.e., greater cerebral activation (or lesser alpha activity) on the left than on the right cerebral hemisphere i.e., $L_a > R_a$ or $L^{\alpha} < R^{\alpha}$. This kind of "asymmetry" has not been given much attention because it does not fit the approach-withdrawal depression model and, as such, it has generally been defined as the absence of alpha EEG asymmetry. For the purposes of discussion here, this kind of asymmetry will be referred to as "+ asymmetry".

Ignoring depression status and gender, whereas significant EEG alpha asymmetry (represented by negative asymmetry scores) was not present across frontal, temporal, parietal and occipital sites, significant "+ asymmetry" of the opposite kind occurred at some temporal and parietal sites (i.e., P8/P7 for the eyes opened condition; TP8/TP7 and P8/P7 for the eyes closed condition), representing about 12.5% of all comparisons. This finding also held true when depression status, but not gender, was ignored. In this instance, male participants showed this kind of "+ asymmetry" at temporal and parietal sites (i.e., CP4/CP3 and P4/P3 for the eyes opened condition; C4/C3 and CP4/CP3 for eyes closed condition) while female participants showed this kind of "+ asymmetry" at a single occipital site (O2/O1 for the eyes closed condition). Therefore, irrespective of depression status and or gender, it appears that this kind of alpha EEG "+ asymmetry" is present at other cerebral sites as well as the frontal sites.

This finding of significant opposite "+ asymmetry" at other cerebral sites than just the frontal sites is of value because it helps put into perspective the findings of some previous studies as regards (traditional) alpha asymmetry at posterior (parietal and temporal) sites. For instance, some previous studies have shown that co-morbid anxiety reduced alpha asymmetry at parietal sites, almost to the point of producing equal levels of activation in the left and right posterior hemispheres in depressed patients (Kentgen, Tenke et al. 2000). Some other studies have also shown that EEG alpha activity at parietal sites in anxious-depressed patients is greater on the right than the left hemisphere ($R^{\alpha} < L^{\alpha}$ or $R_a > L_a$) (Bruder, Fong et al. 1997). Mathersul, et al. (2008) also found that patients with depression co-morbid with anxiety showed increased right parieto-temporal activation ($R^{\alpha} < L^{\alpha}$ or $R_a > L_a$) compared to healthy controls. However, previous reports on parietal asymmetry in depression have

suggested that depression alone is associated with impaired right parietal cortex function, i.e., impaired processing of emotional stimuli (Heller 1993; Heller, Nitschke et al. 1997; Bruder 2003) which manifests as right parietal hypoactivity or greater right parietal alpha activity (i.e., $R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) in depressed individuals when compared with healthy controls (Henriques and Davidson 1990; Bruder, Fong et al. 1997; Allen, Coan et al. 2004; Blackhart, Minnix et al. 2006). Therefore, it may be that at the parietal sites, individuals with co-morbid anxiety and depression undergo a reversal of cerebral activation from ($R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) (seen in depression alone) to $R_a>L_a$ or $R^{\alpha}<L^{\alpha}$ (seen in depression with co-morbid anxiety) due to hypo-activation of the left hemisphere (Bruder, Wexler et al. 1999), or that anxious-arousal facilitates hyper-activation of the right parietal and or temporal sites (Heller, Nitschke et al. 1997). Depending on the extent of this hyper-activation, alpha asymmetry may reach a point of equal activation of the left and right parietal and/or temporal hemispheres (Kentgen, Tenke et al. 2000). With a much greater activation of the right than left parietal and or temporal hemispheres, a complete reversal of hemispheric activation may also occur (Bruder, Fong et al. 1997; Heller, Nitschke et al. 1997).

In contrast, the findings from this current study do not support these propositions on parietal asymmetry (i.e., hypofunctioning of right parietal lobe in depression alone, or hyperfunctioning of right parietal lobe in co-morbid anxiety and depression). In fact, it was found that significant "+ asymmetry" (indicating right lobe hypoactivity/hypofunctioning i.e., $R_a<L_a$ or $R^{\alpha}>L^{\alpha}$) occurred at some parietal, temporal and occipital sites (during baseline EEG measurements) even when depression and/or gender was ignored. This outcome may suggest that a balanced system of cerebral activation might be lacking at these posterior sites. Therefore, this finding questions the basis upon which those previous propositions were built because it shows that, at baseline, significant right lobe hypofunctioning occurred at some parietal, temporal and occipital sites in the absence of depression.

6.4.2 Non-significant trends in alpha EEG asymmetry across depressed *vs* non-depressed individuals

It was also found that there was a non-significant trend in the relationship between alpha EEG asymmetry and depression severity (i.e., the occurrence of alpha EEG asymmetry at different cerebral sites increases with increasing depression severity).

This was a new observation in this field. For example, individuals with SDS scores of 40+ showed negative asymmetry scores (indicative of the presence of alpha asymmetry) at nine sites (37.5% of all compared paired sites, i.e., 9/24) while individuals with SDS scores of < 40 showed negative asymmetry scores at seven sites (25.9% of all compared paired sites, i.e., 7/24). This trend was more pronounced for the SDS cut-off score of 50, as individuals with SDS scores of 50+ showed negative asymmetry scores at twelve sites (50% of all compared paired sites) as opposed to individuals with SDS scores of < 50 who showed negative asymmetry scores at five sites (20.8% of all compared paired sites, i.e., 5/24). Eight out of the seventeen sites with negative asymmetry scores occurred at the frontal sites in individuals with SDS scores of 50+ (representing 33.3 % of all compared sites, i.e., 8/24). Despite the differences at only one of these frontal sites (FP2/FP1, eyes opened condition for SDS scores of < 50 vs 50+) reaching statistical significance, it appears that depressed individuals (but not non-depressed individuals) were more likely to demonstrate alpha asymmetry (negative asymmetry scores) especially at the frontal sites.

6.4.3 Experimental conditions (eyes opened *vs* eyes closed)

The influence of experimental conditions (eyes opened and eyes closed) on the findings of EEG alpha asymmetry between depressed and non-depressed male and female individuals had not been previously reported. Some researchers presented their findings of alpha asymmetry from the data obtained by averaging the EEG measures collected under both experimental conditions (Henriques and Davidson 1990; Henriques and Davidson 1991; Reid, Duke et al. 1998; Blackhart, Minnix et al. 2006) and others presented significant findings from the eyes closed condition only (Bruder, Tenke et al. 2007; Quinn, Rennie et al. 2014). However, the significant findings from this current study occurred mainly under the eyes opened experimental condition. For instance, significant differences in the alpha activity of participants with SDS scores < 50 *vs* 50+ occurred under the eyes opened condition. For the SDS < 50 *vs* 50+ category of depression, significant interactions between depressive status and gender occurred at the frontal site FP2/FP1, and at the combined five frontal sites under the eyes opened condition. Similarly, for the SDS < 40 *vs* 40+, significant interaction between depressive status and gender occurred at the parietal site P4/P3 under eyes opened condition.

While it is common practice to measure EEG under both experimental conditions of eyes opened and eyes closed (as adopted in this current study), the rationale for this is still largely speculative as the precise implication of closing or opening one's eyes (during resting EEG measurement) on EEG alpha asymmetry is unknown. It may be that cleaner EEG data are obtained during eyes closed conditions (as there are fewer eye blinks) or that varying the conditions of experiments so that participants are not familiar with them is generally acceptable in this field of research. However, the results of this study suggest that significant findings in alpha EEG asymmetry of depressed *vs* non-depressed individuals across different cerebral sites in males and females can also be demonstrated under the eyes opened condition.

6.5 Implications for the asymmetry model of MDD

The exploratory nature of this research study was well suited to confirm the validity of the asymmetry (approach-withdrawal) model of MDD. To a large extent, the findings from this study validate and support the explanation that severely depressed individuals activate the right frontal site more than they activate the left frontal site. This activation of the frontal site is explained as behavioural withdrawal or avoidance of negative and aversive environmental stimuli in an attempt to reduce the sum total of negative emotional experiences they are undergoing. Therefore, the asymmetry model of MDD holds true for severe depression *vs* not-severe depression.

However, it appears that this finding is largely due to a gender-based confound, as significant frontal alpha asymmetry which occurred with increasing depression severity in female participants did not also occur in male participants. This finding cannot be due to the effects of female sex hormones such as oestrogen and oestradiol because female sex hormones do not have any influence on the occurrence of frontal alpha asymmetry in depression (Saletu, Brandstätter et al. 1995; Saletu, Brandstatter et al. 1996). It is difficult to explain these findings at this time as there have been no other valid suggestions in the literature as to why alpha EEG asymmetry might differ on the basis of gender. Thus, this issue requires further investigation.

6.6 Clinical implications for treatment of MDD

The finding of frontal alpha asymmetry in depression has implications for the treatment or management of depression. This is because frontal alpha asymmetry results from hypo-activation of the left frontal site (which reflects hypo-activation of the behavioural approach system that is responsible for engaging with pleasant stimuli) (Davidson 1998), and the hyper-activation of the right frontal site is responsible for disengaging from or avoiding aversive stimuli (behavioural withdrawal system) (Henriques and Davidson 2000). Thus, any therapeutic intervention which will facilitate an increase in the activation of the left frontal site and/or a decrease in the activation of the right frontal site should (according to the data collected here) potentially hold some chance of therapeutic success in the treatment of depression. This therapeutic effect could be confirmed by measuring EEG pre- and post-therapy, in order to establish the presence of a reversed alpha asymmetry, or at least an improvement in asymmetry scores from negative towards positive values as an outcome of treatment.

Interestingly, some studies have shown that certain therapeutic interventions are able to bring about an increase in the activation of the left frontal site with a corresponding improvement in asymmetry scores from negative towards positive (not complete reversal) and this change in cerebral activation has been shown to be accompanied by an improvement in depression symptoms and overall depression status. Examples of such therapeutic interventions include neurofeedback (where depressed persons are trained to increase the difference in activation levels between right and left frontal cortices) (Rosenfeld, Baehr et al. 1996; Earnest 1999; Peeters, Oehlen et al. 2014), Repetitive Transcranial Magnetic Stimulation (rTMS) (Deslandes, Moraes et al. 2010; Choi, Chi et al. 2011; Valiulis, Gerulskis et al. 2012; Mantovani, Aly et al. 2013; Noda, Nakamura et al. 2013; Sutin, Terraccino et al. 2013), Meditation therapy (Barnhofer, Chittka et al. 2010), Mindfulness-based interventions (Keune, Bostanov et al. 2013; Moynihan, Chapman et al. 2013), Cognitive therapy (Deldin and Chiu 2005), Music therapy (Fachner, Gold et al. 2013), Choir therapy (Petchkovsky, Robertson-Gillam et al. 2013), Aerobic training (Deslandes, Moraes et al. 2010) and Deep brain stimulation surgery (Quraan, Protzner et al. 2014). These treatment models may hold some promise in addressing alpha asymmetry in severely depressed

individuals but require measurement of changes in alpha activity to confirm the association between such treatments and outcomes in depressive status and also alpha activity.

In addition, frontal alpha asymmetry has been suggested as a predictor of response to antidepressant therapy (i.e., medication). Previous studies have revealed that, while responders to antidepressants (selective serotonin re-uptake inhibitors and tricyclic antidepressants) showed frontal alpha asymmetry (with greater alpha activation over right than left hemisphere), non-responders showed the opposite pattern of asymmetry (Bruder, Stewart et al. 2001; Bruder, Sedoruk et al. 2008; Khodayari-Rostamabad, Reilly et al. 2010; Saletu, Anderer et al. 2010). Therefore, a pre-therapy alpha EEG asymmetry check may be useful in determining which depressed individuals would benefit from this kind of antidepressant therapy.

6.7 Limitations of this study

Some limitations which may have a potential impact upon the findings of this research study have been identified. First, due to the constraint of time, it was impossible to recruit more than 100 adult participants from the community. A larger sample size would boost the statistical power of the analyses undertaken. Second, we used the Zung SDS rating scale for the classification of depression status. The use of a comprehensive Structured Clinical Interview for DSM V Disorders could assist in confirming a diagnosis of depression, but may not be feasible considering time constraints. However, the Zung SDS is ideally recognised as a simple tool for monitoring changes in depression severity over time in research studies and clinical practice (Zung, B. et al. 1965; WHO 2016). Third, the participant sample in this study was limited to adult individuals, and inclusion of children and adolescent participants could have provided additional information on the status of alpha EEG asymmetry across different age groups. Fourth, the participants in this study were drawn from the community, whereas a clinical sample could help provide a broader range of depression severity from which the status of alpha EEG asymmetry could be confirmed. Lastly, EEG measurements were collected during a resting period, and it may be that the EEGs of depressed and non-depressed individuals are better differentiated during cognitive or emotional tasks. A replication of this study using EEG measures obtained during a designated task might clarify the effects found here.

6.8 Future research issues

There are a number of issues which may result in a clearer understanding of the phenomenon of alpha asymmetry as it relates to depression development and treatment. For instance, the multiplicity of forms in which depression usually presents in individuals who meet the criteria for MDD needs to be considered in future research. This is particularly important because, rather than being a unitary mental disorder, MDD is actually a heterogeneous disorder and at least five subtypes of MDD have been identified (as discussed in Chapter 2). Therefore, an investigation of the pattern of alpha EEG seen in the different subtypes of MDD is warranted for future research, and this may have significant relevance to clinical treatment of depression according to subtypes and symptom profile.

Also, the presence and the pattern of alpha asymmetry in other depression-associated mental disorders such as anxiety, panic disorder, obsessive compulsive disorder, PTSD, Schizophrenia, ADHD and conduct disorder, requires further investigation of the nature of alpha asymmetry which may occur in these disorders (in the presence or absence of depression). More importantly, the influence of the site, the severity and gender difference upon the finding of alpha asymmetry in these disorders is also of potential value in increasing understanding of their underlying neurobiological pathways.

Furthermore, technical developments in EEG measurements which can improve the overall methodological process should be considered. An example of such a development is the use of Current Source Density (CSD) in EEG acquisition. CSD could help refine and improve the spatial resolution and quantification of EEG signals and it has been suggested as being a suitable candidate for overall improvement in EEG signal acquisition (Tenke, Kayser et al. 2015). This could help resolve the challenges posed by differing reference styling which may contribute to inconsistencies in many EEG studies (Tenke, Kayser et al. 2015).

Lastly, the use of other neuroimaging devices such as CT scan, MRI, fMRI, PET and SPECT may be helpful in clarifying the relationship between frontal alpha asymmetry and depression. For example, the true status of alpha asymmetry may be better determined if fMRI (which shows brain connectivity) is used in conjunction with EEG.

6.9 Conclusions

Despite the challenges and inconsistencies reported in the body of research which has investigated the overall significance of the association between alpha EEG asymmetry and depression, this study found evidence in support of the approach-withdrawal model of depression, but mainly at the frontal sites. More importantly, gender played a significant role in the occurrence of frontal alpha EEG asymmetry in depressed individuals in this study. Therefore, frontal asymmetry could represent a logical hypothesis for explaining depression, and could serve as a possible biomarker for MDD. It may provide a valid explanation for the biological withdrawal from negative aversive stimuli or stressors which depressed individuals display.

Overall, this study clarified some aspects of the asymmetry-depression relationship and extended the field in several directions that will benefit from further research. Although depression remains a major health burden in most societies, with only relatively low effectiveness treatments, understanding how the withdrawal behaviours that have been identified as underlying depressive symptomatology are initiated within the brain, and linking those overt behaviours to neurobiological activities, can help to eventually develop more effective treatments for this disorder.

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APPENDIX 1: DETAILED DESCRIPTIONS OF THE STUDIES WHICH INVESTIGATED THE RESTING AND TASK-RELATED FRONTAL EEG ASYMMETRY AND DEP

Year	Authors	Journal	Location (Country)	Sample Population (T=Total sample size, D= Depression, C= Control, Co=Comorbid)	Age (years)	Gender Split (M:F)	Handedness (Right=R, Left=L)	Study Type (A=Adult, C=Children, I=Infants)	Test of Depression	Test of Anxiety	EEG band investigated (EEG = A-alpha, B-Beta, D-Delta, G-Gamma and T- Theta) and Scalp site	Duration of Baseline Recordings	Online Reference Scheme
1983	Schaffer et al	Biological Psychiatry	New York, USA	D=6; C=9	Not provided	5:10	R=All	A	Beck Depression Inventory; Marlowe- Crowne Scale of Social Desirability		A (Frontal and Parietal)	30 seconds	Cz
1986	Nystrom	Acta Psychiatr Scand	Gothenburg, Sweden	T=25	24-64	11:14		A	DSM III		A, B, T, D (Frontal, Temporal, Parietal and Occipital)	30mins	
1990	Henriques and Davidson	Journal of Abnormal Psychology	Wisconsin, USA	T=14, D=6, C=8	Mean=36	Not provided	Not provided	A	Beck Depression Inventory, Hamilton Depression Rating Scale		A, B, D, T (Frontal, Central, Parietal and Temporal)	30 seconds	Cz

1991	Henriques and Davidson	Journal of Abnormal Psychology	Wisconsin, USA	T=31, D=16, C=15	Mean=40.5	13:18	R=All	A	Schedule for Affective Disorders and Schizophrenia		A, B, D, T (Frontal, Central, Parietal and Temporal)	1min	Cz, Computer average ear lobes and average reference
1992	Dawson et al	Child Development	Washington, USA	T=27 infants	11-17 months	Not provided	Not provided	I	CES-D	State-Trait Anxiety Inventory for Children(STAIC)	A (Frontal and Parietal)	3 mins	Cz
1995	Field et al	Developmental Psychopathology	Florida, USA	Mothers/ infants: T= 32, D=17, C=15.	Mean = 17.5 (mothers); Infants=4.8 months	Adult sample=Women only, Infant sample=1:1	Not provided	A, I	DISC diagnostic interview and Beck Depression Inventory		A (Frontal and Parietal)	3 mins	Cz
1996	Rosenfeld et al	International Journal of Psychophysiology	Illinois, USA	T=5, D=5	22-48	1:4	R=All	A	DSM-IV, Beck Depression Inventory		A (Frontal)	30mins	Cz

1996	Saletu et al	Journal of the Climacteric and Postmenopause	Vienna, Austria	T=118, Depreesed menopausal=60, Nondepressed menopausal=29, Healthy Control=29	Mean=52.11	All=Women	Not provided	A	DSM-III, Hamilton Depression Scale		A, B, D, T (Frontal, Central, Parietal and Temporal)	3mins	Not provided
1997	Baehr et al	Journal of Neurotherapy	Illinois, USA	T=2, D=2	Case study 1 = 65, Case Study 2 = 40	Women only	Not provided	A	DSM-IV		A (Frontal)	30mins	Cz

1997	Bruder et al	Biological Psychiatry	New York, USA	T=70, D=19, Co=25, C=26	20 - 60	1:1	R=60, L=10	A	DSM III	DSM III, Trait Anxiety scale, State Anxiety Scale	A (Frontal, Temporal, Parietal, Centeral and Occipital)	3mins	Nose, Cz
1997	Dawson et al	J Child Psychol Psychiat	Washington, USA	Infant sample: T=117, D=54, C=63	13-15 months	65:52	Not provided	A, I	SCID for DSM-III, CES-D, Longitudinal Interval Follow-up Evaluation		A (Frontal and Parietal)	1 min	Linked mastoid

1997	Harmon-Jones and Allen	Journal of Abnormal Psychology	Arizona, USA	T=36	Not provided	Women only	All	A	BIS, BAS	BIS, BAS	A (Frontal and Parietal)	4mins	Cz
1997	Henriques and Davidson	Biol Psychiatry	Wisconsin, USA	T= 30, D=11, C=19	21.6	Women only	All	A	Beck Depression Inventory	State Trait Anxiety Inventory	A, T, B, D (Frontal, Central and Parietal)	Not provided	Cz

1997	Jones et al	Development and Psychopathology	Florida, USA	T=44, D=20, C=24	Infants= 1 month oldMean age of mothers = 18.5	Not provided	Not provided	I, A	DISC diagnostic interview using DSM-III		A (Frontal and Parietal)	3mins	Cz
1998	Baehr et al	International Journal of Psychophysiology	Illinois, USA	T=24, D= 13, C=11	25 - 62	Not provided	Not provided	A	Beck Depression Inventor, DSM-IV		A (Frontal)	5mins	Cz
1998	Bell et al	Biol Psychiatry	Arizona, USA	T=35, D=10, Chemical intolerance=14, C=11	30-50	All= Women	Not provided	A	Hamilton Depression Rating scale, DSM-III	Anxiety Sensitivity Index	A (Frontal, central and parietal)	1 min	Linked ears
1998	Gotlib and Rosenfeld	Cognition and Emotion	Stanford, USA	Study1: T=77, Currently depressed=16, Previously depressed=31, Never depressed =30	Not provided	All= Women	R=All	A	Inventory to Diagnose Depression, SCID for DSM-III		A (Frontal)	4 mins	Cz
1998	Gotlib and Rosenfeld	Cognition and Emotion	Stanford, USA	Study2: T=59, Previously depressed=29, Never depressed =30	Not provided	All= Women	R=All	A	Inventory to Diagnose Depression, SCID for DSM-III		A (Frontal)	4mins	Cz

1998	Jones et al	Infant Behav Dev	Florida, USA	T=63, D=35, C=28	1 week	Not provided	Not provided	I	Hollingshead Four Factor Index, Center for Epidemiological Studies-Depression Scale, and the Diagnostic Interview Schedule.		A (Frontal and Parietal)	3mins	Cz
1998	Reid et al	Psychophysiology	Arizona, USA	Study 1: T= 36, D= 17, C=19; Study 2: T=27, D=13, C=14	Study1=17.94 ; Study 2= 27.46	Female only (Both studies)	R=All (Both studies)	A	Beck Depression Inventory (Study1) and Structured Clinical Interview for DSM-III-R (study 2)		A, B, D, G and T (Frontal, Central, Parietal and temporal)	8mins	A1
1999	Earnest	Journal of Neurotherapy	New mexico, USA	T=1, D=1	14years	Female Adolescent	Not provided	Adolescent	DSM-IV, Beck Depression Inventory		A (Frontal)	30mins	Cz

1999	Pauli et al	Pain	Tubingen, Germany	T=8	Mean=23.6	3:5	R=All	A	Beck Depression inventory		A (Frontal, central and Parietal)	1 min	Cz
1999	Wiedemann et al	Ach Gen Psychiatry	Tuebingen, Germany	T=48, Panic Disorder=23, C=25	Mean=36.55	9:39	Not provided	A	Beck Depression Inventory	DSM-III, Agrophibic Cognition and Body Sensation Questionnaires, State and Trait version of Spielberger Anxiety Inventory	A (Frontal and Parietal)	1mins	Not provided
2000	Debener et al	Neuropsychobiology	Arnsdorf, Germany	T= 37, D= 15, C=22	23 - 64	12:25	L:R = 33:4	A	Composite International Diagnostic Interview		A (Mid-frontal, Lateral frontal, mid-parietal (control) and anterior temporal)	2mins	Linked-ears

2000	Jones et al	Child Psychiatry and Human Development	Miami, USA	T= 55, D= 28, C=27 (for both mothers and children)	Children 3 - 6yrs, Mothers mean age 23.7	3:11	Not provided	A, I	Children of Depressed mothers. Mothers diagnosis via Clinical interview DISC), the Center for Epidemiological Studies-Depression Scale (CES-D) and DSM-IV criteria		A (Frontal and Parietal)	3mins	Cz
2000	Kentgen et al	Journal of Abnormal Psychology	New York, USA	T=35, D=8, Co=11, A=6, C=10	12.2 t0 18.8	Women only	R=All	Adolescence	DSM-IV	DSM-IV	A (Frontal, Central, Temporal and Posterior)	3mins	Nose
2001	Bruder et al	Biol Psychiatry	New York, USA	T=53, Responders to SSRI=34, Non-responders=19	Mean= 39.6	25:28	R=All	A	Beck Depression Inventory, DSM-IV	Trait Anxiety Inventory	A (Frontal, Central, Parietal, Temporal and Occipital)	3 mins	Nose

2001	Diego et al	Depression and Anxiety	Florida, USA	T= 163	Average 23	Women only	L=27%, R=83%	A	The Centre for Epidemiological Studies Depression Scale		A (Mid-frontal and parietal)	3mins	Cz
2001	Field et al	Infant Behav Dev	Florida, USA	T=120, D=80 (Infants = 80), C=40 (Infants =40)	Mean 27	Women and their infant children	Not provided	A, I	Center for Epidemiological Studies-Depression scale, Profile of Mood State (POMS) Anger Scale, BIS/BAS	The State-Trait anxiety Inventory	A (Frontal and Parietal)	3mins	Cz

2001	Jones et al	Journal of Reproductive Infant Psychology	Florida, USA	T=38, D=18, C=20	Mean=10.1 months	7:8	R=All mothers	I	CES-D		A (Frontal and Parietal)	5-6mins	Cz
2001	Knott et al	Psychiatry Research	Ontario, Canada	T=93, D= 70, C=23	Mean age=37	Male only	R=All	A	DSM-IV, Hamilton Depression Scale (HAM-D)		A, B, d and T (Mid-frontal, Lateral frontal, Central, posterior temporal, parietal and occipital)	20mins	Linked-ears
2002	Harmon-Jones et al	Journal of Personality and Social Psychology	Wisconsin, USA	T=68		34:34	R=All	A	General behaviour Inventory, Positive and Negative Affect Schedule		A (Frontal, Temporal, Central, Parietal, Occipital)	3mins	Left Ear

2002	Miller et al	Am J Psychiatry	Pittsburg, USA	T=110 D=55 (with history of childhood-onset depression at age 15), C=55	26.6	44:66	L=14, R=96	A	Semi-structures Interview Schedule for Children and Adolescents, Follow-Up Interview Schedule for Adults, Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Edition (SCID-I/P) adapted to include selected childhood and axis II diagnoses, DSM iv and DSM III and Research Diagnostic Criteria. Beck Depression Inventory	Beck Anxiety Inventory	A (Frontal, Central, Parietal and temporal)	6mins	Cz
2002	Pizzagalli et al	Biol Psychiatry	Zurich, Switzerland	T=56	Mean=36.06	23:33		A	SCID, Hamilton Rating Scale of depression, BDI, DSM IV	STAI	A, B, T, D, G (Frontal, Central, Occipital, Parietal and Temporal)	3mins	Left ear
2004	Allen et al	Psychophysiology	Arizona, USA	T=30, D=30	18-45	All=Women	R=All	A	SCID for DSM-III, Hamilton Rating Scale for Depression		A (Frontal, Central, Parietal, temporal and occipital)	1min	Off-line derived ocular channel
2004a	Field et al	Infant Behav Dev	Florida, USA	T=140, D=70, C=70	Mean 25.8	Adult sample=Women only, Infant sample=11:14	Not provided	A, I	Center for Epidemiological Studies-Depression scale, Profile of Mood State (POMS) Anger Scale	The State-Trait anxiety Inventory	A (Frontal and Parietal)	3mins	Cz

2004b	Field et al	Infant Behav Dev	Florida, USA	D & A = 92	Mean 29	Women only	Not provided	A, I	Center for Epidemiological Studies-Depression scale	The State-Trait anxiety Inventory	Not provided	Not provided	Not provided
2004	Flor-Henry et al	Psychiatry Research: Neuroimaging	Alta, Canada	T= 90, D=25, C=65	Mean=35.4 (SD = 10.7)	Male only	R=All	A	DSM-IV		A(Frontal, Temporal, Central, Parietal and Occipital)	3mins	Common left ear
2004	Diego et al	Psychiatry	Florida, USA	Infants Sample: T=80, D=60, C=20	Mean=1.7 weeks	7:9	Not provided	A, I	CES-D		A (Frontal and parietal)	3mins	Cz

2004	Jones et al	Biological Psychology	Florida, USA	T=78, D=31, C=47	Infants: One month and Three months old; Mothers: 32.2	1:1	Not provided	A, I	CES-D, Diagnostic Interview Schedule		A (Frontal, Central, Parietal and Occipital)	Not provided	Cz
2004	Minnix et al	Biological Psychology	Florida, USA	T=12	Mean=32	6:6	R=All	A	Clinical interview based on DSM IV, BDI		A(Frontal, Temporal, Parietal and Occipital)	1min	Linked ears
2004	Tomarken et al	Biological Psychology	Tennessee, USA	T=38, D= 25 (High risk adolescents), C= 13 (Low risk adolescents)	12-14	18:20	Not provided	Adolescent	SCID for DSM, Children's Depression Inventory		A, B, D, T (Frontal, Central, Parietal and Temporal)	1min	Cz

2005	Bruder et al	Biol Psychiatry	New York, USA	Adult offsprings of both parents with MDD=18, one parent with MDD=40, neither parent with MDD=29, T=87	8 - 50	34:53	R=All	A	Schedule for Affective Disorders and Schizophrenia Lifetime Version modified for DSM IV (for adults, children), DSM-IV		A (Frontal, Central, Parietal and temporal)	2 mins	Linked-ears
2006	Blackhart et al	Biological Psychology	Florida, USA	T= 28	18 - 25	5:23	R=All	A	Beck Depression Inventory	State-Trait Anxiety Inventory (STAI)	A (Frontal, Parietal and temporal)	6 mins	Cz
2006	Diego et al	Infant Behav Dev	Florida, USA	T= 66, D=38 mothers and 38 infants, C=28 mothers and 28 infants	Mothers: 28 ± 6.8 (SD), Neonates 0-3weeks and Infants 12 - 23 weeks	A= Female only, Infants 1:3	R=All	A, I	Center for Epidemiological Studies-Depression scale, the Behavioural Inhibition and behavioural Approach System Questionnaire		A (Mid-frontal and parietal on infants)	Not provided	Cz

2006	Fingelkurts et al	Neuroscience Research	Espoo, Finland	T=22, D=12, C=10	Mean 41.7	6:5	All	A	Structured Diagnostic Interview for DSM-IV, Hamilton Depression Rating Scale		A (Frontal, Central, Parietal, Occipital and temporal)	20mins	Cz
2006a	Forbes et al	Journal of Psychology and Psychiatry	Pittsburg, USA	T=148 (74 mothers and 74 children)	3yrs - 9yrs	Women only, 32: 42	R and L	A, C	Becks Depression Inventory		A(Frontal, Central, Occipital, Parietal)	3mins	Cz
2006	Forbes et al	Biological Psychology	Pittsburg, USA	T=57	3yrs - 9yrs	21:36	R and L	C	Structural Clinical Interview for DSM-IV; Interview Schedule for Children and Adolescents		A(Frontal, Temporal, Central, Parietal and Occipital)		Cz
2006	Niemiec and Lithgow	Engineering in Medicine and Biology Society	Victoria, Australia	T=21							A (Frontal)		
2006	Vuga et al	International Journal of Psychophysiology	Pittsburg, USA	T=99, D=49, C=50	Mean=26.42	2:1	R=90,L=9	A	DSM-III, DSM-IV		A (Frontal, Parietal, Occipital and Temporal)	1mins	Cz

2007	Bruder et al	Biol Psychiatry	New York, USA	T=49 (highest risk=19, intermediate=16, low risk=14)	Mean 13.2	23:26	All	C	Schedule for Affective Disorders and Schizophrenia Lifetime Version modified for DSM IV (for adults, children)		A (Frontal, Central, Temporal and Parietal)	2mins	Linked-ears
2007	Smit et al	Biological Psychology	Amsterdam, Netherlands	T = 732 twins, 760 non-twin sibling	Mean 26.2 (Young cohort), Mean 49.4 (Middle age cohort)	T=760	R=12.6%, L=81.6%	A	Spielberger Anxiety Inventory, Young Adult Self Report Scale	Spielberger Anxiety Inventory, Young Adult Self Report Scale, Amsterdamse Biografische Varagenlijst	A (Frontal, Central, Temporal, Parietal and Occipital)	3mins	Cz

2008	Bruder et al	Biological Psychology	New York, USA	D= 18, C=18, T=36	35.9 ± 9.6	26:10	R=31, L=5	A	DSM-IV		A (Frontal, Central, Parietal and Occipital)	2mins	Nose
2008	Deslandes et al	Biological Psychology	Rio de Janeiro, Brazil	T=36, D=22, C=12	Mean age=72	17:1	R=All	A	DSM-IV		A (Frontal, Parietal and Temporal)	8mins	Linked-ears
2008	Kline and Allen	International Journal of Psychophysiology	Alabama, USA	T=45	13:32	17: 25	All	A	Beck Depression Inventory	Taylor Manifest Anxiety Scale	A (Frontal)	1min	

2008	Mathersul et al	Emotion	Sydney, Australia	T=428,	18 -60	1:1	Not provided	A	DASS-21 (shortened version of Depression Anxiety Stress Scale), BDI	DASS-21 (shortened version of Depression Anxiety Stress Scale)	A, D, T, B (Frontal, Parietal and temporal)	2mins	Cz
2009	Jones et al	Infant Behav Dev	Florida, USA	T=30, D=16, C=14	Mothers 19.3 ; Infants 2.5	A = All Women, Infant sample = 7:8	Not provided	A, I	CES-D, POMS		A (Frontal, Parietal, Occipital and temporal)	3mins	Cz
2010	Barnhofer et al	Mindfulness	Oxford, UK	T= 15, (Participants on breathing and Loving kindness therapy are 8 and 7 respectively)	Mean age=28	1:4	Not provided	A	Beck Depression Inventory, Response Style Questionnaire		A (Frontal, Central, Parietal, Temporal and Occipital)	2mins	Average

2010	Bismark et al	Biological Psychology	Arizona, USA	D=146, C=167, T=313,	18 to 33	100:213	All right-handed	A	Structured Clinical Interview for DSM IV		A (Frontal, Parietal, Temporal and Occipital)	8mins	Posterior to Cz
2010	Deslandes et al	Brazilian Journal of Medical and Biological Research	Rio de Janeiro	T=20 MDD elderly patients, Exercise group=10, control=10	Mean = 71	3:7	R=All	A	Beck Depression Inventory, Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, DSM-IV		A (Frontal, Central, Parietal, Temporal and Occipital)	8 mins	Linked ears

2010	Field et al	Infant Behav Dev	Florida, USA	D=181, A=77, C=308	18 -40	Women only	Not provided	A, I	SCID, CES-D,	State Anger Inventory (STAI)	A (Frontal)	Not provided	Not provided

2010	Gordon et al	Clinical EEG and Neuroscience	Sydney, Australia	T=2475, Schizophrenia=50, MDD=92, PTSD=48, Panic Disorder=48, ADHA=309, Conduct Disorder=20	6 - 87	1341:1134	Not provided	A, C	DSM-IV	Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Clinician-Administered PTSD scale (CAPS) and the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID) for PTSD, Diagnosis of panic disorder was made according to the panic disorder module of the MINI and the Composite International Diagnostic Interview (CIDI-Auto 2.1). Semi structured clinical interview for ADHD, ADHD and conduct disorder were both diagnosed in accordance with DSM-IV diagnostic criteria.	A (Frontal, Central, Parietal, Temporal and Occipital)	4mins	Ground
2010	Kemp et al	Biological Psychology	Sydney, Australia	T=44, D= 15, A= 14, C=15	18 to 65	17:27	R=42, L=2	A	Structured, Mini-International Neuropsychiatric Interview and the Hamilton Rating Scale for Depression , Depression, Anxiety and Stress Scales (DASS)	Clinician Administered PTSD Scale	A (Frontal, Parietal and temporal)	2mins	A1 and A2

2010	Saletu et al	Clinical EEG and Neuroscience	Vienna, Austria	T=120, D=60, C=60	Mean=51.1	All women	Not provided	A	DSM-III, Hamilton Depression Scale		A, B, D, T (Frontal, Central, Parietal and Temporal)	7mins	Not provided

2010	Stewart et al	J Abnorm Psychol	Arizona, USA	T= 306, D=143; C=163	17 - 34	95:211	R=All	A	Beck Depression Inventory		A (Frontal)	8mins	Cz
2011	Carvalho et al	Journal of Affective Disorders	Rio de Janeiro, Brazil	T= 27, D= 12, Remitted=8, C=7	Mean 71	9:18	Not provided	A	DSM-IV, Beck Depression Inventory		A (Frontal, Parietal, Occipital and temporal)	8mins	Cz
2011	Choi et al	Neuropsychobiology	Seoul, Republic of Korea	T=23 Depressed, Neurofeedback Training group= 12, Placeb group=11	Mean= 28.5	6:17	R=All	A	DSM-IV		A (Frontal)	8 mins	Cz

2011	Jaworska et al	J Addict Med	Ottawa, canada	T=8, D=8	15-19	All= Women	Not provided	A	DSM-IV, Beck Depression Inventory-II		A, B, D, T (Frontal, central and parietal)	5mins	Linked ears
2011	Lopez-Duran et al	Psychophysiology	Michigan, USA	D= 135	6 - 13yrs	75:60	L=5, R=130	Children	At risk for depression based on having one parent with a documented history of childhood onset depression (Parents were interviewed using Interview Schedule for Children and Adolescents and Structural Clinical Interview for DSM-IV)		A, B, T(Mid-frontal, Lateral frontal, Central, posterior temporal, parietal and occipital)	3mins	
2011	Nusslock et al	J Abnorm Psychol	Illinois, USA	T= 40	Mean 20.3	23:17	R=All	A	Beck Depression Inventory		A, T (Frontal, Parietal, Central and Temporal)	1min	A1

2011	Segrave et al	Clinical EEG and Neuroscience	Melbourne, Australia	T=34, D=16, C=18	Mean= 41.47	All Women	R=All	A	M.I.N.I International Neuropsychiatric interview for DSM-IV, Montgomery and Asberg depression Rating Scale (MADRS), Beck Depression Inventory-II		A (Frontal)	3 mins	Central in-cap reference (located between Cz and CPz)
2011	Shankman et al	International Journal of Psychophysiology	Chicago, USA	T=99 , D= 65 (48 Nonmelancholic, 17 Melancholic), C=34	34.4	Not provided	R= All	A	Structured Clinical Interview for DSM-IV, Hamilton Rating Scale for Depression		A, B, D and T (Frontal, Parietal, Central and temporal)	11 secs each (for pre and post goal phases)	Linked ears (left and right ear lobes digitally derived offline)

2011a	Stewart et al	Psychophysiology	Arizona, USA	T= 306, D=143; C=163	17 - 34	95:211	R=All	A	Beck Depression Inventor, Structured Clinical Interview for DSM-IV		A (Frontal, Parietal, Temporal, Occipital)	8mins	Posterior to Cz
2011b	Stewart et al	Journal of Affective Disorders	Arizona, USA	T=306, D=143, C=163	17 to 34	95:211	All	A	Beck Depression Inventory, Structured Clinical Interview for DSM-IV		A (Frontal, central, Temporal, Parietal and occipital)	1min	Cz
2012	Bruder et al	Human Brain Mapping	New York, USA	T= 75 (with 37 high risk and 38 low-risk for depression)	Mean age= 30.65	35: 40	R=73, L=2	A, C	The Scheduled for Affective Disorders and Schizophrenia Lifetime Version for adults and children modified for DSM IV, DSM IV		A (Frontal, Central, Temporal and Parietal)	2mins	Left-ear

2012	Chang et al	Psychosomatic Medicine	Seoul, Republic of Korea	T=60, D=20, C=40	Mean= 35.8	All= Women	Not provided	A	DSM-IV, Hamilton Depression scale		A, B, D, T (Frontal, central and parietal)	15 mins	Cz
2012	Feng et al	J Abnorm Child Psychol	Ohio, USA	T= 73, D= 43 children of mothers with Childhood-onset depression, C=30	6 to 13	36:37	R=All	C	Standard clinical evaluation, Structured Clinical Interview for Axis I DSM-IV (SCID), Children's Depressive Inventory:Patient Version.		A (Frontal, Central, Parietal, temporal and occipital)	30secs	Cz
2012	Jaworska et al	Journal of Psychiatric Research	Ottawa, Canada	T=96, D=53, C=43	Mean=38.7	11:13	R=90, L=6	A	DSM-IV, Hamilton Rating Scale for Depression, Montgomery-Åsberg Depression Rating Scale; Beck Depression Inventory-II		A, T (Frontal and parietal)	6 mins	Mastoid

2012	Leuchter et al	Open access	Los angeles, USA	D= 121, C37, T=158	21 - 70	95:63	R=99, L=1 and Ambiguous =1	A	Standard clinical evaluation, Structured Clinical EvInterview for Axis I DSM-IV Disorders- Patient Edition (SCID-I/ P) and the Hamilton Depression Rating Scale		A, B, D and T (Frontal, Parietal, Central, temporal and occipital)	10mins	Cz
2012	Valiulis et al	Acta Neurobiol Exp	Vilnius, Lithuania	T=45	Mean=52.16	12:33	Not provided	A	Montgomery Asberg Depression rating scale, Beck Depression Inventory, Hamilton Rating Scale		A, B, D, T (Frontal, Central, Parietal, Temporal and Occipital)	10mins	Ear electrodes

2013	Gold et al	Scandinavian Journal of Psychology	Bergen, Norway	T=79, D=79	18-50	17:79	Not provided	A	Mini-SCID, Montgomery and Asberg depression Rating Scale (MADRS)	Hospital Anxiety and Depression Scale (HADS-A)	A, T (Frontal and Frontal midline)	5mins	Cz
2013	Liao et al	Brain and Health Informatics	Beijing, China	T=22	Mean=33.33	13:09	R=All	A	DSM IV, BDI, HAMD, QIDS-SR, T-AI		A, B, T, D, G (Frontal and Parietal)	8mins	
2013	Talati et al	Phil Trans R Soc B	New York, USA	T=151				A, C			A (Frontal, Central and Parietal).		
2014	Lusby et al	Developmental Psychopathology	Atlanta, USA	T=83	18-45 (women); 3months and 6months (Infants)	Women only, 59:41 (Infants)		A, I	DSM IV, BDI		A(Frontal, Temporal, Central, Parietal and Occipital)	3mins	Cz

2014	Nelson et al	Journal of Affective Disorders	New York, USA	T=154	Mean=32.92		R=L	A	SCID for DSM IV		A (Frontal)		Between Cz and CPz
2014	Stewart et al	Psychophysiology	California, USA	T=306, D=143, C=163	17 - 34	95:211		A	BDI, DSM IV		A (Frontal, Central, Occipital and Parietal).	1min	Cz, and linked mastoid references
2014	Quinn et al	Psychiatry Research	Sydney, Australia	T=237, D=117, C=120				A	Mini international Neuropsychological Interview, SCID DSM IV, Depression, Anxiety and Stress Scales		A (Frontal, Temporal and Parietal)	2mins	Average ears

APPENDIX 2: DETAILED DESCRIPTIONS OF THE STUDIES WHICH INVESTIGATED THE FRONTAL EEG ASYMMETRY AND DEPRESSION WITH OTHER CO-MORBID PSYCHO

Year	Authors	Journal	Location (Country)	Sample Population (T=Total sample size, D= Depression, C= Control, Co=Comorbid)	Age (years)	Gender Split (M:F)	Handedness (Right=R, Left=L)	Study Type (A=Adult, C=Children, I=Infants)	Test of Depression	Test of Anxiety	EEG band investigated (EEG= A- alpha, B- Beta, D-Delta, G-Gamma and T-Theta) and Scalp site	Duration of Baseline Recordings	Online Reference Scheme
1975	Siciliani et al	Acta Psychiatr Scand	Verona, Italy	T=20		Men only		A			A(Frontal)		
1988	Gaebel and Ulrich	Acta Psychiatr Scand	Berlin, Germany	T=36				A		Researc Diagnostic Criteria	A (Frontal, Temporal, Parietal and Occipital)		

1994	Petruzzello and Landers	Med Sci Sports Exerc	Illinois, USA	T=19	Mean=22.7	Men only	R=All	A		Trait for (Y-2) of the Spielberger et al. anxiety inventory	A (Frontal and Temporal)	65.53s	Left and right mastoid
1994	Tomarken and Davidson	Journal of Abnormal Psychology	Tennessee, USA	T=90		Women only	R=All	A	BDI	Marlowe-Crowne Social Desirability Scale (MC), STAI	A (Frontal, Central, Temporal and Parietal)	1min	Average Ears
1997	Bruder et al	Biological Psychiatry	New York, USA	T=70, D=19, Co=25, C=26	20 - 60	1:1	R=60, L=10	A	DSM III	DSM III, Trait Anxiety scale, State Anxiety Scale	A (Frontal, Temporal, Parietal, Central and Occipital)	3mins	Nose, Cz

1997	Heller et al	Journal of Abnormal Psychology	Illinois, USA	T=40		18:22	R=All	A	General behaviour Inventory	Trait Scale of the STAI, Positive and Negative Affect Schedule (PANAS)	A(Frontal, Central and Parietal)	1 min	Average mastoid
1999	Nitschke	Psychophysiology	Illinois, USA	T=67	Mean=18.26	27:40	R=All	A	Anxious Arousal Scale of Mood and Anxiety Symptom Questionnaire (MASQ)	Penn State Worry Questionnaire (PSWQ), Anxious Arousal Scale of Mood and Anxiety Symptom Questionnaire (MASQ)	A (Frontal, Temporal and Parietal)	8mins	Average mastoid
1999	Wiedemann et al	Ach Gen Psychiatry	Tuebingen, Germany	T=48, Panic Disorder=23, C=25	Mean=36.55	9:39	Not provided	A	Beck Depression Inventory	DSM-III, Agrophibic Cognition and Body Sensation Questionnaires, State and Trait version of Spielberger Anxiety Inventory	A (Frontal and Parietal)	1mins	Not provided
2000	Kentgen et al	Journal of Abnormal Psychology	New York, USA	T=35, D=8, Co=11, A=6, C=10	12.2 t0 18.8	Women only	R=All	Adolescence	DSM-IV	DSM-IV	A (Frontal, Central, Temporal and Posterior)	3mins	Nose

2001	Papousek and Schulter	International Journal of Psychophysiology	Austria	Study 1: T= 50; Study 2: T=90		Study 1: 25:25; Study 2: 47:43	R=All	A		STAI	A (Frontal, Parietal and Central)	2mins	
2002	Baving	Journal of Child Psychology and Psychiatry	Germany	T= 138	8 - 11yrs	62:76	R=All	C		Mannheim Parent Interview	A (Frontal, Central, parietal and Occipital)	3 mins	Average mastoid
2002	Harmon-Jones et al	Journal of Personality and Social Psychology	Wisconsin, USA	T=68		34 - 34	R=All	A	General behaviour Inventory, Positive and Negative Affect Schedule		A(Frontal, Temporal, Central, Parietal, Occipital)	3mins	Left Ear

2002	Pizzagalli et al	Biol Psychiatry	Zurich, Switzerland	T= 56	Mean=36.06	23:33		A	SCID, Hamilton Rating Scale of depression, BDI, DSM IV	STAI	A, B, T, D, G (Frontal, Central, Occipital, Parietal and Temporal)	3mins	Left ear
2003	Field et al	Depression and Anxiety	Carlifonia, USA	T=332	-	Women and their infants	-	A, I	Centre for Epidemiological Studies Depression Scale	Trait Anxiety Inventory	A (Frontal and Parietal)	3mins	Cz
2004	Metzger et al	Journal of Abnormal Psychology	Manchester, NH	T= 50, PTSD=32, C=18		Women only		A	DSM IV	DSM IV, Clinician-Administered PTSD Scale	A (Frontal, Temporal and Parietal)	6mins	Lined ears electrodes
2006	Blackhart et al	Biological Psychology	Florida, USA	T= 28	18 - 25	5:23	R=All	A	Beck Depression Inventory	State-Trait Anxiety Inventory (STAI)	A (Frontal, Parietal and temporal)	6 mins	Cz

2006	Rabe et al	Journal of Abnormal Psychology		T=87				A				A(Frontal)	
2006	Thibodeau et al	Journal of Abnormal Psychology	Syracuse	Meta-analysis of 31 separate studies on EEG asymmetry in depression, anxiety and comorbid anxiety and depression. Total participants included= 2,761 (1,673 adults and 1,088 infants)	Mean age of adult participants=24.4 (12 - 64), Mean age of infant participants=3.9 months (newborn - 17months)	1:4	Not provided	A, I	Various psychometric depression instruments	Various psychometric anxiety instruments	A (Frontal and Parietal)	1 - 8mins	Cz (mostly)
2007	Lee et al	J Korean Neuropsychiatr Assoc	Goyang, Korea	T=22, D=11, C=11					Hamilton Depression Rating Scale (HDRS) and Zung Self-Rating Depression Scale (SDS)	Speielberger's Sate-Trait Anxiety Inventory (STAI)	A (Frontal, Temporal and Occipital)		
2007	Smit et al	Biological Psychology	Amsterdam, Netherlands	T = 732 twins, 760 non-twin sibling	Mean 26.2 (Young cohort), Mean 49.4 (Middle age cohort)	T=760	R=12.6%, L=81.6%	A	Spielberger Anxiety Inventory, Young Adult Self Report Scale	Spielberger Anxiety Inventory, Young Adult Self Report Scale, Amsterdamse Biografische Varagenlijst	A (Frontal, Central, Temporal, Parietal and Occipital)	3mins	Cz

2008	Beaton et al	Neuropsychiatric Disease and Treatmet	Ontario, Canada	T=330	Mean=20.32	84:246		A	Depression Anxiety Stress Scale: 21-item version	Social Phobia Inventory, Cheek and Buss Shyness and Sociability Scale	A (Frontal and Parietal)	2mins	Cz
2008	Crost et al	Biological Psychiatry	Marburg, Germany	T=89	18 - 30	Men only	R=All	A		State-Trait Anxiety Inventory (German version), Marlowe-Crown Social Desirability Scale	A(Frontal and Parietal)	1min	Linked mastoid
2008	Mathersul et al	Emotion	Sydney, Australia	T=428,	18 -60	1:1	Not provided	A	DASS-21 (shortened version of Depression Anxiety Stress Scale), BDI	DASS-21 (shortened version of Depression Anxiety Stress Scale)	A, D, T, B (Frontal, Parietal and temporal)	2mins	Cz
2008	Shankman et al	Journal of Traumatic Stress	Chicago, USA, and Austrlia	T=74	18 - 64	43:31	R=All	A		Clinician Administered PTSD Scale	A (Frontal, Central, parietal and Temporal)	2mins	Average Scalp Reference
2010	Avram et al	Appl Psychophyiol Biofeedback	Cluj-Napoca, CJ, Romania	T=24	19-22		R=All	A		State-Trait Anxiety inventory (Romanian Version)		31 secs	Left ear, re-referenced to average ear lobes

2010	Field et al	Infant Behav Dev	Florida, USA	D=181, A=77, C=308	18 -40	Women only	Not provided	A, I	SCID, CES-D,	State Anger Inventory (STAI)	A (Frontal)	Not provided	Not provided

2010	Gordon et al	Clinical EEG and Neuroscience	Sydney, Australia	T=2475, Schizophrenia=50, MDD=92, PTSD=48, Panic Disorder=48, ADHA=309, Conduct Disorder=20	6 - 87	1341:1134	Not provided	A, C	DSM-IV	Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Clinician-Administered PTSD scale (CAPS) and the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID) for PTSD, Diagnosis of panic disorder was made according to the panic disorder module of the MINI and the Composite International Diagnostic Interview (CIDI-Auto 2.1). Semi-structured clinical interview for ADHD, ADHD and conduct disorder were both diagnosed in accordance with DSM-IV diagnostic criteria.	A (Frontal, Central, Parietal, Temporal and Occipital)	4mins	Ground
2010	Kemp et al	Biological Psychology	Sydney, Australia	T=44, D= 15, A= 14, C=15	18 to 65	17:27	R=42, L=2	A	Structured, Mini-International Neuropsychiatric Interview and the Hamilton Rating Scale for Depression , Depression, Anxiety and Stress Scales (DASS)	Clinician Administered PTSD Scale	A (Frontal, Parietal and temporal)	2mins	A1 and A2

2010	Manna et al	Clinical EEG Neuroscience	New York, USA	T= 49, Co= 28 (14 depressed with low trait anxiety, and 14 depressed with high trait anxiety)	35.1 ± 12.1		R=All	A	DSM-IV, Beck Depression Inventory	The State-Trait Anxiety Inventory-Forum Y	A (Frontal, Central, Parietal and temporal)		PO1 and PO2 re-referenced to Mastoids
2011	Demerdzieva and Pop-Jordanova	Contributions, Sec. Biol. Med. Sci.	Skopje, Macedonia	T= 26	Jul-18	17:9	-	C		ICD-10	A, B, D, T(Frontal, Central, Temporal and Parietal)	10mins	-
2012	Schmidt et al	International Journal of Psychophysiology	Canada	T=26				A					
2013	Nelson	Journal of Abnormal Psychology	Chicago, USA	T=171	Mean=32.55	111:60		A	Structured Clinical Interview for DSM IV	Structured Clinical Interview for DSM IV	A (Frontal and Parietal)	5mins	Near vertex (between Cz and CPz)

2013	Shankman et al	Journal of Abnormal Psychology	Chicago, USA	T=191	Mean=33.48	70:121		A	Structured Clinical Interview for DSM IV	Structured Clinical Interview for DSM IV	A (Frontal and Parietal)	5mins	Near vertex (between Cz and CPz)
2013	Yang et al	International Winter Workshop on Brain-Computer Interface	Daejeon, South Korea	T= 30		18:12		A		State-Trait Anxiety Inventory, Trait version, Form Y(STAI-T)	A(Frontal, Central and Parietal)	8mins	Cz
2014	Beeney et al	Personality Disorders: Theory, Research, and Treatment	Pittsburg, USA	T=57	18 - 60	Women only	R=All	A	Beck Depression Inventory-II	Buss-Perry Aggression Scale; Positive and Negative Affect Schedule-Expanded Form; Adult Rejection Sensitivity Questionnaire	A(Frontal)	8mins	Cz
2014	Ischebeck et al	Psychophysiology	Berlin, Germany	T=40, OCD=20, C=20	Mean=32.85	17:23		A	Structured Clinical Interview for DSM IV	Structured Clinical Interview for DSM IV, Obsessive Compulsory Inventory Revised	A (Frontal and Parietal)	60 secs	Cz
2014	Nelson et al	Journal of Affective Disorders	New York, USA	T=154	Mean=32.92		R=L	A	SCID for DSM IV		A (Frontal)		Between Cz and CPz

APPENDIX 3: DETAILED DESCRIPTIONS OF THE STUDIES WHICH INVESTIGATED THE IN
INTERVENTIONS ON ALPHA EEG ASYMMETRY.

Year	Authors	Journal	Location (Country)	Sample Population (T=Total sample size, D= Depression, C= Control, Co=Comorbid)	Age (years)	Gender Split (M:F)	Handedness (Right=R, Left=L)	Study Type (A=Adult, C=Children, I=Infants)	Test of Depression	Test of Anxiety	EEG band investigated (EEG = A-alpha, B-Beta, D-Delta, G-Gamma and T-Theta) and Scalp site	Duration of Baseline Recordings	Online Reference Scheme
1991	Matousek	International Journal of Psychophysiology		T=23				A			A, B, T, D (Frontal, Temporal, Parietal and Occipital)		
1996	Rosenfeld et al	International Journal of Psychophysiology	Illinois, USA	T=5, D=5	22-48	1:4	R=All	A	DSM-IV, Beck Depression Inventory		A (Frontal)	30mins	Cz

1997	Baehr et al	Journal of Neurotherapy	Illinois, USA	T=2, D=2	Case study 1 = 65, Case Study 2 = 40	Women only	Not provided	A	DSM-IV		A (Frontal)	30mins	Cz
1998	Bell et al	Biol Psychiatry	Arizona, USA	T=35, D=10, Chemical intolerance=14, C=11	30-50	All= Women	Not provided	A	Hamilton Depression Rating scale, DSM-III	Anxiety Sensitivity Index	A (Frontal, central and parietal)	1 min	Linked ear
1999	Earnest	Journal of Neurotherapy	New Mexico, USA	T=1, D=1	14years	Female Adolescent	Not provided	Adolescent	DSM-IV, Beck Depression Inventory		A (Frontal)	30mins	Cz
2001	Bruder et al	Biol Psychiatry	New York, USA	T=53, Responders to SSRI=34, Non-responders=19	Mean= 39.6	25:28	R=All	A	Beck Depression Inventory, DSM-IV	Trait Anxiety Inventory	A (Frontal, Central, Parietal, Temporal and Occipital)	3 mins	Nose

2004	Jones et al	Biological Psychology	Florida, USA	T=78, D=31, C=47	Infants: One month and Three months old; Mothers: 32.2	1:1	Not provided	A, I	CES-D, Diagnostic Interview Schedule		A (Frontal, Central, Parietal and Occipital)	Not provided	Cz
2005	Deldin et al	Biological Psychology	Michigan, USA	T=33, D= 15, C= 18	18 - 65	8:25	R=All	A	Structures Clinical Interview for DSM-IV		A (Frontal and Parietal)	6mins	Cz
2006	Anokhin et al	Biol Psychol	Washington, USA	T=246	17 - 27	Women only		A, Adolescent			A (Frontal)	4mins	Left mastoid
2008	Bruder et al	Biological Psychology	New York, USA	D= 18, C=18, T=36	35.9 ± 9.6	26:10	R=31, L=5	A	DSM-IV		A (Frontal, Central, Parietal and Occipital)	2mins	Nose

2010	Barnhofer et al	Mindfulness	Oxford, UK	T= 15, (Participants on breathing and Loving kindness therapy are 8 and 7 respectively)	Mean age=28	1:4	Not provided	A	Beck Depression Inventory, Response Style Questionnaire		A (Frontal, Central, Parietal, Temporal and Occipital)	2mins	Average
2010	Bismark et al	Biological Psychology	Arizona, USA	D=146, C=167, T=313,	18 to 33	100:213	All righthande d	A	Structured Clinical Interview for DSM IV		A (Frontal, Parietal, Temporal and Occipital)	8mins	Posterior t Cz
2010	Deslandes et al	Brazilian Journal of Medical and Biological Research	Rio de Janeiro	T=20 MDD elderly patients, Exercise group=10, control=10	Mean = 71	3:7	R=All	A	Beck Depression Inventory, Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, DSM-IV		A (Frontal, Central, Parietal, Temporal and Occipital)	8 mins	Linked ear
2010	Khodayari-Rostamabad	Conf Proc IEEE Eng Med Biol Soc.	Ontario, Canada	T=22	Mean age=48.9	9:13		A	HAMD-17		A, B, D, T, G (Frontal, Temporal, Central, Parietal and occipital).	3.5mins	

2010	Saletu et al	Clinical EEG and Neuroscience	Vienna, Austria	T=120, D=60, C=60	Mean=51.1	All women	Not provided	A	DSM-III, Hamilton Depression Scale		A, B, D, T (Frontal, Central, Parietal and Temporal)	7mins	Not provided
2011	Choi et al	Neuropsychobiology	Seoul, Republic of Korea	T=23 Depressed, Neurofeedback Training group= 12, Placeb group=11	Mean= 28.5	6:17	R=All	A	DSM-IV		A (Frontal)	8 mins	Cz
2011	Garcia-Anaya et al	Salud Mental	Queretaro, Mexico	T=20, D=20	19 - 46	6:14	R=All	A	DSM-IVR (SCID)		A, B, D, T (Frontal, Parietal, Central, Temporal and Occipital)	20-30mins	Linked ear lobes

2011	Iakovlev et al	Zh Nevrol Psikhiatr Im S S Korsakova	Russia	T=17	15-17			Adolescent					
2011	Jaworska et al	J Addict Med	Ottawa, canada	T=8, D=8	15-19	All= Women	Not provided	A	DSM-IV, Beck Depression Inventory-II		A, B, D, T (Frontal, central and parietal)	5mins	Linked ear
2011	Moscovitch et al	Biological Psychology	Ontario, Canada	T=23	19 - 73	12:11	R=All	A	BDI-II	Clinical severity Rating	A (Frontal, Temporal, Parietal and occipital)	6mins	Cz
2012	Valiulis et al	Acta Neurobiol Exp	Vilnius, Lithuania	T=45	Mean=52.16	12:33	Not provided	A	Montgomery asberg Depression rating scale, Beck Depression Inventory, Hamilton Rating Scale		A, B, D, T (Frontal, Central, Parietal, Temporal and Occipital)	10mins	Ear electrodes

2013	Fachner et al	Brain Topogr	Jyvaskyla, Finland	T=79, D=79	18-50	17:62	R=All	A	Montgomery–Asberg Depression Rating Scale	Hospital Anxiety and Depression Scale—Anxiety Subscale (HADS-A)	A, B, D, T (Frontal, Parietal, Central and Temporal)	5 mins	Cz
2013	Gonzalez-Olvera et al	Salud Mental	Queretaro, Mexico	T=18				A	DSM-IV		A, B, D, T (Frontal, Parietal, Central, Temporal and Occipital)		Linked ear lobes
2013	Iznak et al	Human Physiology	Moscow, Russia	T=40	20 - 51	17:23	R=All	A	International Classification of Diseases 1oth version (ICD 10), HDRS, Montgomery-Asberg Depression Rating Scale (MADRS)		A, B, T, D (Frontal, Temporal, Parietal and Occipital)	6mins	Ear electrodes
2013	Keune et al	Biological Psychology	Germany			Women only		A			A (Frontal)		
2013	Moynihan et al	Neuropsychobiology	Rochester, USA	T=110	Mean age=73.5	38:52		A	CES-D-R		A (Frontal, Temporal, Parietal and occipital)	8mins	Right mastoid

2013	Noda et al	Neuroscience Research	Tokyo, Japan	T=25	Mean age=44.6	17:8		A	HAMD-17, DSM-IV		A, B, D, T, G (Frontal, Temporal, Central, Parietal and occipital).	15MINS	Ear electrodes
2013	Petchkovsky et al	Advances in Mental health	Sydney, Australia	T=32	48-73			A	BDI-II		A, B, D, T, G (Frontal, Temporal, Central, Parietal and occipital).	3mins	
2013	Quraan et al	Neuropsychopharmacology		T=12					HAMD-17				
2014	Gollan et al	Biological Psychology	Illinois, USA	T= 72, D=37, C=35	18 - 65	27:45		A	Structural Clinical Interview for DSM-IV Axis II disorders, Longitudinal follow-up Evaluation, Inventory of Depressive Symptomatology (Clinician Related and Self Related), Behavioural Inhibition System/ Behavioural Activation System, Positive Affect and Negative Affect Schedule		A(Frontal)	8mins	
2014	Peeters et al	PLOS ONE	Netherlands	T=9	27-62	5:4		A	Quick Inventory of Depressive Symptoms self-report version		A(Frontal, Temporal, Parietal and Occipital)		Average Earlobes

APPENDIX 4: STUDY QUESTIONNAIRE

UNIVERSITY OF NEW ENGLAND

SCHOOL OF SCIENCE & TECHNOLOGY

BRAIN-BEHAVIOUR RESEARCH GROUP: PROFILE-D STUDY

PARTICIPANT SCREENING QUESTIONNAIRE

NO..... DATE.....

1. Your age in years: _____
2. Gender: Male Female (circle one)
3. Your occupation: _____
4. Are you in fulltime ___ or Part-time ___ employment?
5. Your living situation (tick one): With spouse/partner: _____
   Widowed: _____
   Separated/divorced _____
   Never married _____
6. How many people live in the same house/flat that you do? _____
7. How much do you value your social interactions with other people (circle a number on the line below):

Not at all	A little	A good amount	Fairly highly	Very highly
1	2	3	4	5

8. How much do you value your work or job (circle a number on the line below):

Not at all	A little	A good amount	Fairly highly	Very highly
1	2	3	4	5

Below are some statements about how you might feel. Please tick the relevant column for each statement for how you have felt during the last two weeks.

Statements	None or a little of the time	Some of the time	Good Part of the time	Most OR all of the time
1. I feel downhearted and blue.				
2. Morning is when I feel the best.				
3. I have crying spells or feel like it.				
4. I have trouble sleeping at night.				
5. I eat as much as I used to.				
6. I still enjoy sex.				
7. I notice that I am losing weight.				
8. I have trouble with constipation.				
9. My heart beats faster than usual.				
10. I get tired for no reason.				
11. My mind is as clear as it used to be.				
12. I find it easy to do the things I used to.				
13. I am restless and can't keep still.				
14. I feel hopeful about the future.				
15. I am more irritable than usual.				
16. I find it easy to make decisions.				
17. I feel that I am useful and needed.				
18. My life is pretty full.				
19. I feel that others would be better off if I were dead.				
20. I still enjoy doing the things I used to.				
21. I do not feel much better, even when good things happen.				
22. I have been waking up at least 2 hours before I usually do.				
23. I feel bad about myself, or that I am a failure, or have let myself or my family down.				

APPENDIX 5: CONSENT FORM

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CONSENT FORM for PARTICIPANTS

PROFILE-D: An investigation of the psychological, neurological, and biological aspects of depression

I, ..., have read the information contained in the Information Sheet for Participants and any questions I have asked have been answered to my satisfaction. Yes/No

I agree to participate in this activity, realizing that I may withdraw at any time. Yes/No

I agree to answer the study questionnaire and undergo an EEG session as described on the Information Sheet for Participants. Yes/No

I do not have any bleeding disorder and I agree to provide a blood sample. Yes/No

I agree that research data gathered for the study may be published anonymously. Yes/No

I agree to the interview having my audio recorded and transcribed. Yes/No

I would like to receive a copy of the transcription of my interview. Yes/No

I am older than18 years of age. Yes/No

....
Participant Date

....
Researcher Date

APPENDIX 6: STANDARDIZED LABORATORY PROTOCOL

1. Greet and welcome the participant to the lab by saying "you are welcome to our laboratory, and thank you for taking time out to participate in our study; we do appreciate your time and effort".
2. Briefly re-explain the purpose of the study and describe all the component of the study.
   State that "this study is on the investigation of the psychological, neurological, and biological aspects of depression. Our aim is to develop a 'map' of the psychological electrophysiological, immunological, endocrine and proteomic descriptors of varying degrees of depression and also 5 subtypes od depression that may be used to identify more effective treatment models.
   The complete study requires each participant to:
   a. Complete a basic psychological questionnaire.
   b. Undergo a laboratory session of about 1.5 hours involving the measurement of your Electro-encephalography (EEG).
   c. Collection of a sample of saliva and,
   d. Collection of a small sample of your blood (50mls) which is an optional component of the study.
3. Remind the participant that they are free at any time to withdraw from the study if they so wish and they do not have to provide any reasons for doing so.
4. Present the participant with a copy of the study information sheet and ask them to read through it.
5. Ask if the participant is still willing and ready to proceed with the study.
6. If their response is positive, present the participant with a copy of the consent form and ask them to read through, and to indicate 'yes' to which ever part of the study they agree to participating in. Ask them to sign the consent form on the space provided for the participant, and also append your signature on the space provided for the researcher in the presence of the participants.
7. Present the participant with a copy of the participant screening questionnaire and ask them to fill it, providing details of their responses as much as they can.
8. Take participant clinical history using the clinical history form prepared for that purpose.
9. If participants consent to giving blood, take blood samples in three green vacutainer tubes (containing the anticoagulant Lithium heparin) and one red vacutainer tubes (which has no anticoagulant in it). Follow aseptic procedures and secure haemostasis after the venepuncture is completed.
10. Proceed to the EEG component by first preparing the scalp of the participant. This should be done by brushing the scalp with a bristle hairbrush for about 3-5mins. This will help to exfoliate the scalp surface. (Participants should have been instructed to wash their hair with a normal shampoo that does not contain any conditioner the night or morning before the EEG session. Conditioner coats the scalp and makes it much more difficult to obtain low impedance connection).

11. Measure the head circumference of the participant to determine the EEG cap size. Use small, medium and large size if the circumference measures 50-53cm, 55-59cm and 60-65cm respectively.
12. Locate the position of the Cz electrode (reference electrode) by measuring the distance from the glabella to the inion. The position of the Cz electrode is half way in between these two landmarks.
13. Also prepare the skin sites for the frontal pole electrodes and the four drop or external electrodes (one below the right and left eyes, one on each mastoid prominence at the back of the ears). To do this, apply the 'Nuprep gel' (a gritty gel which removes any dead and dry skin from the scalp) to the electrode sites clean with alcohol or acetone swab immediately after gel application to the scalp. Otherwise, use alcohol or acetone swabs only to clean the electrode sites. Make sure these areas are clear of makeups and foundation in order to ensure that impedance is low at these sites.
14. Put the EEG cap containing the electrodes on the head of the participant making sure that Cz is rightly placed half way between the glabella to the inion. Ensure that the cap is firmly attached to the scalp by applying the cap fasten (Velcro tape) at the chin. If necessary, cut 10-15cm length of a wound gauze mesh and apply it over the top of the EEG cap by pulling the mesh over the cap to enhance adequate contact with the scalp. Avoid placing the mesh on the frontal pole electrodes as they are already in good contact with the scalp, and this may result in discomfort for the participant.
15. Apply four drop or external electrodes (one below the right and left eyes, one on each mastoid prominence at the back of the ears) with the aid of a butterfly tapes to make sure the electrodes are in secure contact with the skin.
16. Load all electrodes with electrode gel, beginning with the ground, Cz and the two ear electrodes. Do not apply too much gel as gel can spread beyond the proximity of the electrode reservoir, and these can result in in a salt bridge with other electrode locations. Also, if too little gel is loaded, the conductive column between the scalp and the electrode will contain gaps and this may result to intermittent contact between the electrode and the scalp.
17. Allow the gel to soak in before testing the impedances. The gel will significantly lower the impedance without further abrading the scalp. While waiting perform step 18, 19 and 20 below.
18. Connect the EEG cap containing the electrodes to the Neuroscan machine in the cubicle. Do not check for the impedance yet!
19. Clean a bony area on the right and left forearm, and the left leg. Connect the ECG electrodes in the following other: Red electrode to the right forearm, white electrode to the left forearm and black electrode to the left leg.
20. Switch on the powerlab, the Curry Neuroscan and the Stroop test software on the computer, making sure all three programs are displayed on the screen at once.
21. On the powerlab software, click on the "new" button, and then click on channel 2 drop down menu to select GSR Amp. This should open a new window with "subject zero" and "open circuit zero" at the base.

22. Perform "open circuit zero" first without connecting the GSR electrodes to the participant's fingers. This should be done by clicking on "open circuit zero" and allowing it to run for about 10 seconds, then Click 'OK'.
23. After this, clean the palmer surface of the middle phalanx of the middle and index fingers with alcohol swabs and apply a little isotonic gel (this will improve skin contact and GSR recording quality). Apply the stainless steel GSR Bipolar finger electrodes to these sites keeping them fitted and secure with Velcro tape.
24. Now perform "subject zero" by clicking on channel 2 drop down menu to select GSR Amp, and then click on "subject zero", allowing it to run for about 10 seconds, then click 'OK'.
25. Click on the start button to check if the powerlab tracings for ECG and GSR are normal. If not adjust the electrodes again and the tracings should be correct. Stop the tracings and close the window. Do save this recording and do not close the entire powerlab program.
26. Open a recording section by clicking on the "new" button again. There should be no need to perform zeroing again.
27. On the Curry software, click on the "start acquisition" on the "workflow" control panel on the left. This should open a new control panel "Acquisition". Select "NuAmps" and '36 channels" for "amplifier" and "Configuration" respectively.
28. Under "filter parameters", select "off" and "EAR" for "filter type" and "Reference" respectively.
29. Under "Amplifier control", click on the start button (green). Do not record any tracings yet!
30. Click on the "Ω" button to perform impedance check. This will display all the impedances on all connected channels. Ensure that all channels have impedance bellow 5 ohms
31. To reduce high impedance, inserting the blunt needle first into the ground electrode and introduce additional gel and move the needle in and out of the electrode, monitoring change of impedance with needle movement. This should bring down the impedance in most electrodes. If not, perform the same manoeuvre in the Cz electrode, and in any individual electrode with high impedance.
32. Once all the electrode impedances are below 5 ohms, return to tracing mode by clicking on the "Ω" button again.
33. Inform the participant that you are about to start recording and ask them to close their eyes.
34. Click on the "start" button on the powerlab software and then click on "record" (red button) on the curry software. Record for 3 mins after the commencement of recording on the curry software. This represents baseline recording in "eyes closed" condition.
35. At about 3 mins recording after the commencement of recording on the curry software, open a comment chart on the powerlab by clicking on the "command" menu and then selecting "add comments". Type in the words "eyes open" and press the "enter" key. This marks the beginning of eyes open baseline recordings. Record for

another 3 mins and then press the "record" (red button) on the curry software to stop the baseline recording process. Stop the recording on the powerlab also.

36. Save the EEG tracings as follows. Click on the file drop down menu on the top left corner and select "Save study as". This will open a new window from which you should select "My documents" in the "save in" drop down menu. Select 'PROFILE D" file and then select "EEG" file. Select "Baseline EEG" and type in "the participant's code" in the "file name" section and then select save.
37. Save the powerlab recordings as follows. Click on the file drop down menu on the top left corner and select "Save as". This will open a new window under "documents" from which you should select "PROFILE D" under "document library". Select "ECG and GSR" file, then select "Baseline ECG and GSR" and type in "the participant's code" in the "file name" section and then select save.
38. Switch on the computer screen in the EEG cubicle and extend the Stroop test screen from the desktop screen unto the screen in the EEG cubicle.
39. Inform the participant about the second part of the laboratory session (as previously discussed in the information leaflet and pre-lab session). Instruct them to listen and follow to the audio instructions which will be played to them via the two ear pieces.
40. Gently apply the ear pieces into the participant's ears. Adjust the volume level as necessary.
41. Put on the voice recorder which has been placed in the EEG cubicle and start recording.
42. Put on your own ear pieces to monitor the process.
43. Start recording on both the power lab and the Curry software programs.
44. Then Click the start button on the Stroop test screen. Allow this to run through. This program has been pre-set to allow for sufficient resoponse time for all questions in both sections of the test. At the end of this session (i.e. when the slide displays "The End"), allow for further 1 min recording on both the power lab and the Curry software programs and then stop all recordings including voice recording.
45. Quickly play back the recorded voice and documents participant's response on the questionnaires which carries the same set of questions as shown/displayed on the screen during the Stroop test session. The timing of this should be cross-checked by playing the stroop test again as the recorder is playing in order to ensure that all responses (including omitted responses) are noted properly.
46. Save the EEG tracings for the stroop test as follows. Click on the file drop down menu on the top left corner and select "Save study as". This will open a new window from which you should select "My documents" in the "save in" drop down menu. Select 'PROFILE D" file and then select "EEG" file. Select "Subtypes and Stroop test EEG" and type in "the participant's code" in the "file name" section and then select save.
47. Save the powerlab recordings as follows. Click on the file drop down menu on the top left corner and select "Save as". This will open a new window under "documents" from which you should select "PROFILE D" under "document library". Select "ECG and GSR" file, then select "Subtypes and Stroop test ECG and GSR" and type in "the participant's code" in the "file name" section and then select save.

48. Save the voice recordings under the folder "Voice Recordings" in the "PROFILE D" folder under "Document" section of the computer libraries.
49. Gently detach the ECG and GSR electrodes from the participants. Also remove the ear pieces and the EEG electrode cap with the external electrodes.
50. With the aid of antimicrobial wipes, clean up the electrode gel form the scalp of the participant, ensuring no gel is left on the scalp. Ask the participant to wash their hair/head/scalp as soon as the get home.
51. Thank the participant for their time and cooperation. Lead them out of the lab and bid them farewell.
52. Keep the ECG and GSR electrodes with their connection together the ear pieces on the hook in the EEG cubicle to keep them from lying around on the floor.
53. With the aid of the water floss in the lab, clean each EEG electrode on the cap and the external electrodes too. Allow them to dry by placing the external electrodes on a paper towel on the bench and the EG cap on the hook hanging on the wall in the lab.