The Comparative Effectiveness of EEG Biomarkers in Antidepressant Response and Illness Prediction in Major Depressive Disorder

by

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the degree of Doctor of Philosophy

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Abstract

Background: There is growing evidence that individual EEG differences may aid in classifying patients with major depressive disorder (MDD) and also help predict clinical response to antidepressant treatment. This study aims to compare the effectiveness of EEG frequency band power, alpha asymmetry and prefrontal theta cordance towards escitalopram response prediction and MDD diagnosis, in a multi-site initiative.

Methods: Resting EEG (eyes open and closed) was recorded from 64 electrodes in 44 depressed patients and 20 healthy controls at baseline, 2 weeks post-treatment and 8 weeks post-treatment. Clinical response was measured as change from baseline MADRS of 50% or more. EEG measures were analyzed (1) at baseline (2) at 2 weeks post-treatment and (3) as an “early change” variable defined as change in EEG from baseline to 2 weeks post-treatment.

Results: At baseline, responders exhibited greater absolute alpha power in the left hemisphere versus the right while non-responders showed the opposite. Responders further exhibited a cortical asymmetry of greater right relative to left activity in parietal areas. Groups also differed in baseline relative delta power with responders showing greater power in the right hemisphere versus the left while non-responders showed the opposite. At 2 weeks post-treatment, responders exhibited greater absolute beta power in the left hemisphere relative to right and the opposite was noted for non-responders. The opposite pattern was noted for absolute and relative delta power at 2 weeks post-treatment. Responders exhibited early reduction in relative alpha power and early increments in relative theta power. Non-responders showed a significant
early increase in prefrontal theta cordance. Absolute delta power helped distinguish MDD patients from healthy controls.

**Conclusions:** Hemispheric asymmetries in the alpha and delta bands at pre-treatment baseline and at 2 weeks post-treatment have moderate to moderately strong predictive utility towards antidepressant treatment response. These findings have significant potential for improving clinical practice in psychiatry by eventually guiding clinical choice of treatments. This would greatly benefit patients awaiting relief from depressive symptoms as treatment optimization would help overcome problems associated with delayed recovery. Our results also indicate that resting EEG activity may have clinical utility in predicting MDD diagnosis.
Co-Authorship

This thesis consists of manuscripts that have been published or are in the process of being prepared for submission to peer-reviewed journals. The text of the original manuscripts comprising this thesis has been slightly modified either to avoid redundancy or to reflect recent literature. The authorship of the manuscript comprising the general introduction and Chapter 2.4 is: Anusha Baskaran, Roumen Milev, and Roger McIntyre. The authorship of the manuscript comprising the section titled “EEG as a Predictor of Antidepressant Treatment Outcome” in chapters 4, 5 and 6 is: Anusha Baskaran, Roumen Milev, Faranak Farzan, Colleen Brenner, Sidney Kennedy and CAN-BIND Study Team.

Anusha Baskaran (MSc) was implicated in study conceptualization, data collection, analysis, and preparation of all manuscripts.

Roumen Milev (MD, PhD, FRCPsych, FRCPC) was one of the site principal investigators of the clinical trial called Canadian Depression Biomarker Network Study (CAN-BIND) within which this thesis work was embedded in, as well as one of the clinicians involved in patient assessment and treatment. He contributed to the conceptualization and design of this thesis research and edited manuscript drafts.

Roger McIntyre (MD, FRCPC) helped edit manuscript drafts.

Faranak Farzan (PhD) was the EEG co-lead of CAN-BIND. She contributed to the conceptualization of this thesis research, data collection, and edited manuscript drafts.

Colleen Brenner (PhD) was an EEG collaborator of CAN-BIND. She contributed to the conceptualization of this thesis research, data collection, and edited manuscript drafts.
Sidney Kennedy (MD, FRCPC) was the principal investigator of CAN-BIND, as well as one of the clinicians involved in patient assessment and treatment. He contributed to the conceptualization and design of this thesis research.

The CAN-BIND study team includes an established network of clinician researchers through the Canadian Network of Mood and Anxiety Treatments (CANMAT) and leading scientists with expertise in neuroscience, psychology, psychiatry, genomics, proteomics, informatics, clinical trials methodology, and knowledge translation. Participating clinical sites were: University Health Network and Centre for Addiction and Mental Health at University of Toronto (Toronto), McMaster University (Hamilton), Queen’s University (Kingston), University of Calgary, and the University of British Columbia.

The general introduction and Chapter 2.4 are a modification of the following published manuscript: Baskaran, A., Milev, R., McIntyre, R. S. (2013). The Neurobiology of the EEG Biomarker as a Predictor of Treatment Response in Depression. Neuropharmacology, 63(4), 507-513.

The sections titled “EEG as a Predictor of Antidepressant Treatment Outcome” in chapters 4, 5 and 6 are a modification of the following manuscript: Baskaran, A., Milev, R., Farzan, F., Brenner, C., Kennedy, S., & CAN-BIND Study Team. (2016). The Comparative Effectiveness of Electroencephalographic Biomarkers of Escitalopram Response in Depression: A Pilot Study. Manuscript in preparation.
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Statement of Originality

I hereby certify that all of the work described within this thesis is the original work of the author.

Any published (or unpublished) ideas and/or techniques from the work of others are fully
acknowledged in accordance with the standard referencing practices.

(Anusha Baskaran)

(August, 2016)
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<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
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<td>5-HT</td>
<td>Serotonin</td>
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<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ATR</td>
<td>Antidepressant treatment response</td>
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<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
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<td>BOLD</td>
<td>Blood-oxygen-level-dependent</td>
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<tr>
<td>BRITE-MD</td>
<td>The Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression Study</td>
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<tr>
<td>CAN-BIND</td>
<td>Canadian Depression Biomarker Network Study</td>
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<td>CANMAT</td>
<td>The Canadian Network for Mood and Anxiety Treatment</td>
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<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>CRH</td>
<td>Corticotropin-releasing hormone</td>
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<td>CSD</td>
<td>Current source density</td>
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<tr>
<td>DA</td>
<td>Dopamine</td>
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<tr>
<td>dACC</td>
<td>Dorsal anterior cingulate cortex</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>ERP</td>
<td>Event-related potential</td>
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<td>EPSP</td>
<td>Excitatory postsynaptic potential</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FFT</td>
<td>Fast Fourier Transform</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothamic-pituitary-adrenal axis</td>
</tr>
<tr>
<td>ICA</td>
<td>Independent Component analysis</td>
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<tr>
<td>IPEG</td>
<td>International Pharmaco EEG Society</td>
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<tr>
<td>IPSP</td>
<td>Inhibitory postsynaptic potential</td>
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<tr>
<td>LDAEP</td>
<td>Loudness dependent auditory evoked potential</td>
</tr>
<tr>
<td>LORETA</td>
<td>Low-resolution electromagnetic tomographic analysis</td>
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<tr>
<td>MADRS</td>
<td>Montgomery Asberg depression rating scale</td>
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<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>MDE</td>
<td>Major depressive episode</td>
</tr>
<tr>
<td>MHPG</td>
<td>3-methoxy-4-hydroxyphenylglycol</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Inventory</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NE</td>
<td>Norepinephrine</td>
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<tr>
<td>NEBA</td>
<td>Neuropsychiatric EEG-based assessment aid</td>
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<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NREM</td>
<td>Non-rapid eye movement</td>
</tr>
<tr>
<td>NRI</td>
<td>Norepinephrine re-uptake inhibitor</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal Component analysis</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<tr>
<td>PSP</td>
<td>Postsynaptic potential</td>
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<tr>
<td>QEEG</td>
<td>Quantitative electroencephalography</td>
</tr>
<tr>
<td>rACC</td>
<td>Rostral anterior cingulate cortex</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized clinical trial</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>rTMS</td>
<td>Repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>SERT</td>
<td>Serotonin re-uptake transporter</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin and norepinephrine re-uptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin re-uptake inhibitor</td>
</tr>
<tr>
<td>STAR*D</td>
<td>The Sequenced Treatment Alternatives to Relieve Depression Study</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>TBR</td>
<td>Theta/beta ratio</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
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<tr>
<td>TNN</td>
<td>Task negative network</td>
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<tr>
<td>TPN</td>
<td>Task positive network</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>TRD</td>
<td>Treatment-resistant depression</td>
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<tr>
<td>vACC</td>
<td>Ventral anterior cingulate cortex</td>
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<tr>
<td>VMPFC</td>
<td>Ventromedial prefrontal cortex</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Chapter 1

General Introduction

Major Depressive Disorder (MDD) is a common and persistent psychiatric illness associated with personal suffering, and significant social and functional impairment (Lopez et al., 2006). The World Health Organization (WHO) ranks depression as the third leading cause of global disease burden and projects that by 2030, it will be the first leading cause worldwide (WHO, 2011). Tremendous societal costs are associated with the disability caused by depression (Greenberg et al., 2003). Higher medical costs, in particular, arise largely from non-response to treatment as initial treatments frequently do not lead to recovery (Simon, Khandker, Ichikawa, & Operskalski, 2006).

The majority of MDD patients experience lengthy trial-and-error periods with different antidepressant medications before a successful medication is identified. In practice, it has been well documented that approximately 6-8 weeks of “watchful waiting” are required to observe full recovery with a certain medication (Bauer et al., 2007; Fochtmann & Gelenberg, 2005). Moreover, only a proportion of patients who receive adequate pharmacotherapy will achieve remission defined as absence or near absence of symptoms (Rush et al., 2006). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that less than 50% of depressed patients respond (defined as 50% or more improvement in depressive symptoms) to the first antidepressant they try (Trivedi et al., 2006). Only approximately 30% of patients achieved full remission. The probability that an individual will achieve remission decreased steadily with each new treatment failure. Patients who fail to achieve full remission have a more recurrent and chronic course of illness, increased medical and psychiatric co-morbidities, greater functional burden, leading to increased social and economic costs (McIntyre & O’Donovan,
Delayed recovery also leaves patients with a heightened risk of suicide (Witte et al., 2009). Hence, the current treatment approach is seriously flawed leading to prolonged patient suffering and risk that patients will discontinue treatment efforts.

The impact of delayed recovery on patient suffering and quality of life has been the premise for identifying indicators early in the course of treatment that could aid in predicting treatment outcome (Hunter, Cook, & Leuchter, 2007). Despite the fact that antidepressant medication is the first line of treatment for MDD patients, to date, there is a no way of selecting treatment to optimize clinical response. Biomarkers could potentially help in predicting the likelihood of whether or not a patient will benefit from certain medications. This would allow for better optimization of treatment and would also help overcome the problems associated with delayed recovery.

A promising area of research that has recently attracted great attention is the development and application of biomarkers that are predictive of treatment response. According to Frank and Hargreaves (2003), biomarkers are objectively measured characteristics that indicate the intrinsic causes of illness, the clinical course, and its modification by treatment. A more relevant definition has been proposed by the “Biomarkers Definitions Working Group” in the context of drug discovery: biomarkers are objectively measured indices of pharmacological response or biological process that are quantifiable, precise, and reproducible (Atkinson et al., 2001). According to the latter definition, a biomarker may be used to predict clinical response to treatment. Identifying reliable biomarkers will not only greatly aid clinicians in selecting antidepressant treatment for individual patients but will also provide a critical step in drug discovery, both of which could have a significantly positive impact on patient suffering and economic burden by reducing or eliminating lengthy and ineffective treatment trials.
Various parameters of genetics, proteomics, metabolomics, neuroendocrinology, neuroimaging, neurophysiology, and clinical characteristics have been suggested as potential biomarkers of antidepressant treatment outcome. For example, functional polymorphisms in genes of monoaminergic pathways have been shown to be predictive of outcome to selective serotonin re-uptake inhibitor (SSRI) treatment (McMahon et al., 2006; Serretti, Benedetti, Zanardi, & Smeraldi, 2005). Studies employing the combined dexamethosone/corticotrophin releasing hormone test have demonstrated that hypothalamic-pituitary-adrenal axis (HPA) activity can also predict the efficacy of antidepressant medication in patients with MDD (Ising et al., 2007; Paslakis, Heuser, Schweiger, & Deuschle, 2010; Schule et al., 2009). Functional neuroimaging studies have indicated a positive link between increased pre-treatment resting activity in the rostral anterior cingulate cortex (rACC) and response to various antidepressants (Chen et al., 2007; Davidson, Irwin, Anderle, & Kalin, 2003; Langenecker et al., 2007; Mayberg et al., 1997; Saxena et al., 2003). However, many of these findings have not made their way into routine clinical use because they have not been consistently replicated or they do not hold sufficient predictive value to be implemented in clinical settings. Moreover, the invasiveness associated with genetic and biochemical predictors and the high cost of neuroimaging make such predictors problematic for widespread clinical use (Iosifescu, 2011).

A neurophysiological biomarker that has promise in MDD is quantitative electroencephalography (QEEG). Electroencephalography (EEG) is a measure of the brain’s spontaneous electrical activity acquired from electrodes placed on the scalp. Recorded activity at each electrode is generally the gross measure of electrical activity arising from a number of different neurons in cortical areas surrounding the electrode. The source of the EEG signal arises from the temporal and spatial summation of thousands of postsynaptic potentials generated by
pyramidal cells found in the cortex of the brain (Olejniczak, 2006). Graphically, EEG is a representation of the difference in voltage between two different cerebral locations plotted over time. This function of time can be mathematically transformed into a function of frequency using the Fast-Fourier Transform (FFT) which results in a voltage by frequency spectral graph referred to as the power spectrum. The EEG spectral domain can be conventionally divided into the alpha (8-13 Hz), beta (13-30 Hz), theta (4-8 Hz) and delta (< 4 Hz) frequency bands. The power of the EEG signal is defined as the square of the EEG magnitude, which is the integral average of the EEG amplitude. Power can either be measured in absolute or relative terms. Absolute power describes the amount of power in a frequency band at a given electrode and relative power is the percentage of power contained in a frequency band, relative to the total power across the entire spectrum, computed separately for each electrode (Cook et al., 2002).

EEG has clear advantages over other proposed biomarkers as it is non-invasive, widely available, and is cost-effective. Furthermore, EEG has good temporal resolution and it directly measures neuronal electrical activity, rather than being a proxy such as blood oxygenation concentration, as is the case in functional magnetic resonance imaging (fMRI). These features of EEG make it a good candidate for routine clinical use towards MDD. This is not to say that EEG is not without important limitations, namely lower spatial resolution compared with fMRI and other imaging techniques. Source localization methods such as low-resolution electromagnetic tomographic analysis (LORETA) have been used to help overcome the problems associated with this limitation (Pascual-Marqui, Michel, & Lehmann, 1994).

Over the past several decades, EEG has been used in understanding the psychopathology of MDD and in examining the neural target of treatment (Alhaj et al., 2011; Baskaran et al., 2013; Jaworksa & Protzner, 2013; Olbrich & Arns, 2013; Sayar, Onen, & Tan, 2013). EEG
biomarkers have also been probed for their predictive utility towards antidepressant treatment response (Baskaran et al., 2012; Hunter et al., 2007; Sayar, Onen, & Tan, 2013). There is growing evidence that individual differences among depressed patients in QEEG parameters measured early in the course of treatment are predictive of therapeutic response to a variety of antidepressant drugs.

Elevated parieto-occipital alpha power has been shown to differentiate responders from non-responders to treatment with tricyclic antidepressants (TCAs) such as clomipramine and imipramine and with SSRIs such as paroxetine and fluoxetine (Bruder et al., 2001; Knott et al., 1996, 2000; Ulrich, Haug, Stieglitz, & Fahndrich., 1988). Given that alpha activity is inversely related to cortical activation, elevated pre-treatment alpha power is thought to reflect cortical hypoactivity (Laufs et al., 2003). Keeping with this, it is has been hypothesized that increased pre-treatment alpha activity may be indicative of the correspondence between low serotonergic activity and low arousal (Bruder et al., 2008). Interestingly, MDD patients characterized by decreased alpha demonstrate poor treatment response (Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1984).

Reports of the predictive utility of alpha asymmetry (a score derived from computing the difference in log alpha power between right and left hemispheres) towards antidepressant response also exist but with less consistency. While some studies report left hypoactivation of the occipital region to be predictive of favourable outcome (Ulrich et al., 1984), others have noted the opposite (right hypoactivation) (Bruder et al., 2001, 2008) and still, a handful of studies have failed to replicate either of these findings (Jaworksa et al., 2014; Tenke et al. 2011). While the meaning of alpha asymmetry in the context of antidepressant treatment response remains unclear, Bruder et al. (2001) hypothesized that the 5-HT neurotransmitter system may
have a lateralized distribution in the brain and may be asymmetrically disrupted in a subtype of depressed patients.

Reports of scalp-assessed theta band activity have reported decreased pre-treatment theta to predict treatment response to the TCA, imipramine and to open-label SSRIs (Iosifescu et al., 2009; Knott et al. 1996, 2000). However, studies utilizing source localization methods such as LORETA have supported findings of increased, pre-treatment theta activity in the rACC as being predictive of eventual response to a variety of different antidepressants (Korb, Hunter, Cook, & Leuchter, 2009; Mulert et al., 2007; Pizzagalli et al., 2001). It has been hypothesized that elevated resting rACC activity may lead to treatment response through adaptive self-referential functions such as mindfulness and non-evaluative self-focus (Pizzagalli, 2011). The discrepancies in previous findings of alpha asymmetry and theta band activity have been explained as arising from the heterogeneity of MDD patients and also from the methodological differences amongst studies (Jaworska & Protzner, 2013; Olbrich & Arns, 2013). Activity in other frequency bands have been less conclusive with one study showing trend level findings of elevated beta power and reduced delta power at pre-treatment baseline to predict response to imipramine (Knott et al., 1996) and a latter study confirmed similar findings to be statistically significant in paroxetine responders (Knott et al., 2000).

In more recent years, custom EEG-derived parameters, namely theta cordance and the antidepressant treatment response index (ATR) have been developed with the intention of aiding response prediction. Theta cordance is a QEEG measure that combines information from both absolute and relative power from the EEG theta spectra according to a specific algorithm (Leuchter et al., 1994). Decreased prefrontal theta cordance measured in MDD patients as early as 48 hours to 1 week post-treatment has been shown to be predictive of treatment response with
different antidepressant medication types (Cook & Leuchter, 2001; Cook et al., 2002; Bares et al., 2007, 2008, 2010). The ATR is a QEEG measure that integrates frontal alpha and theta power extracted at pre-treatment baseline and at 1 week post-treatment (Leuchter, Cook, Hunter, & Korb, 2009). It has been shown to predict overall response and remission in MDD patients treated with escitalopram or bupropion, with an ability to also be predictive of differential response to monotherapy with either of these medications. Although both theta cordance and ATR have been shown to have good sensitivity and specificity, the complexity of these markers make it difficult to interpret what exactly they reflect at the level of the brain. Moreover, ATR has not been subjected to independent replication, limiting its generalizability to clinical practice.

Although various QEEG-derived biomarkers have been shown to hold promise in predicting antidepressant treatment response, there is limited research regarding the utility of EEG indices in predicting response to escitalopram therapy, which has been shown to have superior efficacy over other antidepressant medications (Ciprani et al., 2009; Kennedy et al., 2009; Montgomery et al., 2007; Sanchez et al., 2014). It is also unclear whether the predictive utility of some EEG indices is superior to others. Moreover, multi-site initiatives examining the comparative effectiveness of EEG-derived biomarkers of clinical response are lacking. In order for candidate EEG biomarkers to be clinically useful, reliability is key. A biomarker that can be translated into psychiatric practise must be one that can be replicated irrespective of what site data is collected at.

The research comprising this thesis aimed to investigate if EEG-derived brain activity measured during resting state will help differentiate responders and non-responders to treatment with escitalopram, and to cross-compare their predictive utility towards clinical response, across multiple sites. The research presented within this thesis specifically examined the utility of EEG
frequency band power, alpha asymmetry and prefrontal theta cordance at pre-treatment baseline, 2 weeks post-treatment and as early change variables in predicting response to escitalopram treatment. In addition, the same EEG markers were also examined for their ability to characterize patients with MDD versus healthy controls.
2.1 Major Depressive Disorder

2.1.1 Clinical Characteristics

Major Depressive Disorder also known as unipolar depression is a psychiatric mood disorder that involves one or more major depressive episode(s) (MDE). According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (American Psychiatric Association, 2013), a MDE consists of five or more of the following symptoms occurring nearly every day for at least a two week period, during which significant distress or functional impairment is experienced: 1) depressed mood most of the day; 2) markedly diminished interest or pleasure; 3) significant weight loss or decrease/increase in appetite; 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue; 7) feelings of worthlessness or excessive guilt; 8) diminished ability to concentrate; 9) recurrent thoughts of death, suicidal ideation, or suicide attempt.

2.1.2 Epidemiology

Major depressive disorder is a significant public-health concern with immense social and economic burden, most notably, due to its impact on quality of life and individual suffering (Olbrich & Arns, 2013). In a systematic review of the epidemiological literature of MDD, the global point prevalence of MDD was reported as 4.7% and the pooled annual incidence was 3.0% (Ferrari et al., 2013). The cross-national epidemiology of DSM-IV MDE has been explored in population-based samples of adults from 18 high and low- to middle-income countries as part of the World Mental Health Survey Initiative (Bromet et al., 2011). The
average lifetime and 12-month prevalence estimates of MDE were 14.6% and 5.5%, respectively in the ten high-income and 11.1% and 5.9%, respectively in the eight low- to middle-income countries. The average age of onset was 25.7 in the high-income countries and 24.0 in low- to middle-income countries. Functional impairment was associated with recency of MDE and females were shown to be twice as likely as males to develop MDE. Young age was associated with elevated 12-month prevalence in high-income countries, whereas, old age was associated with increased likelihood of MDE in several of the low- to middle-income countries. The strongest demographic correlate in high-income countries was being separated from a partner, and in low- to middle-income countries, the strongest correlate was being divorced or widowed.

Recently, Patten et al. (2016) demonstrated the first international effort to examine the long-term changes in the epidemiology of MDD. Two mental health surveys [The Canadian Community Health Survey: Mental Health and Well-Being (2002) (Gravel & Belan, 2005) and the Canadian Community Health Survey–Mental Health (2012) (Pearson, Janz & Ali, 2013)] with identical MDE modules have examined the epidemiology of MDE in the national population of Canada, 10 years apart. Selected variables from the two surveys were compared to assess whether any change has occurred in the prevalence, treatment and impact of MDE. The annual prevalence of MDE was 4.7% in 2012, almost the same as 4.8% in 2002. The frequency of potentially adequate treatment (defined as taking an antidepressant or 6 or more visits to a health professional for mental health reasons) increased from 41.3% in 2002 to 52.2% in 2012. However, there was no evidence to support a reducing prevalence or impact (assessed as symptoms of distress) of illness. This is interesting considering that the use of antidepressant medication was shown to increase over time. In 2011, Canada ranked third globally, for reporting the highest level of consumption of antidepressants (Organisation for Economic Co-
operation and Development, 2013). Increase in antidepressant use has been explained as arising from greater intensity and duration of drug treatment (Moore et al., 2009). Therefore, a lack of change in the epidemiology of MDE even in the face of a recent increase in antidepressant is of serious concern.

In a prospective, 12-year study assessing subsyndromal and syndromal depressive symptoms in MDD, patients with recurrent depression were shown to have more chronic symptoms than patients with first lifetime MDE (65% versus 46% of follow-up weeks) (Judd et al., 1998). Greater symptom severity in MDD is associated with overall reduced health-related quality of life (Trivedi et al., 2006) and recurrent MDD is associated with an increased risk of suicide (Witte et al., 2009). Furthermore, a longer duration of MDE (>12 weeks) has been associated with an approximately 40% lower rate of recovery in subsequent episodes (Spijker et al., 2004). An investigation of the impact of various sociodemographic and clinical factors as predictors for 2-year outcome of MDE reported rapid remission as the most important predictor for favourable long-term outcome (Sza
do
czky, Rozsa, Zambori, & Furedi, 2004). Remission is defined as the absence or near absence of symptoms (Rush et al., 2006). The presence of residual depressive symptoms due to partial or incomplete remission is associated with significant morbidity and mortality (Bakish, 2001). For example, the prevalence of suicide attempt is four times higher during partial remission than in full remission (Holma et al., 2010). These findings highlight the importance of rapid recovery in MDD.

Depression is associated with high economic burden via lost work productivity and overall health care costs. The annual costs of depression are estimated at 83 billion US dollars (Greenberg et al., 2003). Higher health care costs in MDD largely arise from non-response to medication (Russell et al., 2004). In contrast to persistent depression, remission is associated
with significantly lower costs across mental health and general medical services (Simon et al., 2006). Given that persistent and recurrent MDD is associated with greater symptom severity, decreased quality of life, elevated risk of suicide, and increased medical costs, greater emphasis should be placed on the improvement of treatment quality and optimization in order to achieve full recovery.

2.1.3 Pathophysiology

Studies utilizing biochemical, neuroendocrine and neuroimaging strategies have uncovered that the psychobiology of MDD includes an interplay between monoamine signaling dysfunction, neurotrophin dysregulation, HPA disruption, and a number of central nervous system abnormalities (Davidson, Pizzagalli, Nitschke, & Putname, 2002; Delgado, 2000; Drevets et al., 1992; Palazidou, 2012).

The Monoamine Hypothesis of Depression

Clinical research strategies over the years led to the monoamine hypothesis of depression which posits that the underlying pathophysiology of depression is the depletion of serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA) levels in the central nervous system (Delgado, 2000). Biogenic amine neurotransmitter systems are extensively involved in the maintenance of the interconnected limbic, striatal and fronto-cortical neuronal circuits (Manji, 1992). Regulation of emotion states, sleep, appetite, arousal, sexual function and endocrine function is largely mediated by this interconnected network. Clinically, MDD involves disruption in all of these areas (Holsboer, 1995). Furthermore, it has been discovered that various pharmacological agents that act at monoamine receptor sites produce improvements in depression (Goodwin & Jamison, 1990). These findings led to the development of re-uptake inhibitors of specific monoamine systems. The efficacy of these selective re-uptake inhibitors further strengthened the monoamine
hypothesis of depression. Below, we will examine the literature pertaining to evidence of monoamine system implications in MDD.

Serotonin plays a significant role in the core symptoms of depression including mood, sleep, appetite, sexual activity, circadian patterns, motor activity and cognitive functions (Meltzer, 1990). Furthermore, it has been reported that deficits in the 5-HT regulation of NE and DA are important in the etiology of mood disorders (Depue & Zald, 1993). The neurons of the raphe nuclei are the principal source of serotonergic cells in the brain, which mainly project to the forebrain (Frazer & Hensler, 1999). There is converging evidence that both peripheral and central 5-HT dysfunction, are implicated in the pathophysiology of depression. Depressed individuals have been shown to have reduced platelet 5-HT, and total plasma tryptophan, the precursor to 5-HT (Quintana, 1992). This peripheral deficiency has been linked to the central hypoactivity of presynaptic 5-HT neurons (Maes et al., 1995). Interestingly, levels of both platelet 5-HT and plasma tryptophan have been shown to normalize with antidepressant treatment leading to clinical recovery (Quintana, 1992). Investigators have also reported reduced cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Asberg et al., 1984). A positron emission tomography (PET) study showed evidence of down-regulated or desensitized postsynaptic 5-HT$_{1A}$ transporter receptor binding potential in the raphe and hippocampus-amygda of depressed individuals (Drevets et al., 1999). Agonists to postsynaptic 5-HT$_{1A}$ receptors have been well documented in relieving depression and anxiety, by enhancing 5-HT neurotransmission (Naughton, Mulrooney, & Leonard, 2000). These findings suggest that a series of 5-HT-related biological parameters are altered in depression, some of which tend to normalize with antidepressant treatment.
Norepinephrine has an important role in executive functioning by regulating cognition, motivation, and intellect, which are fundamentally altered in depressed patients, greatly affecting their quality of life (Moret & Briley, 2011). A tightly clustered nucleus of NE-containing neurons in the brainstem pons called the locus coeruleus, is the primary source of NE in the forebrain and the sole source of NE in the cortex and hippocampus (Valentino & Bockstaele, 2008). Delgado and Moreno (2000) proposed that NE’s role in depression is specifically linked with the prefrontal cortex (PFC), where it plays an important role in the acquisition and consolidation of emotionally arousing memories, and also in fear conditioning through activity in the amygdala. Paradigms studying NE receptor function in depression tend to suggest supersensitivity of the inhibitory α2- adrenergic autoreceptor leading to an overall decrease in NE activity (Ressler & Nemeroff, 1999). Peripheral measures of NE function in MDD have yielded mixed results. Some studies demonstrate reduced urinary excretion level and cerebrospinal fluid level of NE and its metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG) in patients with depression (Linnolia et al., 1982; Schatzberg et al., 1989; Schildkraut et al., 1978), while other studies show elevated plasma levels of NE (Roy, Pickar, Linnolia, & Potter, 1985). The major problem in using urinary concentrations or even peripheral levels of a neurotransmitter as an indicator of brain neuronal dysfunction is that multiple sites of production exist for these compounds outside of the central nervous system. To overcome this problem, Lambert, Johansson, Agren, & Friberg (2000) used venoarterial plasma concentration gradients from precutaneously placed catheters in the internal jugular vein to demonstrate a deficit in NE in the brain of depressed patients. Interestingly, antidepressant treatment normalizes the reduction in NE turnover in MDD, leading to improved neurotransmission.
Several lines of evidence point to a crucial role of the DA system in the ventral tegmental area, in mood disorders. Dopamine neurons from here project to the limbic and fronto-cortical regions of the brain, which constitute the mesolimbic and mesocortical pathways, respectively. Both of these dopaminergic systems underlie the neural circuitry of reward, pleasure, and motivational behavior (Depue & Zald, 1993). Indeed, loss of pleasure and motivation are central features of MDD. In fact, excessively low DA activity is posited to be one of the hallmarks of depression. The strongest direct finding from clinical studies implicating this is low cerebrospinal fluid levels of the DA metabolite, homovanillic acid (Goodwin & Jamison, 1990). Hence, DA reuptake inhibitors such as bupropion that increase DA availability at the synapse have been shown to be efficacious antidepressants (Naranjo, Tremblay, & Busto, 2001).

Although there is a wealth of research implicating monoamine dysfunction in MDD, the pathophysiology of depression is far from being a simple deficiency of central monoamines. Over the years, the hypothesis that brain monoamine systems have a primary direct role in depression has been through several modifications (Heninger, Delgado, & Charney, 1996). It is now understood that depression involves other complex neurobiological systems such as neurotrophin and HPA dysfunction.

**Neurotrophin Dysregulation**

Neurotrophin dysregulation, particularly altered brain-derived neurotrophic factor (BDNF) signaling has been implicated both in the etiology of depression and in antidepressant drug action (Castren & Rantamaki, 2009). Neurotrophins such as BDNF play a pivotal role in neuronal survival, differentiation, and in mediating synaptic plasticity. Duman, Heninger & Nestler (1997) made the original observation that antidepressant drugs caused an increase in the synthesis of BDNF, which led to the suggestion that a deficiency in neurotrophic factor synthesis
and signalling could underlie the pathophysiology of depression and that antidepressants would act by increasing the levels of these growth factors. Several studies have supported this suggestion by showing that patients with MDD have reduced levels of serum BDNF, which is normalized by treatment (Karege et al., 2005; Monteleone, Serritella, Martiadis, & Maj, 2008; Sen, Duman, & Sanacora, 2008). Furthermore, animal models of depression have shown that the administration of BDNF into the hippocampus area induces antidepressant-like effects (Koponen et al., 2005; Siuciak, Boylan, Fritsche, Altar, & Lindsay, 1996; Shirayama, Chen, Nakagawa, Russell, & Duman, 2002). While stress has been shown to suppress BDNF synthesis in the hippocampus, antidepressants drugs have been shown to increase its synthesis and signalling in the hippocampus and PFC (Shimizu et al., 2003). Neurotrophin signaling disruption may therefore act as a mediator of altered neuronal plasticity in MDD.

**Hypothalamic-Pituitary-Adrenal Axis Dysfunction**

Depression is associated with hyperactive HPA response to psychological stressors, higher baseline cortisol concentrations, and dexamethasone non-suppression, all of which are indicative of impaired negative feedback in the axis (Palazidou, 2012). This poses important long-term consequences when persistently elevated levels of corticosteroids interacting with neurotransmitter systems and brain peptides result in neuroplastic alterations (Holsboer, 2001). Chronic stress and glucocorticoid administration have both been demonstrated to produce atrophy and death of vulnerable hippocampal neurons in rodents and primates (Sapolsky, 2000). In fact, hippocampal volume loss has been associated with recurrent MDEs and may represent a consequence of corticosteroid neurotoxicity (MacQueen et al., 2003). Interestingly, serotonergic mechanisms have been shown to modulate the negative feedback of glucocorticoids on central HPA-axis regulation (Maes et al., 1995).
These findings suggest that the pathophysiology of MDD is a complex interplay of alterations in the levels of monoamines, neurotrophins and HPA activity. Depression may be more directly caused by dysfunction in brain areas or neuronal systems modulated by the interaction of these complex systems. Moreover, antidepressant medication may improve depressive symptomology by balancing neurotransmission while also normalizing neurotrophin and HPA dysfunction, leading to restored function in brain areas modulated by these chemicals.

**Neuroanatomical Abnormalities**

Evidence from studies employing various imaging techniques such as magnetic resonance imaging (MRI), PET, and fMRI converge to implicate the PFC, anterior cingulate cortex (ACC), hippocampus and amygdala as critical neural substrates for depression. Below, we examine each of these brain regions and their involvement in the pathophysiology of depression.

The main functions of the PFC include problem solving, decision making and emotive control. The PFC can be divided into two major sections based on anatomical connectivity and functional specialization: 1) the dorsolateral prefrontal cortex (DLPFC), and 2) the ventromedial prefrontal cortex (VMPFC). The DLPFC receives input from sensory cortices and has dense connections with premotor areas, the lateral parietal cortex and the frontal eye fields (Barbas, 2000). The VMPFC has dense connections with the amygdala, which is involved in threat detection and fear conditioning. It also projects to the hypothalamus and periaqueductal gray, which mediate visceral autonomic activity associated with emotion, and the ventral striatum, which signals reward and motivation. While the DLPFC has mainly been associated with cognitive or executive functions, the VMPFC is largely linked with emotional or affective functions (Koenigs & Grafman, 2009). Results from imaging studies in individuals with MDD
demonstrate abnormally low levels of DLPFC activity (Baxter et al., 1989; Biver et al., 1994; Galynker et al., 1998). This reduction has been associated with emotive control, particularly reappraisal or suppression (Koenigs & Grafman, 2009). Recently, bilateral volume reduction of DLPFC gray matter was reported in late-life depression (Chang et al., 2011). In contrast, imaging studies in depression have indicated hyperactivity in VMPFC activity (Biver et al., 1994; Drevets et al., 1992; Greicius et al., 2007). Koenigs and Grafman (2009) discussed VMPFC’s role in depression as being related to the generation of negative emotion, and self-awareness or self-reflection. Interestingly, recovery from MDD with response to psychotherapy or antidepressant medication is associated with increased activity in DLPFC (Kennedy et al., 2001; Mayberg et al., 2000). Less consistent findings have been documented for VMPFC (Brody et al., 1999; Kennedy et al., 2001; Mayberg et al., 1999).

The ACC lies in a unique position in the brain, with connections to both the emotional limbic system and the cognitive PFC. Based on functional differentiation, at least two subdivisions of the ACC can be discerned: 1) the affect subdivision encompassing the rostral and ventral areas of the ACC (rACC and vACC respectively) and 2) the cognitive subdivision which includes the dorsal region of the ACC (dACC) (Davidson et al., 2002). The rACC and vACC have extensive connections with limbic and paralimbic regions including the amygdala, nucleus accumbens and periaqueductal grey. This subdivision is thought to be involved in regulating visceral and autonomic responses to stressful behavioural and emotional events, emotional expression and social behaviour (Ongür et al., 1998). The cognitive subdivision, on the other hand, is largely linked with the DLPFC and plays a role in response selection and processing of cognitively demanding information (Davidson et al., 2002). Studies using single photon emission computed tomography, PET and fMRI in depressed individuals have demonstrated
decreased regional cerebral blood flow and overall reduced activation in the dACC compared to controls (Beauregard et al., 1998; Drevets et al., 1997; Mayberg, Lewis, Regenold, & Wagner, 1994). Remission from MDD has been characterized by elevated activity in the dACC (Bench et al., 1995; Mayberg et al., 1999). Hypoactivation in the dorsal region of the ACC may be linked with impaired modulation of attention or executive functions and impaired monitoring of competition among various response options. Interestingly, elevated pre-treatment activity in the rACC is associated with eventual treatment response in MDD (Mayberg et al., 1997, Pizzagalli et al., 2001).

The amygdala is involved in recruiting and coordinating cortical arousal and neuroendocrine response to surprising and ambiguous stimuli as well as in emotional learning and memory (Palazidou, 2012). Structural imaging studies have shown enlarged amygdalar volume in patients with depression (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999; Tebartz van Elst, Woermann, Lemieux, & Trimble, 1999, 2000). Further, significant asymmetry in amygdalar volume with greater left than right, has been observed in MDD patients relative to controls, where left amygdala volume has been shown to positively correlate with depression severity (Mervaala et al., 2000; Tebartz van Elst et al., 1999). A meta-analysis of MRI studies, which took into account the possible role of medication on the size of the amygdala, demonstrated that amygdala volume is reduced in unmedicated depressed patients (Hamilton, Siemer, & Gotlib, 2008). Hence, the evidence from volumetric studies of amygdala depression has been inconsistent. Functional imaging studies have shown increased regional cerebral blood flow/glucose metabolism in the amygdala of depressed patients (Drevets et al., 1992). Abnormal activation of the amygdala has been shown to correlate with the severity of depression (Abercrombie et al., 1998; Drevets et al., 1992). Hyperactivation of
the amygdala may bias initial evaluation of and response to incoming stimuli which may help explain cognitive biases and rumination towards aversive or emotionally arousing stimuli in MDD (Davidson et al., 2002). Davidson and colleagues (2002) discussed an additional possibility for elevated amygdalar activation in MDD to represent a possible biological substrate for anxiety. This notion has been supported by evidence indicating that elevated levels of glucocorticoid hormones are associated with increased corticotropin-releasing hormones (CRH) in the amygdala which may increase anxiety, fear and expectation for adversity (Schulkin, 1994). Interestingly, following pharmacologically induced remission from depression, activation in the amygdala has been demonstrated to decrease to normative values (Drevets, 2001). However, in cases of familial pure depressive disease, elevated left amygdalar activation has been reported to persist during remitted phases, suggesting that at least in some subtypes of MDD, amygdalar activation may be a trait-like abnormality (Drevets et al, 1992).

The hippocampus plays an important role in episodic, declarative, and spatial learning and memory (Tulving & Markowitsch, 1998). Preclinical studies suggest that the amygdala exerts a modulatory influence on hippocampal-dependent memory systems, possibly through direct projections from the basolateral nucleus of the amygdala (Davis & Whalen, 2001). In humans, hippocampal activation elicited by aversive affective manipulations, has been shown to be associated with activation in the amygdala (Isenberg et al., 1999; Mirz, Gjedde, Sodkilde-Jorgensen, & Pederson, 2000). Imaging studies have reported reduced hippocampal volumes in patients with MDD (Bremner et al., 2000; Shah, Ebmeier, Glabus, & Goodwin, 1998; Sheline, Sanghavi, Mintun, & Gado, 1999). A systemic review and meta-analysis of volumetric studies of the hippocampus in MDD patients showed an 8% reduction of hippocampal volume in the left hemisphere of the brain versus a 10% reduction on the right (Videbech & Ravnkilde, 2004).
Interestingly, total number of MDE significantly correlated to the right but not left hippocampal volume reduction. Hippocampal dysfunction in MDD may be a reflection of inappropriate context-dependent emotional responses (Fanselow, 2000). Although it is not clear whether hippocampal dysfunction precedes or follows the onset of depression, it has been proposed that volume reduction in the hippocampus may be a consequence of repeated periods of MDE. Particularly, higher levels of cortisol (hypercortisolemia) resulting from negative feedback dysfunction in the HPA may lead to neuronal damage in the hippocampus (Carroll, Curtis, & Mendels, 1976). Indeed, the hippocampus is rich in glucocorticoid receptors and glucocorticoids have been shown to be neurotoxic (Sapolsky et al., 2000; MacQueen et al., 2003). Consistent with this theory, hippocampal volume loss in depression has been demonstrated to be associated with lifetime duration of MDD (Sheline et al., 1999), suggesting that long-term exposure to high levels of cortisol may lead to hippocampal atrophy. Interestingly, clinical improvement in MDD is associated with reversal of structural changes, with remitted patients demonstrating larger hippocampal volumes compared to non-remitted patients (Frodl et al., 2004). However, medication-free, remitted patients with a history of recurrent MDEs, have smaller hippocampal volumes, hence, such structural abnormalities may be a trait characteristic for MDD (Neumeister et al., 2005). This notion is supported by reports that adolescents at high risk of MDD, especially those who also experienced early life adversity and who are not currently depressed, have smaller hippocampal volumes (Chen, Hamilton, & Gotlib, 2010; Rao et al., 2010).

Based on the findings mentioned above, neurobiological models of depression have highlighted the roles of the PFC, ACC, amygdala and hippocampus in the pathogenesis of depression and in the manifestation of its symptomatology. It has further been established that balance amongst these structures and other important areas of the brain is responsible for
maintaining emotional stability and their malfunction is considered central to the pathophysiology of depression.

### 2.1.4 Antidepressant Treatment

Pharmacological treatment remains the most studied and best evidenced treatment for MDD. The Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines propose SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), and the newer ‘second-generation’ agents as first-line options for the management of MDD because they have better safety and tolerability profiles than older medications (Lam et al., 2009). The second-line treatment options include the TCAs, trazadone and quetiapine XR. Tricyclic antidepressants are recommended as second-line antidepressants because of tolerability and safety issues. Trazodone is also considered a second-line antidepressant because it is very sedating at therapeutic doses. Quetiapine XR also falls under the second-line antidepressant category due its tolerability profile and relative lack of comparative data with SSRIs and second-generation antidepressants. After second-line treatments have failed, treatment options include the monoamine oxidase inhibitors (MAOI) which are recommended as third-line because of tolerability and safety issues, and dietary and drug restrictions.

It is known that newer antidepressants, such as SSRIs, provide advantages in tolerability over antidepressants such as TCAs. However, even within the SSRI class, differences in efficacy or tolerability exist between individual drugs (Sanchez, Reines, & Montgomery, 2014). In a comprehensive analysis of remission with venlafaxine versus SSRIs, a modest advantage to fluoxetine was noted (Nemeroff et al., 2008). Kennedy et al. (2009) conducted a meta-analysis of 16 randomized controlled trials and reported superior efficacy for escitalopram compared to other SSRIs and SNRIs. A multiple-treatments meta-analysis integrating both direct (when
treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are compared with a common comparator treatment) of the efficacy and acceptability of 12 new-generation antidepressants showed a small superiority in response rates for escitalopram, mirtazapine, sertraline and venlafaxine compared to the others (Cipriani et al., 2009). Reboxetine was the only agent in the network meta-analysis to show a significantly lower response rate than the other antidepressants. An international group of experts assessed evidence from randomized, controlled trials (RCTs) and meta-analyses comparing antidepressant treatments and concluded that clomipramine, escitalopram and venlafaxine had definite superiority (defined as two RCTs that demonstrate superiority on the primary efficacy measure, or one RCT supported by consistent results from meta-analyses) while duloxetine, milnacipran and mirtazapine had probable superiority (criterion based on consistent positive results from meta-analyses of studies) against SSRI comparators (Montgomery et al., 2007).

Although an abundance of antidepressant medications exist for the treatment of MDD, one of the most significant challenges in the management of depression involves selecting the antidepressant medication that is most likely to lead to response or to remission for an individual patient. While remission is typically defined as absence or near absence of symptoms, response is usually defined as a 50% or greater improvement in depressive symptoms (Rush et al., 2006). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated that less than 50% of depressed patients respond to the first antidepressant they try and even less, that is, approximately 30% of patients achieved full remission (Trivedi et al., 2006). The probability that an individual will achieve remission decreased steadily with each new treatment failure. Patients who fail to achieve full remission have a more recurrent and chronic course of
illness, increased medical and psychiatric co-morbidities, greater functional burden, and increased social and economic costs (McIntyre and O’Donovan, 2004). Hence, the management of depression remains a constant challenge in clinical practice, largely due to the fact that initial treatments frequently do not lead to remission and recovery.

The CANMAT guidelines propose that when there has been no improvement following an optimized (i.e., increased) dose of an antidepressant, the first step should be to re-evaluate diagnostic issues such as depressive subtype and comorbidity, along with treatment issues such as adherence, side effects and suicidality (Lam et al., 2009). The majority of studies investigating pharmacological approaches for limited response have focused on treatment-resistant depression (TRD), defined as failure (i.e., lack of improvement, or 20% reduction in depression scores) following adequate trials of two or more antidepressants. Pharmacological strategies for TRD include switching to a different antidepressant monotherapy, or adding another agent to the first antidepressant. The term “augmentation” has been used to describe adding a medication that is not considered an antidepressant (e.g., lithium or thyroid hormone), while “combination” refers to adding a second antidepressant to the first (Lam et al., 2009). In practice, it has been well documented that approximately 6-8 weeks of “watchful waiting” are required to observe full recovery with a certain medication (Bauer et al., 2007; Fochtmann and Gelenberg, 2005). Sequential treatment in which a subsequent treatment is utilized either alone or in combination further extends the period of watchful waiting. Delayed treatment significantly delays recovery which leaves patients with prolonged suffering, risk of discontinuing treatment efforts and heightened risk of suicide (McIntyre and O’Donovan, 2004). Moreover, lack of treatment response is cited as one of the main reasons for early discontinuation of antidepressant treatment (Hodgkin et al., 2007). Early discontinuation rates of antidepressant
treatments are high with about 30% of patients discontinuing medications within 30 days and more than 40% discontinuing within 90 days (Olfson et al., 2006). Hence, the current treatment approach of lengthy trial-and-error periods with different antidepressant medications before a successful medication is identified, is seriously flawed. The management of depression could be greatly improved with indicators early in the course of treatment that predict the likelihood of response, remission and non-response.

2.1.5 Escitalopram

Given that the treatment trial in our study involved standardized antidepressant treatment with escitalopram, for which we investigated the predictive properties of EEG-derived biomarkers during resting state, a brief overview of the pharmacology of escitalopram is warranted.

Escitalopram is commonly referred to as an SSRI, but it also has well-documented allosteric properties, and thus can be further classed as an allosteric serotonin reuptake inhibitor (ASRI) (Sanchez et al., 2014). Escitalopram is the S(+) -enantiomer of citalopram, a 1:1 mixture of the R(−)-enantiomer and S–enantiomer. In studies investigating the enantiomers individually, the S–enantiomer has been shown to be responsible for nearly all of the 5-HT re-uptake inhibition and antidepressant effect of citalopram (Hogg & Sanchez, 1999; Hyttel, Bogeso, Perregaard, & Sanchez, 1992). These findings led to the development of escitalopram as an antidepressant on its own, and in 2002, it was launched as a new single-enantiomer drug (Sanchez, Bogeso, Ebert, Reines, & Braestrup, 2004). Since that time, escitalopram has been shown to be more effective than a range of other antidepressants.

Sanchez and colleagues (2014) recently reported that among the three most widely prescribed SSRIs including paroxetine, sertraline, and escitalopram, escitalopram demonstrates
superiority in combined efficacy and tolerability. Non-clinical data have offered insight into the possible mechanisms by which escitalopram could be more clinically advantageous. In addition to blocking the 5-HT re-uptake transporter (SERT), escitalopram also binds to an allosteric site on the complex (Kennedy et al., 2009). This dual action of binding to two sites on SERT (both the primary site and the allosteric site) is hypothesized to be responsible for a longer binding to, and therefore greater inhibition of SERT by escitalopram (Sanchez, 2006). Chen and colleagues (2005) demonstrated that escitalopram increases SERT inhibition through an allosteric mechanism more significantly than citalopram, sertraline or paroxetine, whereas other antidepressants (fluoxetine, venlafaxine and duloxetine) do not exhibit any allosteric effects.

As an ASRI, escitalopram is somewhat different from the classical SSRIs. Moreover, its unique pharmacological properties such as its dual effect on SERT may help explain its clinical superiority over other antidepressant medications.

2.2 Electroencephalography

Electroencephalography is a measure of the brain’s spontaneous electrical activity acquired from electrodes placed on the surface of the scalp. EEG could also measure evoked activity as in event-related potential (ERP) studies (see Chapter 2.2.4: Event Related Potentials). Recorded activity at each electrode generally represents the gross measure of electrical activity arising from a number of different neurons in cortical areas surrounding the electrode. EEG is a representation of the difference in voltage between two different cerebral locations plotted over time. Hence, the scalp EEG signal can be modified by electrical conductive properties of the tissues between the electrical source and the recording electrode on the scalp such as dura mater, cerebrospinal fluid, skull, and scalp, conductive properties of the electrode itself such as electrical properties of the materials the electrode is made of and size of the electrode, as well as
the orientation of the electrical generator to the recording electrode (i.e. the extent to which the generator is aimed towards the electrode) (Olejniczak, 2006).

2.2.1 The History of EEG

The earliest recordings of electrical currents in the brain were observed in 1875 by an English physician, Richard Caton (Colura, 1993). Caton recorded the activity of electrical currents in the exposed brains of rabbits and monkeys using a mirror galvanometer (Caton, 1875). He studied variations in electrical activity linked with sleep and wakefulness, anesthesia and death. He also recorded electrical responses to the presentation of food and stimulation of the skin, and retina (Colura, 1993). Hence, these were some of the first recordings of motor-related and sensory evoked potentials. Caton also investigated brain regions in relation to motor activity such as head movement, chewing and movements of the eyelids, in animals (Caton, 1877). Therefore, Caton’s efforts could be further understood in the context of functional topography, making him the first EEG brain mapper.

Hans Berger, a German neurologist was the first to record electrical activity in the human brain in 1924 (Teplan, 2002). Berger used ordinary radio equipment to amplify the electrical currents generated by the brain and found that this activity can be recorded without opening the skull (Berger, 1929). Berger was the first to observe that when an individual was at rest and relaxed, rhythmic wave sequences were generated at about 10 Hz but when the individual became alert, this rhythm disappeared and was replaced by a new, higher frequency varying between 15 and 50 Hz (Gloor, 1969). Berger introduced the terms “alpha wave” and “beta wave” to describe the relaxing waves and the alertness waves, respectively. The occurrence of alpha and beta waves in states of relaxing drowsiness and alertness make up one of the major characteristics of the EEG. Berger further went on to observe that EEG activity changed
according to the functional state of the brain, such as in sleep, anesthesia, lack of oxygen and in neurological diseases, like epilepsy (Gloor, 1969).

Caton and Berger’s accomplishments laid the foundations for many of the present applications of EEG. They are both responsible for introducing the term ‘electroencephalogram’ as the first for describing brain electric potentials. Their contributions to experimental and clinical EEG are substantial and have been detailed elsewhere (Gloor, 1969; Haas, 2003; Ormerod, 2006).

2.2.2 Source of the EEG signal

The source of the EEG signal arises from the temporal and spatial summation of thousands of postsynaptic potentials (PSPs) generated by pyramidal cells found in the cortex of the brain (Olejniczak, 2006). Pyramidal neurons can be considered dipoles whose axes are oriented perpendicular to the surface of the cortex. Source and sink are poles of each dipole where source represents current inflow at the synapse and sink represents the current outflow at the soma, body of the neuron. Cortical cells have a resting membrane potential, which is the difference in the electrical potential between the interior and exterior spaces of the cell, usually measuring -65 mV (varying from -40 to -80mV) (Teplan, 2002). The membrane potential can be reduced to a critical level at which the membrane loses its charge completely, generating an action potential of brief duration that is propagated along the axon. Action potentials have an amplitude of 110 mV and only last about 1 ms. They are referred to as the all-or-none phenomena because they do not vary in amplitude. The action potential itself causes only a very brief local current that does not penetrate far into the extracellular space. The arrival of an action potential from an afferent neuron causes a temporary change in permeability to certain ions in the postsynaptic membrane of the efferent neuron. This generates a local change in the resting
potential, either an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP). An EPSP is a transient partial reduction in membrane potential which is caused by an increased local permeability to sodium and potassium ions. Since sodium is positively charged, its entry into the cell makes the negative intracellular resting potential less negative (i.e. partially depolarizes the cell). In contrast, an IPSP is a transient increase in intracellular negativity produced by the entry of negatively charged chloride ions into the cell or the exit of potassium ions from the cell. These changes lead to hyperpolarisation of the cell, making it less likely to fire.

The summation of PSPs that occurs mainly at the vertically oriented large pyramidal cells of the cortex gives rise to the EEG signal. Excitatory postsynaptic potentials and IPSPs sum up in time through synchronization and in space due to cortical architecture: closed electrical fields (Olejniczak, 2006). A single neural event such as an action potential does not contribute to the EEG signal as it is too small and too short to be detected on the scalp. The pyramidal cells of the cortex are especially suited for the role of PSP summation because the dendrites of these neurons extend through all layers of the cortex, guiding the flow of currents and these cells are closely packed into parallel functional vertical columns, facilitating spatial summation. Moreover, groups of these cells receive similar input and respond to it with changes that produce electrical currents of similar direction and timing and input to such cells is magnified by the number of synapses on each cell (Teplan, 2002). Hence, the principal generators of EEG fields measured on the surface of the scalp are graded synaptic potentials constituting EPSPs and IPSPs of the pyramidal neurons.

The synchronization of PSPs that lends to temporal summation is due to the interaction between thalamic nuclei and the cortical region (Olejniczak, 2006). The main subcortical EEG
rhythm generator is considered the dorsal thalamus. Hence, EEG synchronicity depends on the interaction between the thalamus and the cortex where the thalamus is responsible for pacing rhythmical activities and the cortex is responsible for providing a synchronous output in response to thalamic input in the form of recordable potentials at the level of the scalp. Two leading models of how the thalamus interacts with the cortex to produce such synchronous activity have been proposed: the facultative pacemaker theory and the nucleus reticularis hypothesis.

Andersen and Anderrson (1968) proposed the facultative pacemaker theory which assumes that thalamocortical relay neurons send fibers to the cortex as well as give off branches that turn back and end on thalamic inhibitory interneurons (biofeedbackservomechanism). Hence, the firing of the thalamocortical neurons, not only affects cortical neurons but also excites thalamic inhibitory interneurons. In turn, the interneurons inhibit a large number of thalamocortical cells. Once the period of inhibition ends, the pool of thalamocortical neurons overshoots into excitation, giving off a synchronized volley which again affects both cortical cells and the inhibitory thalamic interneurons. And this pattern continues repeatedly creating rhythmical discharges (Andersen & Anderrson, 1974).

The nucleus reticularis hypothesis assumes that the nucleus reticularis thalami are responsible for producing EEG synchronous activity (Buzsaki, 1991). The nucleus reticularis is a thin layer of neurons covering much of the anterior, ventral and lateral surfaces of the thalamus. These so called “pacemaker cells” release the inhibitory transmitter gamma-aminobutyric acid (GABA) in rhythmic bursts which are directed to the neurons of the dorsal thalamus and rostral brainstem. The excitatory thalamocortical cells have the intrinsic property of producing bursts of depolarizations as a rebound response to each inhibitory stimulus of the
pacemaker cells (Olejniczak, 2006). Hence, stimulation of the thalamocortical cells of the thalamus produce rhythmic excitation at the level of the cortex.

In conclusion, EEG rhythmicity appears to be dependent on the interactions between the cortex and thalamus. The rhythmic pattern of the EEG wave is generated by cyclical changes caused by synchronizing impulses from thalamocortical neurons, which establishes current loops that produce rhythmic neuronal activity in the cortex.

2.2.3 EEG Rhythms

The EEG recordings of an individual are sensitive to a continuum of cognitive and emotional states ranging from resting, alertness, stress, sleep, etc. Berger, the first human electroencephalographer recognized that the brain waves he recorded changed in frequency and amplitude with the altering state of the individual. He observed higher frequency and smaller amplitude waves in states of arousal and very large amplitude and slow frequencies in sleep (Hugdahl, 1995). In the present day, quantitative EEG allows for voltage potentials measured at the level of the scalp to be digitally sampled and then spectrally analyzed. The raw EEG signal can be decomposed into its constituent frequency components by means of Fast-Fourier Transform (FFT). The FFT is a mathematical method for transforming a function of time into a function of frequency. This is often described as decomposing the EEG time series into a voltage by frequency spectral graph called the spectrum. Power is defined as the square of the EEG magnitude, and magnitude is the integral average of the amplitude of the EEG signal. Power can either be measured as absolute power ($\mu$V$^2$) or relative power (%). Absolute power describes the amount of power in a frequency band at a given electrode and relative power is the percentage of power contained in a frequency band, relative to the total power across the entire spectrum, computed separately for each electrode (Cook et al., 2002).
The EEG spectral domain can be conventionally divided into the alpha, beta, theta and delta frequency bands. Brain oscillations in these frequency bands are correlated with various functions depending on task, sensation and structures (Basar, Basar-Eroglu, Karakas, & Schurmann, 2001). The best-known and most extensively studied EEG rhythm of the human brain is the normal alpha rhythm. The alpha rhythm has a characteristic 8-13 Hz frequency with a mid range amplitude that typically measures 50 μV (Hugdahl, 1995). Alpha is most easily observed from the posterior part of the brain such as the parietal and occipital regions (Shagass, 1972). Closing the eyes and relaxation induces alpha activity while opening the eyes attenuates the alpha wave. Alpha oscillations are thought to reflect a neural baseline with “inattention” as they have been shown to inversely correlate with functional cortical activation in lateral frontal and parietal cortices that are known to support attentional processes (Laufs et al., 2003). Hence, while the presence of alpha band activity indicates reduced cortical activity in underlying generators, alpha oscillations are typically abolished during arousal or cognitive activity.

The beta waveform is the most common form of brain wave observed in the normal adult waking EEG. Beta waves are of higher frequency than alpha waves, ranging from 13 to 30 Hz and the amplitude of beta activity is almost always lower than that of the activity in the other frequency bands (Hugdahl, 1995). Beta activity occurs over most parts of the scalp, often with frontal predominance although posterior dominance may also occur (Neidermeyer & da Silva, 2005). Beta activity has been shown to correlate with thinking and active concentration, hence, beta rhythms are thought to index spontaneous cognitive operations during conscious rest (Gevins et al., 1979). Opposite to alpha band activity, beta rhythms have been shown to positively correlate with cortical activation in retrosplenial, temporo-parietal, and dorsomedial prefrontal cortices, regions comprising the default mode network (DMN), a resting state neural
network (Laufs et al., 2003). Since beta activity is recorded during arousal and the alpha wave is attenuated, beta band activity is sometimes synonymously referred to as alpha desynchronization or alpha blocking (Hugdahl, 1995).

Theta waves are slow, high amplitude waves with frequencies ranging between 4-8 Hz. Theta-band activity appears to play a role in memory and emotion processing (Mitchell, McNaughton, Flanagan, & Kirk, 2008). Scalp EEG recordings in humans have demonstrated local increases in theta activity over medial frontal electrode sites during successful encoding of new information (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996). Activity in the theta band has also been reported to correlate with working memory and/or sustained attention (Mitchell et al., 2008). Mid-frontal theta has additionally been localized to the rACC (Pizzagalli, Oakes, & Davidson, 2003), an area of the brain shown to be functionally abnormal in MDD patients. Theta activity is also a prominent feature of light sleeping and dreaming such that it reflects a state of drowsiness, a preconscious state just upon waking and just before falling asleep (Hugdahl, 1995).

Delta waves are very irregular slow wave patterns with frequencies of 4 Hz and lower and variable high amplitudes. Delta activity tends to be prominent in midline fronto-central regions (Hugdahl, 1995). They are a prominent feature of alter sleep stages, especially when the subject is in deep sleep (Nofzinger et al., 2000). More recently, frontal delta band power in the DMN was shown to highly correlate with fMRI BOLD signal in the parahippocampal gyrus, suggesting that delta frequencies may play a role in memory processes (Neuner et al., 2014).

Frequency band power has been shown to characterize patients with MDD relative to healthy controls and other patient groups (see Chapter 2.3 EEG Abnormalities in Major Depressive Disorder), and has also been shown to help predict antidepressant treatment response.
(see Chapter 2.4 EEG Biomarkers of Antidepressant Treatment Response in Major Depressive Disorder).

### 2.2.4 Event Related Potentials

Different from spontaneous EEG, evoked potentials represent electrical potentials recorded from the central nervous system following the presentation of a stimulus. Event-related potentials (ERPs) are a measure of change in voltage, which represent brain activity elicited in response to sensory stimulation (i.e., visual or auditory). Recorded ERPs comprise distinctive peaks and troughs reflective of positive and negative fluctuations in voltage and are referred to as ‘components’. Different components have been identified and named based on the direction of the waveform deflection (P for positive and N for negative) and on the specific time course of the waveform at which it occurs post-stimulus (Picton et al., 2000). Event-related potentials can be separated out, for example, using either a spatial or temporal principal component analysis (PCA). To extract the ERP of interest, EEG is recorded time-locked to the presentation of the stimuli or responses of interest and averaged together to increase the signal-to-noise ratio. The reader is referred to other sources for more detailed description of ERP recording methodology and analysis (Handy, 2004; Nunez & Srinivasan, 2006; Picton et al., 2000). Mainly, two ERP components have been the focus of investigation in depression including the P300 (or P3) and the Loudness Dependent Auditory Evoked Potential (LDAEP).

The auditory evoked P300 component measured as part of the oddball paradigm, is one of the most widely studied ERPs. The oddball paradigm typically involves presentation of auditory tones, the majority of which are identical with random deviant tones occurring at a low frequency. When the ERPs elicited by the standard tones are compared with those related to deviant ones, the deviant ERPs demonstrate a large positive deflection occurring around 300 ms
following the onset of the tone (Alhaj et al., 2011). This ERP index is believed to reflect the cognitive processes of attention and working memory updating (Mulert et al., 2004; Volpe et al., 2007). Although the precise neurobiological basis of the P300 is unknown, it is thought to originate from multiple cortical areas. The P300 component has been shown to be an illness marker of MDD and a biomarker of antidepressant treatment response (see Chapters 2.3 and 2.4, respectively).

The LDAEP is a measure of the N1/P2 ERPs, taken 100-200 msec after presentation of an auditory stimulus. The amplitude of the waveform changes with increasing loudness of the stimulus and is thought to reflect cortical processing strength. The LDAEP slope is constructed by plotting the N1/P2 amplitude against tone intensity and is thought to have an inverse relationship to the magnitude of 5-HT neurotransmission in the primary auditory cortex (Hegerl, Gallinat, & Juckel, 2001). A steep LDAEP slope likely reflects 5-HT hypoactivity and a shallow LDAEP slope is thought to reflect enhanced 5-HT activity (Mulert et al., 2005). The LDAEP has been shown to have promise as a predictive biomarker of treatment outcome in MDD (see Chapter 2.4).

2.2.5 Factors affecting EEG

Sleep

Objective information about the process of sleep can be obtained using the methodology of polysomnography (PSG). Three fundamental PSG measures include brain wave activity as measured by EEG, muscle tone measured by electromyogram, and eye movements recorded with an electro-oculogram. When experts chart sleep stages on a hypnogram, the pattern that the different levels create is referred to as sleep architecture. Sleep architecture can be separated into two main components, namely non-rapid eye moment (NREM) and rapid eye movement (REM)
sleep. EEG patterns consist of low-voltage rhythmic alpha activity during the transition from wakefulness to sleep. This is immediately followed by periods of both NREM and REM sleep that alternate in a cyclic fashion.

The first hours of sleep normally include a high percentage of time spent in NREM sleep, divided into four stages with transition from one stage to the next. Hence, the process of falling asleep is indicated by subsequent occurrences of sleep stages 1, 2, 3 and 4. Stages 1 and 2 are relatively light stages of sleep with diminished muscle activity, little or no eye movements, and a low arousal threshold leaving individuals to be easily awoken (Erwin, Somerville, & Radtke, 1984). Stage 1 sleep described as transition from drowsiness to light sleep, is characterized by a slowing of EEG activity and mainly low voltage, mixed frequency theta waves. Theta activity continues into stage 2 sleep with interspersed, distinctive waveforms called sleep spindles defined by the characteristic ‘spindle-like’ increase and decrease of amplitudes over consecutive 12-14 Hz oscillations (Pinel, 1992). The duration of spindles may range anywhere from 0.5 to 3 seconds (Dijk, 1995). Stages 3 and 4 are collectively known as slow wave sleep (SWS) or delta sleep because they are characterized by synchronized slow (0.5-2 Hz), high amplitude delta waves. Slow wave sleep is considered deep sleep as it has a much higher arousal threshold, eye movements are not observed and muscle tone continues to decline (Hirshkowitz, 2004). During this period, some restorativ processes in the body take place. For instance, growth hormone is released and further, SWS follows a homeostatic pattern; the longer the time since last sleep, the more SWS occurs (Wilson & Argyropoulos, 2005). Typically, stage 3 is considered delta sleep in which, less than 50 percent of the waves are delta waves, and in stage 4, there is a quantitative increase such that they represent more than 50% the EEG tracing (Pinel, 1992). NREM sleep is maintained through oscillations between the thalamus and the cortex. Sleep spindles, a
hallmark of stage 2 sleep, are generated by bursts of hyperpolarizing GABAergic neurons in the reticular nucleus of the thalamus, which project to and inhibit thalamocortical relay neurons, which in turn project to the cortex. The relay neurons discharge after GABA-release related inhibition subsides, which subsequently results in synchronized EPSPs in the cortex, which become visible by EEG (Olejniczak, 2006). Delta waves representative of SWS are produced by interactions from both thalamic reticular and cortical pyramidal sources (Steriade, 2003). Interestingly, lesions of the nucleus reticularis abolish sleep spindle oscillations but not slow waves (Dijk, 1995). Hence, while sleep spindles are synaptically driven, slow waves can appear in isolated thalamocortical and cortical neurons as long as their membrane potential is sufficiently hyperpolarized.

REM sleep is characterized by faster EEG activity (alpha waves similar to wakefulness) that allows for dream sleep to occur. REM is also characterized by frequent, horizontal rapid eye movements and atonia of the skeletal muscles (Wilson & Argyropoulos, 2005). However, many small muscle twitches may occur against the low EMG background and cardio-respiratory irregularities also often accompany REM. The physiology of REM sleep is so dramatically different from the other four stages that sleep has been distinguished into the two major categories of sleep: NREM and REM sleep.

Aging

A large body of literature reports aging effects on EEG activity, the majority of which support altered EEG alpha power. Alpha power has been shown to reduce with age in healthy people, especially during the latter part of life (Babiloni et al., 2006; Rossini, Rossi, Babiloni, & Polich, 2007). Studies investigating the effects of age on slower EEG frequencies such as theta and delta have reported mixed results. Some studies have found that the power of these slow
EEG frequencies increased with age, described as an overall “slowing” of the EEG activity (Klimesch, 1999; Rossini et al., 2007). In contrast, there are studies that found no changes in delta or theta power with increasing age (Caplan et al., 2015) or a decreased power in elderly compared with young adults (Babiloni et al., 2006; Cummins & Finnigan, 2007). Babiloni and colleagues (2006) dispute that EEG slowing does not necessarily reflect an increase of slow wave activity with age, in the context of good health status. That is, a significant increase of slow EEG activity might not be a marker of physiological aging and rather, it may be an indicator of subclinical cognitive deterioration such as mild cognitive impairment or Alzheimer’s disease, in which pathologic increases in slow-wave EEG activity are generally observed even in the earlier stages of the disease (Babiloni et al., 2006; Rossini et al., 2007). This might explain why decreased slow EEG activity or no change is observed in some healthy elderly samples compared with healthy young people.

**Gender**

Beside age-related effects on EEG activity, there is also some evidence of gender differences in electrical brain activity (Kober, Reichert, Neuper, & Wood, 2016). A few studies have reported elevated delta and theta power in women compared with men while undertaking various cognitive tasks (Bekkedal, Rossi, & Panksepp, 2011; Güntekin & Basar, 2007; Klados et al., 2009; Kober & Neuper, 2011). As discussed by Kober and colleagues (2016), gender differences in EEG activity have been attributed to underlying biological mechanisms, such as callosal size or interhemispheric transmission efficacy (Davatzikos & Resnick, 1998; Hoffman & Polich, 1999), cultural and environmental influences, and gender differences governing cognitive processes in the brain (Davatzikos & Resnick, 1998; Klados et al., 2009), or genetic factors (Volf, Belousova, Knyazev, & Kulikov, 2015).
2.2.6 Clinical Utility of EEG

The possible utility of EEG in neuropsychiatric disorders has been highlighted since the very beginning of EEG research after the first descriptions of human scalp recordings of neuronal activity by Hans Berger (Olbrich & Arns, 2013). Indeed, EEG has been used in understanding neurological and psychiatric conditions, specifically in aiding diagnosis, classification, prognosis and/or predicting response to treatment (Alhaj et al., 2011; Jaworksa & Protzner, 2013; Olbrich & Arns, 2013; Sayar, Onen, & Tan, 2013). EEG has clear advantages as it is non-invasive, widely available, easy to administer and has a relatively low cost. Further, the EEG provides a temporal resolution in a time scale of milliseconds, which is the time-frame at which neuronal activity, and especially cognition, takes place. The EEG does not assess a proxy marker of neuronal activity, such as blood oxygenation or glucose utilization, but instead directly captures on-going electric activity from the brain (Olbrich & Arns, 2013). These features of EEG make it a good candidate for routine clinical use of neuropsychiatric disorders. This is not to say that EEG is not without important limitations, namely lower spatial resolution compared with fMRI and other imaging techniques. For a detailed discussion of the limitations of the clinical utility of EEG, please see Chapter 2.2.7: Limitations of EEG.

Neuropsychiatric conditions that benefit from the use of EEG include conditions such as delirium, dementia, and attention deficit hyperactivity disorder (ADHD). Delirium and dementia are both neurodegenerative diseases that are marked with abnormal EEG findings. Delirium is a sudden severe confusion that is usually temporary and reversible. Patients present with diffuse slowing of slow waves that is synchronous and symmetrical involving both hemispheres, and they also show a marked decline in alpha rhythm (van der Kooi, Slooter, van Het Klooster, & Leijten, 2014; van Dellen et al., 2014). Dementia is a progressive and irreversible decline of
Abnormal EEG findings in dementia include diffuse slowing of delta and theta waves. As the disease progresses, alpha rhythm slows and some patients show epileptiform discharges (myoclonic jerks or seizures) (Adamis, Sahu, & Treloar, 2005). Brain waves have been used as a predictor of dementia’s progression, that is EEG slowing and abnormal alpha in the early stages (mild cognitive impairment) of dementia are associated with worse outcome at follow-up: greater decline in praxis, more extrapyramidal symptoms and greater risk for institutionalization (Adamis et al., 2005). Attention deficit hyperactivity disorder is a neurodevelopmental disorder marked with symptoms such as inattentiveness, impulsivity and hyperactivity. A consistent EEG finding in ADHD includes increased theta in frontal and central areas which seems to continue into adulthood (Loo & Barkley, 2005). Another finding includes decreased beta which seems to normalize with adulthood, however, this EEG finding is only found in some but not all children with ADHD. Based on these two findings, investigators who study EEG abnormalities in ADHD tend to examine and report on theta/beta ratio (TBR). The food and drug administration (FDA) approved the TBR as part of the Neuropsychiatric EEG-Based assessment aid (NEBA) in diagnosing ADHD (Lenartowics & Loo, 2014).

Abnormalities of EEG have also been reported elsewhere in other psychopathological conditions including schizophrenia, panic disorder, and mood disorders. Schizophrenia is a brain disorder that affects a person’s ability to perceive reality. Individuals with schizophrenia are affected by hallucinations, delusional thoughts, social withdrawal, and disturbed thinking. A consistent EEG finding in the schizophrenia population includes elevated low-frequency power in delta and theta bands in frontal areas, at rest (Boutros et al., 2008). Individuals also demonstrate lower power in the alpha band and elevated beta power (Kam et al., 2013). Panic
disorder is a type of anxiety disorder that is plagued by recurrent and unexpected panic attacks. Features that distinguish them from other types of anxiety are their abrupt onset, intensity and brief duration. Individuals with panic disorder tend to display abnormalities in EEG, specifically, decreased absolute alpha power in the frontal cortex, and elevated slow wave activity in temporal regions (Adamaszek, Olbrich, & Gallinat., 2011). Sometimes, epileptiform activity including spikes and/or sharp waves can be detected in the EEG of those suffering from panic disorder (Carvalho et al., 2013). Mood disorders encompass both unipolar depression and bipolar disorder. EEG findings in patients with MDD will be discussed in detail in chapter 2.3. Bipolar disorder also known as manic depression involves unusual shifts of mood and energy. Bipolar disorder patients experience distinct emotional states called mood episodes that include mania, hypomania and major depression. Manic episodes are defined as distinct periods of exceptional euphoria or irritability encompassed by elevated levels of energy and activity that last at least one week in duration or lead to hospitalization (Geller et al., 2002). Individuals with bipolar disorder demonstrate elevated theta activity, along with diminished alpha and increased beta activity (Hughes & John, 1999; Kam et al., 2013).

While neurodegenerative disease and ADHD seem to benefit from routine EEG use, EEG is not being used clinically in the management of other neuropsychiatric illnesses, despite research indicating the diagnostic value of clinical EEG in detecting abnormal brain activity. One reason for this is because different researchers investigating the same EEG parameters within an illness have reported heterogeneous results. Perhaps, such discrepancies could be explained by the heterogeneity of patients. Due to the heterogeneous nature of psychiatric disorders, it would be naive to expect a single biological test such as EEG to identify all patients that are classified as having a particular illness. Rather, it is more likely that EEG abnormalities
will be able to identify one or more subgroups within a psychiatric disorder. Another important limitation to consider from the evidence above is that some EEG abnormalities are not unique or specific to a certain illness, as they have been reported elsewhere in different clinical populations. For example, elevated slow wave activity in the theta and delta bands has been reported in depression, schizophrenia, developmental disorders, and in neurodegenerative diseases (Hughes & John, 1999). An EEG abnormality that is equally common to disorders that frequently need to be differentiated from one another is not likely to be useful clinically. Hence, to improve the clinical utility of EEG in psychiatric practise, markers not only need to be demonstrated as being deviant from healthy controls but it is also essential that they are shown to be different from appropriate comparison groups that commonly appear on the differential diagnostic list.

2.2.7 Limitations of EEG

The Inverse Problem

The major limitation to consider with the use of EEG technology, compared to other neuroimaging techniques is low spatial resolution, whereby one cannot infer with certainty the spatial location of sources in the brain from electrical potentials on the scalp, a difficulty that is called the EEG ‘inverse problem’. EEG mainly records electrical activity from superficial cortical areas. As mentioned before, the scalp EEG signal can be modified and attenuated by electrical conductive properties of the tissues between the electrical source and the recording electrode on the scalp. The degree of this attenuation is determined by the degree of synchronization of the postsynaptic potentials, the orientation of the neurons and the size of the participating area of cortex (Alhaj et al 2011). All of these factors work against localizing the source of the electrical activity recorded at the scalp.
A unique solution to the localization of scalp electric activity is the equivalent current dipolar technique which places constraints on data, such as assuming that the potentials are generated by a specified small number of dipolar sources (Koles, 1998; Scherg & Von Cramon, 1986). Other methods include brain electrical source analysis, weighted minimum norm estimation and low-resolution electromagnetic tomographic analysis (LORETA) (Aljah et al., 2011). Compared to equivalent current dipolar technique, these models do not assume a limited number of dipolar point sources on a given known surface.

LORETA uses multichannel surface EEG recording to directly compute a current distribution through the full brain volume. The model assumes that neighbouring neurons are simultaneously and synchronously activated in order to find a unique solution for the 3-dimensional (3D) distribution among the infinite set of different possible solutions. The computational task is to select the smoothest of all possible 3D current distributions, and the result is a true 3D tomography where localization is preserved with a certain amount of dispersion (Pascual-Marqui et al., 1994). Although the inverse problem in EEG can be approached with various source localization methods such as LORETA, it is important to note that these methods are also subjected to limitations of spatial resolution (Alhaj et al., 2011).

The future of EEG for clinical application may lie in the coupling of digital methods of signal analysis with those of image processing, like in simultaneous EEG and fMRI. Functional magnetic resonance imaging works by detecting the changes in blood oxygenation and flow that occur in response to neural activity, referred to as the blood-oxygen-level dependent (BOLD) signal. When a brain area is more active, it consumes more oxygen and to meet this increased demand, blood flow increases to the active area. fMRI can be used to produce activation maps showing which parts of the brain are involved in a particular mental process. fMRI has
significant advantages over other imaging techniques such as PET as it is non-invasive and doesn’t involve radiation, making it safe for the subject, and it also has excellent spatial resolution. However, a major disadvantage fMRI suffers from is a lack of temporal resolution because a fMRI map with regional activations does not readily permit inferences about when and in which order the activations have occurred. Moreover, fMRI is costly and it utilizes a proxy marker of neuronal activity. The lack of temporal resolution in fMRI is analogous to the spatial inverse problem in EEG. Moreover, non-synchronous neuronal activity that will not be present in an EEG signal, may be detectable using fMRI techniques. Conversely, neuronal activity that is not associated with a BOLD oxygen signal and hence not detectable by fMRI may lead to an EEG signal (Alhaj et al., 2011). Since the strengths and weaknesses of EEG and fMRI are complementary, simultaneous EEG-fMRI would allow the recording of human brain activity with both high spatial and high temporal resolution.

**EEG Artefacts**

Another important limitation of EEG technology are artefacts, which are unwanted electrical activity arising from different sources, other than cerebral activity. They can be classified as physiological artefacts such as those arising from a patient’s own generator sources including eye movement, muscle movement, perspiration, and electrocardiogram or extraphysiological artefacts such as those that are externally generated by noise arising from the EEG equipment itself, or from the surrounding environment. EEG artefacts need to be carefully recognized and corrected for by using techniques such as independent component analysis (ICA). The aim of the ICA approach in EEG analysis is to separate independent activities, generated by different cortical sources. It is a computational method that attempts to identify a set of component weights that represent filters which linearly decompose a set of EEG data.
This allows ICA to minimize the common information among the temporal projections derived from single component weights and their accompanying activations, while maximizing the information in each component (Richards, 2004).

2.3 EEG Abnormalities in Major Depressive Disorder

Over the years, several physiological and anatomical alterations in MDD have been demonstrated including altered neurotransmission (Delgado, 2000), abnormal corticosterioid and BDNF levels (Castren & Rantamaki, 2009; Palazidou, 2012), altered cortical volumes in brain areas such as the DLPFC, amygdala and hippocampus (Chang et al., 2011; Davidson et al., 2002), disrupted fronto-cingulate connectivity (Pizzagalli, 2011), etc. However, to date, none of these findings have been implemented in routine clinical use to help identify patients with MDD, mainly due to the lack of ease in translation of these measures into everyday clinical work (Olbrich et al., 2013). Electroencephalography, which is already used in many clinics for routine diagnostic purposes, meets several of the requirements for MDD biomarker research including its ease of administration, wide availability and cost-effectiveness. Furthermore, EEG has good temporal resolution and it directly measures neuronal electrical activity, rather than being a proxy such as the fMRI BOLD signal. Moreover, recent findings have proposed that EEG is one of the most heritable biomarkers, further enhancing its appeal (De Gennaro et al., 2008). Indeed, EEG has been examined for its use in understanding the psychopathology of MDD, in aiding diagnosis, and in examining the neural target of treatment (Alhaj et al., 2011; Baskaran et al., 2013; Jaworksa & Protzner, 2013; Olbrich & Arns, 2013). EEG biomarkers that have been shown to differentiate MDD patients from healthy controls will be discussed in detail below.
2.3.1 EEG Frequency Band Activity

Elevated alpha activity during rest has been one of the main and most consistent findings in MDD patients (Olbrich & Arns, 2013). Increases in both absolute and relative power of the alpha band have been noted, particularly in frontal and posterior regions (Jaworska, Blier, Fusee, & Knott, 2012; Pollock & Schneider, 1990; Possel, Lo, Fritz, & Seemann, 2008; Prichep & John, 1992; Ricardo-Garcel et al., 2009; Roemer et al., 1992). Alpha activity has been shown to inversely correlate with functional cortical activation (Laufs et al., 2003). Therefore, elevated alpha power suggests that diffuse cortical hypoarousal may be a feature of MDD. Still, other studies have failed to find differences in alpha power between MDD patients and healthy controls (Flor-Henry, Koles, Howarth, & Burton, 1979; Knott & Lapierre, 1987) while some have reported decreased relative alpha activity in MDD compared to other patient groups (Pozzi et al., 1995) or in TRD patients with MDD (Price, Lee, Garvey, & Gibson, 2008). Although the exact neurobiology of alpha power is poorly understood, a recent study by Zoon and colleagues (2013) demonstrated an interesting association between the BDNF Val66Met polymorphism and global alpha power. Therefore, the effects of BDNF dysfunction in MDD may be mediated by EEG alpha power (Olbrich & Arns, 2013).

Some evidence exists for increased frontal beta activity in MDD patients (Flor-Henry, Lind, & Koles, 2004; Knott, Mahoney, Kennedy, & Evans, 2001; Lieber & Prichep, 1988; Suzuki, Mori, Kimura, & Endo, 1996). Increased beta activity is typically considered to be characteristic of high-arousal, emotional states. More recently, Grin-Yatsenko and colleagues (2010) reported enhancement of beta power over occipital-parietal regions in MDD patients versus controls. They argued that beta excess may reflect cortical excitation and increased metabolic activity in these regions. Interestingly, a temporal association between EEG beta
power and cortisol secretion has been noted (Chapotot, Gronfier, Jouy, Muzet, & Brandenberger, 1998). This finding suggests a mechanistic link between increased HPA function and higher frequency brain activation. Indeed, depression is associated with hyperactive HPA activity, which is indicative of impaired negative feedback in the axis (Palazidou, 2012).

Low-frequency EEG activity including delta and theta power has been shown to be elevated in MDD patients, particularly over the frontal, right hemisphere (Knott et al., 2000; Knott & Lapierre, 1987; Kwon, Youn, & Jung, 1996; Ricardo-Garcell et al., 2009). Frontal delta band power has been reported to highly correlate with functional activity in the parahippocampal gyrus, suggesting that delta frequencies may play a role in memory processes (Neuner et al., 2014). More recently, elevated theta activity has been reported in parietal and occipital electrode sites from EEG recordings of MDD patients (Grin-Yatsenko et al., 2010). Contrary to this, several studies using source localization methods such as LORETA have indicated decreased theta activity localized to the rACC (Jaworska et al., 2013; Coutin-Churchman & Moreno, 2008; Saletu, Anderer, & Saletu-Zhylarz, 2010; Wienbrueh et al., 2003), an area of the brain shown to be functionally abnormal in MDD patients (Mayberg et al., 1999; Pizzagalli et al., 2001). Discrepancies in the direction of theta activity in MDD may arise from methodological differences. For example, scalp-indexed EEG theta power stems from numerous generators, while source localization methods confine theta activity to specific regions of interest (Jaworska & Protzner, 2013).

Altered theta activity may reflect disrupted connectivity in MDD. Pizzagalli et al. (2003) reported that the rACC produces the largest cluster of positive correlations between theta current density and glucose metabolism. Theta activity is viewed as an EEG index of activity in the
DMN, in which the rACC is a main hub with involvement in self-focused processing (Buckner, Andrews-Hanna, & Schacter, 2008; Scheeringa et al., 2008). The DMN also includes the VMPFC, dorsal media PFC, posterior cingulate, retrosplenial cortex, lateral parietal cortex, lateral temporal cortex, and hippocampal formation. Elevated resting state activity in the DMN is associated with focusing on reflective thought or task-independent introspection such as rumination, remembering, and planning (Simpson, Synder, Gusnard, & Raichle, 2001). In the context of depression, rumination is of particular interest as it reflects a mechanism of responding to distress by repetitively focusing on the symptoms, causes and consequences of the distress (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). When processing external stimuli, DMN regions show reduced activity lending the network an alternate name: the task-negative network (TNN) (Shulman et al., 1997). Conversely, engaging in goal-oriented tasks requiring attention and cognitive control activates the task positive network (TPN), which includes the DLPFC, dACC, the intraparietal sulcus, and the middle temporal area. In MDD, functional and structural abnormalities in fronto-cingulate pathways may impair the relationship between the DMN and TPN, which could lead to disrupted self-focus and maladaptive rumination such as brooding (Pizzagalli, 2011). This could also be explained by impaired amygdalar activity as functional connections also exist between the DMN and limbic/paralimbic regions (Schmitz & Johnson, 2006).

2.3.2 Alpha Asymmetry

MDD tends to be characterized by relative left frontal hypoactivity (increased alpha activity) and right frontal hyperactivity (reduced alpha activity) (Deslandes et al., 2008; Henriques & Davidson, 1990; Jaworska et al., 2012; Possel et al., 2008). Left hypoactivity and right hyperactivity of the frontal lobe have been interpreted as deficits in approach and
withdrawal systems, respectively where the approach system facilitates appetitive behavior and is linked with generating positive affect and the withdrawal system facilitates withdrawal from aversive stimulation and generates negative affect (Henriques & Davidson, 1990). In support of this, Herrington and colleagues (2010) confirmed that emotional stimulus processing and trait depression are associated with asymmetric blood flow in the DLPFC. Hence, frontal alpha asymmetry may be a moderator and/or mediator of emotion (Coan & Allen, 2004).

Some studies have reported a focal increase in alpha power in the right posterior temporal area of MDD patients (Bruder et al., 2005; Kentgen et al., 2000). Activity in this region of the brain appears to be involved in emotion-related autonomic arousal, hence hypoactivity could reflect emotional under arousal in MDD and perhaps features related to anhedonia (Bruder et al., 1997; Heller & Nitschke, 1997).

There is evidence to suggest that alpha asymmetry may be trait-dependent as it has been demonstrated in depressed adolescents and adults; as well as in euthymic patients (Henriques & Davidson, 1990; Kentgen et al., 2000; Reid, Duke, & Allen, 1998). It has also been found in both young and adult offspring of depressed parents (Bruder et al., 2005; Jones et al., 1997). Therefore, alpha asymmetry may relate to fundamental underlying pathophysiologies of MDD, for example, reflecting the hypercortisolaemia often seen in depression (Alhaj et al., 2008). Alternatively, or additionally, asymmetry may reflect certain depressive symptoms, such as rumination and low self-esteem (Putnam & McSweeney, 2008). More recently, Alhaj et al. (2011) discussed the evidence that suggests that gene polymorphisms of the 5-HT_{1A} receptor may be associated with trait EEG alpha asymmetry (Bismark et al., 2010). Not only are 5-HT_{1A} receptor polymorphisms largely associated with the pathophysiology of depression, the 5-HT
transporter of the brain provides one of the primary targets of antidepressant medication (Blier & de Montigny, 1994; Savitz et al., 2009).

Despite of the evidence mentioned above, many studies have failed to replicate alpha asymmetry in MDD (Carvalho et al., 2011; Gold, Fachner, & Erkkil, 2013; Price, Lee, Garvey, & Gibson, 2008; Reid et al., 1998). It has been suggested that this discrepancy may arise largely from the heterogeneity of individuals with MDD and methodological differences among various studies (Davidson, 1998). For example, previous studies have used different reference electrodes and alpha asymmetry has been shown to be influenced by the location of the reference electrode (Hagemann, 2004; Jaworska et al., 2012; Stewart, et al., 2010). Therefore, alpha asymmetry is a problematic EEG biomarker that fails to consistently differentiate MDD patients from healthy controls and the validity potential of alpha asymmetry as a clinical measure for depression still remains unclear.

2.3.3 Event-Related Potentials

In MDD patients, a delay in the latency of the P300 component has been demonstrated over the bilateral temporal lobes, the left frontal region, and the right temporal parietal area (Bruder et al., 1991; Kawasaki et al., 2003; Kemp et al., 2009; Urretavizcaya et al., 2003; Vandoolaeghe, Hunsel, Nuyten, & Maes, 1998). The P300 latency is associated with stimulus evaluation time, providing information on perceptual processing efficiency (Kutas, McCarthy, & Donchin, 1977). ERP studies in MDD also report a reduction of the P300 amplitude, suggesting deficient attention allocation and short term memory updating (Bruder et al., 1991; Kawasaki et al., 2003; Kemp et al., 2009; Urretavizcaya et al., 2003; Vandoolaeghe et al., 1998). Interestingly, while larger reductions in P300 amplitude are reported in melancholic depression, psychotic depression, and depression with suicidal features, prolonged P300 latency seems not to
be influenced by the depressive state (Vandoolaeghe et al., 1998). Furthermore, Bruder and colleagues (2002) demonstrated that while individuals with pure MDD show reductions in P300 amplitude, MDD patients with comorbid anxiety exhibit increases. Hence, co-morbidities such as anxiety should be taken into account when assessing P300 as a MDD biomarker.

2.3.4 Summary and Conclusion

Elevated alpha activity, at rest, has been one of the main and most consistent EEG biomarkers in MDD patients, suggesting that diffuse cortical hypoarousal may be a feature of MDD. Evidence also suggests that MDD is characterized by elevated beta activity which is typically considered to be characteristic of high-arousal, emotional states. Low-frequency EEG activity including delta and theta power has been shown to be elevated in MDD patients, particularly over the right hemisphere, suggesting that dysfunction in the right hemisphere plays an important role in major depression. Interestingly, while scalp-indexed EEG theta activity has been shown to be elevated in MDD, studies using source localization have reported reduced theta activity in the rACC, a region of the brain highly implicated in affective processing. Nevertheless, theta activity may reflect disrupted fronto-cingulate connectivity in MDD. MDD also tends to be characterized by relative left frontal hypoactivity (increased alpha activity) and right frontal hyperactivity (reduced alpha activity) while some studies also report a focal increase in alpha power over the right posterior temporal area. Resting frontal alpha asymmetry in MDD may reflect an affective processing bias, while right parieto-temporal hypoactivity may reflect impaired emotive arousal and may be related to symptoms of anhedonia. However, a lack of consistent findings of alpha asymmetry makes this a problematic EEG biomarker of depression. Lastly, a delay in P300 latency and reduction in P300 amplitude have both been shown to hold discriminative power in MDD patients versus healthy controls.
2.4 EEG Biomarkers of Antidepressant Treatment Response in Major Depressive Disorder

Biomarkers arising from various research domains including genetics, proteomics, metabolomics, neuroendocrinology, neuroimaging and neurophysiology have been shown to predict antidepressant treatment outcome. For example, functional polymorphisms in genes of monoaminergic pathways such as those in the serotonin 5-HT system have been shown to be predictive of SSRI treatment (McMahon et al., 2006; Serretti et al., 2005). Studies employing the combined dexamethasone/corticotrophin releasing hormone test have demonstrated that HPA activity can also predict antidepressant treatment response in patients with MDD (Ising et al., 2007; Paslakis et al., 2010; Schule et al., 2009). Functional neuroimaging studies have indicated a positive association between elevated pre-treatment resting activity in the rACC and response to a variety of antidepressants (Chen et al., 2007; Davidson et al., 2003; Langenecker et al., 2007; Mayberg et al., 1997; Saxena et al., 2003). However, many of these findings have not made their way into routine clinical use because they have not been consistently replicated or they do not hold sufficient predictive value to be implemented in clinical settings. Moreover, the invasiveness associated with genetic and biochemical predictors and the high cost of neuroimaging make such predictors problematic for widespread clinical use (Iosifescu, 2011).

As mentioned previously, the advantages of EEG make it a good candidate for biomarker research in MDD and also allow for easy translation into routine clinical practice. A candidate EEG biomarker that predicts antidepressant response can be examined (1) prior to starting treatment as a pre-treatment baseline measure, (2) shortly after starting treatment, or (3) as a “change variable” defined as change in the EEG from pre-treatment baseline to a time-point after initiating treatment. The only condition is that in order to have clinical utility as a
predictor, the EEG measure must precede the clinical response. As explained by Hunter et al. (2007), the notion behind a baseline EEG biomarker is that state and/or trait factors revealed in the EEG are associated to how a patient will respond to antidepressant medication. For early biomarkers measured shortly after the onset of treatment, it is assumed that antidepressant medication produces changes in the EEG soon after beginning treatment, and that identifiable medication-related EEG changes are associated with eventual treatment outcome. The change in a patient’s brain state after a short period of antidepressant treatment is thought to reflect an interaction between patient factors and exposure to medication (Hunter et al., 2007). Various EEG biomarkers have been probed for their predictive utility towards antidepressant treatment response (Baskaran et al., 2012; Hunter et al., 2007; Sayar, Onen, & Tan, 2013) and each of these will be discussed in detail below.

2.4.1 Alpha Band Activity

Greater pre-treatment alpha power, particularly in the occipital region has been shown to differentiate responders from non-responders anywhere from 3 to 6 weeks of treatment with tricyclic antidepressants (TCAs) such as clomipramine and imipramine, and with selective serotonin reuptake inhibitions (SSRIs) such as paroxetine and fluoxetine (Bruder et al., 2001, 2008; Knott et al., 1996, 2000; Ulrich et al., 1988). Interestingly, MDD patients characterized by decreased alpha do not respond well to antidepressant treatment (Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1984). Reduced alpha can thus be considered an atypical MDD group, given the consistent finding of excess alpha in MDD patients versus healthy controls. However, there remains a question of what baseline alpha power in the treatment of depression actually means.
Given that alpha activity is inversely related to cortical activation, elevated pre-treatment alpha power is thought to reflect cortical hypoactivity (Laufs et al., 2003). Bruder and colleagues (2008) suggested a possible mechanism involving the right temporo-parietal region to account for the increased alpha power seen in depressed patients who respond to SSRI treatment. This hypothesis was based on the notion that increased pre-treatment alpha activity may be indicative of the correspondence between low serotonergic activity and low arousal. It is known that 5-HT activity mediates behavioural arousal. Low serotonergic activity could in turn be reflective of decreased activity of the mesencephalic raphe nuclei and cortical afferents (Bruder et al., 2008). In support of this hypothesis, it has been suggested that depression may be related to dysfunction of temporo-parietal mechanisms, which may mediate emotional arousal (Heller, Etienne, & Miller, 1995). This biological mechanism has been proposed to play a role in both increased alpha power and alpha asymmetry found in SSRI responders, at pre-treatment baseline.

While pre-treatment cortical hypoactivity may be required for eventual response towards antidepressant treatment, this may change with treatment. Although chronic antidepressant administration (12 weeks) has been shown to not alter alpha power (Bruder et al., 2008), acute treatment (1-4 weeks) has been shown to reduce alpha in eventual responders (Jaworska et al., 2014; Ulrich et al., 1984). As explained by Jaworska and colleagues (2014), early alpha power decreases may reflect a positive response to SSRIs which is consistent with the purported arousing effect of antidepressants (Itil, 1983).

### 2.4.2 Theta Band Activity

Studies investigating pre-treatment and early changes in the theta band have reported conflicting results. Decreased pre-treatment theta band activity associated with treatment response has been reported for the TCA, imipramine and with open-label SSRIs at 8 weeks with
63% accuracy (Iosifescu et al., 2009; Knott et al., 1996, 2000). Conversely, a study evaluating mid-frontal theta activity demonstrated elevated pre-treatment theta activity to be predictive of response to a variety of antidepressants (Spronk et al., 2011). Similar findings were reported by a study investigating current source density (CSD) derived EEG activity (Tenke et al., 2011). Discrepancies may arise from the fact that earlier studies have focused on wide-spread theta which is often a reflection of drowsiness, or a sign of low vigilance, while mid-frontal theta activity is thought to reflect ACC activity (Olbrich & Arns, 2013). Keeping with this, studies utilizing source localization methods have supported findings of increased, pre-treatment theta activity being predictive of eventual response. Elevated, pre-treatment theta current density, localized by LORETA to the rACC has been associated with response to nortriptyline, citalopram, reboxetine, fluoxetine, or venlafaxine, in depressed patients (Korb et al., 2009; Mulert et al., 2007; Pizzagalli et al., 2001). The association between elevated rACC theta activity and favorable clinical response was further strengthened by a positive correlation between rACC theta power and improvement in depression scores (Mulert et al., 2007; Pizzagalli et al., 2001).

In a recent review, Pizzagalli (2011) demonstrated that the strength of the link between resting rACC activity and antidepressant treatment response is quite robust. The review also proposed a neurobiological mechanism to explain this association. Specifically, the rACC is a main hub within the DMN of the brain, which is involved in self-focused processing such as rumination, remembering, and planning (Buckner et al., 2008; Simpson et al., 2001). According to a multidimensional view of rumination, it is comprised of two components: reflective pondering and brooding (Treynor Gonzales, & Noel-Hoeksema, 2003). Reflective pondering is viewed as an adaptive process by which, cognitive problem solving is achieved. Conversely,
brooding involves analytic self-focus, which is ultimately destructive because it worsens depressive symptoms (Watkins & Teasdale, 2004). Based on these findings, Pizzagalli (2011) proposed that elevated resting rACC activity may lead to treatment response through adaptive self-referential functions such as mindfulness and non-evaluative self-focus. It was further proposed that increased rACC activity associated with treatment response to antidepressants may also play a key role in re-establishing the functional connections between the DMN and TPN, which are thought to be impaired due to functional and structural abnormalities in fronto-cingulate pathways in MDD.

Early changes in theta activity with acute antidepressant treatment have also been shown to predict antidepressant treatment response. Knott and colleagues (1996) demonstrated that elevated theta to acute treatment with imipramine (2 weeks) was associated with eventual favourable treatment response. Contrary to this, reduced frontal relative theta power at 1 week post-treatment has been shown to predict clinical response to SSRIs or venlafaxine at 8 weeks post-treatment with 60% accuracy (Iosifescu et al., 2009).

2.4.3 Activity in Other Frequency Bands

Studies investigating power in the beta and delta frequency bands in relation to favourable treatment outcome have been limited. Knott et al. (1996) showed a trend for responders of imipramine treatment to exhibit less delta and greater beta power at baseline than non-responders but these differences did not reach statistical significance. In a latter study by the same group, elevated pre-treatment beta power and reduced delta power at frontal sites were shown to predict response to the SSRI, paroxetine at 6 weeks post-treatment (Knott et al., 2000). Due to the scarcity of studies probing activity in the beta and delta bands in relation to antidepressant treatment response, there is a lack of information describing what these findings
may actually reflect at the level of the brain. Resting state activity in the beta and delta bands are inversely related such that beta activity reflects behavioural arousal and attention processes while delta activity is typically noted during reduced alertness (Nofzinger et al., 2000). Therefore, enhanced beta and reduced delta activity in treatment responders may indicate a subtype of MDD patients that display high arousal which leads to favourable antidepressant treatment response.

### 2.4.4 Alpha Asymmetry

The first observations of the predictive ability of alpha asymmetry were made by Ulrich et al. (1984) where they showed that left lateralization of alpha power over the occipital region predicted response to the TCA, amitriptyline at 4 weeks post-treatment. Since that time, two more studies investigating the predictive utility of alpha asymmetry, have demonstrated the opposite. Occipital alpha asymmetry characterized by greater alpha (less cortical activation) over the right hemisphere relative to the left, was noted in treatment response to the SSRI, fluoxetine (Bruder et al., 2001, 2008). Alpha asymmetry was shown to be a significant predictor of treatment outcome at 12 weeks post-treatment with a sensitivity of 64% and a specificity of 71% (Bruder et al., 2008). While greater left than right hemispheric activation at occipital sites was associated with treatment response, non-responders tended to show the opposite pattern of hemispheric activation (greater right than left). In addition, chronic treatment did not alter alpha asymmetry (Bruder et al., 2008). Two recent studies failed to replicate any sort of alpha asymmetry differences between responders and non-responders to various antidepressant interventions (Jaworksa et al., 2014; Tenke et al., 2011).

Findings of right lateralization of alpha power in the posterior region of fluoxetine treatment responders is the same as what is generally observed in MDD patients versus healthy controls (Bruder et al., 2005; Kentgen et al., 2000). Bruder et al. (1996) suggest that decreased
left prefrontal activation in depression may disinhibit left temporo-parietal regions, resulting in enhanced left hemisphere activity in fluoxetine responders. Electrophysiological evidence supports this hypothesis as it demonstrates an inhibitory relationship between frontal and temporo-parietal regions (Knight, Hillyard, Woods, & Neville, 1980; Tucker, Stenslie, Roth, & Shearer, 1981). Furthermore, Bruder et al. (2008) hypothesized that alpha asymmetry in SSRI responders may be reflective of low arousal associated with low serotonergic activity (see Chapter 2.4.1 Alpha Band Activity). On the other hand, patterns of alpha asymmetry in TCA responders and SSRI non-responders are the same as what is generally observed in MDD patients co-morbid with anxiety disorder (Bruder et al., 1997). Activity in the right temporo-parietal region of the brain appears to be involved in emotion-related autonomic arousal, hence hypoactivity could reflect emotional under-arousal in MDD and perhaps features related to anhedonia, while hyperactivity may represent somatic hyperarousal and perhaps features related to anxiety (Heller & Nitsehke, 1997).

While the meaning of alpha asymmetry in the context of antidepressant treatment response remains unclear, attempts have been made to explain it. Bruder et al. (2001) hypothesized that the 5-HT neurotransmitter system may have a lateralized distribution in the brain and may be asymmetrically disrupted in a subtype of depressed patients. This is important because not only is 5-HT implicated in mood disruption; the 5-HT system is also affected by antidepressant medication. Although some studies have supported the hypothesis that 5-HT pathways are asymmetric for homologous sides of the brain (Mandell & Knapp, 1979; Tucker & Williamson, 1984), other studies have failed to replicate this asymmetry (Arora & Meltzer, 1991, Arato et al., 1991). However, due to the mixed results regarding the predictive utility of alpha
asymmetry in antidepressant treatment outcome, further research of this EEG parameter is warranted.

### 2.4.5 Theta Cordance

Theta cordance is a QEEG measure that combines information from both absolute and relative power from the EEG theta spectra according to a specific algorithm (Leuchter et al., 1994). The combined information has been reported to have a stronger correlation with regional cerebral perfusion than either measure alone (Leuchter et al., 1999). Also, compared to standard spectral analysis, cordance is less influenced by age, gender and severity associated with baseline depression (Morgan et al., 2005). Decreased prefrontal theta cordance measured in MDD patients as early as 48 h (trend) to 1 week (significant) post-treatment has been shown to be predictive of treatment response with SSRIs such as fluoxetine, and with the SNRI, venlafaxine, with an accuracy of 72-88% (Cook & Leuchter, 2001; Cook et al., 2002; Bares et al., 2007, 2008). More recently, Bares and colleagues (2010) demonstrated that reduced prefrontal theta cordance after 1 week post-treatment predicts clinical response to buproprion at 4 weeks post-treatment. These findings suggest that measures of early change in prefrontal theta cordance might be of value as predictors of clinical response to SSRI or other antidepressant drugs.

It remains unclear as to what prefrontal theta cordance actually reflects at the level of the brain. Of interesting note, significant differences in theta cordance are observed 1 week post-treatment. Iosifescu (2011) interpreted this as a reflection of early changes in brain activity caused by antidepressant medication. However, no clear mechanisms have been proposed in support of this. Moreover, since prefrontal theta cordance is based on theta band activity, the neurobiological mechanism proposed by Pizzagalli (2011) to explain the association between
rACC activity and antidepressant treatment response may be useful here as well (see Chapter 2.4.2 Theta Band Activity).

### 2.4.6 The Antidepressant Treatment Response Index

The antidepressant treatment response index (ATR) is a QEEG measure that integrates frontal alpha and theta power extracted at pre-treatment baseline and at 1 week post-treatment. ATR was examined for the first time for its usefulness as a neurophysiological biomarker for treatment response in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression study (BRITE-MD) (Leuchter et al., 2009). In BRITE-MD, patients were treated with escitalopram for 1 week, after which time, they were randomized to continue with escitalopram treatment, switch to bupropion treatment or augment with bupropion. Overall, ATR had 74% accuracy in predicting both response and remission. The BRITE-MD study also showed that ATR is predictive of differential response to either escitalopram or bupropion monotherapy. On a receiver operating characteristic (ROC) curve for predictive accuracy of ATR with escitalopram, an optimal threshold of 58.6 was chosen. Patients with high ATR values (above the threshold value) were 2.4 times more likely to respond to escitalopram than those with low ATR values, below threshold (68% versus 28%, p = 0.001). Furthermore, those with ATR values below threshold who were switched to bupropion treatment were 1.9 times more likely to respond to bupropion alone than those who remained on escitalopram treatment (53% versus 28%, p = 0.034). More recent work has confirmed that higher ATR is significantly associated with a positive response to chronic treatment with SSRI but not to placebo (Hunter et al., 2011).

Due to the complexity of ATR and even theta cordance, it is difficult to interpret results derived from these measures, in terms of biological mechanisms. Based on these limitations,
Kuo and Tsai (2010) questioned the use of these measures as biomarkers of antidepressant response. Leuchter (2010) responded to the questions raised by Kuo and Tsai (2010) by explaining that cordance and ATR are largely related. He referred back to the BRITE-MD in which his team theorized that both biomarkers reflect activity arising from frontal rhythmic activity. Rhythmic frontal activity is thought to originate from regions in the ACC and PFC, regions implicated in the pathophysiology of depression (Asada et al., 1991). Hence, it was hypothesized that theta cordance and ATR may reflect early functional changes in these areas of the brain. Moreover, since ATR is a combined measure of alpha and theta activity, mechanisms proposed for each of these frequency band changes in the context of treatment response may be of value here as well (see chapters 2.4.1 and 2.4.2, respectively). However, how ATR is associated with differential response to antidepressant medication remains largely unexplained and merits further investigation.

### 2.4.7 Event-Related Potentials

Higher amplitude of the P300 wave at occipital sites has been shown to be associated with treatment response with TCA and fluoxetine (Bruder et al., 1995). Lower P300 amplitude has been reported to be associated with poor treatment outcome to antidepressant medication (Bruder et al., 1995; Gangadhar, Ancy, & Janakiramaiah, 1993; Jaworska et al., 2013). In a study of elderly MDD patients treated with a variety of antidepressant medications over 6 weeks, patients who did not remit had longer P300 latency at baseline compared to those who did (Kalayam & Alexopoulos, 1999).

The precise neurobiological basis of the P300 component in relation to treatment response is unknown. Of interesting note, while reduced amplitude in treatment non-responders supports what is generally observed in MDD patients, reports of high amplitude in responders,
does not. Similarly, prolonged P300 latency is the same as what is exhibited by MDD patients, in general. Hence, reduced P300 amplitude and delayed P300 latency in non-responders may reflect trait markers for individuals with MDD (Karaaslan et al., 2003), indicating deficits in attention allocation and short term memory updating, and perceptual processing efficiency, respectively. In addition, Alhaj et al. (2011) discuss in their review article an interesting finding: the P300 latency correlates with the prolactin response to the 5-HT\textsubscript{1A} agonist fleinoxan (Hansenne & Ansseau, 1999). This is interesting because the 5-HT\textsubscript{1A} receptor plays an important role in the therapeutic action of antidepressants.

Paige and colleagues (1994) demonstrated that a larger slope of the P2 amplitude in response to stimulus intensity, at baseline was associated with response to SSRIs at 4-8 weeks post-treatment. In a subsequent study, they showed similar results for bupropion (Paige et al., 1995). The majority of other studies investigating LDAEP in antidepressant treatment response have divided their samples into a top 50% range (representative of higher slopes; ‘strong’ LDAEP) and bottom 50% range (lower slopes; ‘weak’ LDAEP) based on LDAEP slope construction (by plotting N1 to P2 amplitude against intensity). These studies found that strong LDAEP at baseline was associated with response to SSRIs such as fluoxetine, paroxetine, and citalopram (Gallinat et al., 2000; Juckel et al., 2007; Lee, Yu, Chen & Tsai, 2005). In contrast, weak LDAEP was found to be associated with response to the norepinephrine reuptake inhibitor (NRI), reboxetine (Juckel et al., 2007; Lee et al., 2005; Mulert al., 2007). Hence, LDAEP may be a differential biomarker of response to antidepressant drugs with differing mechanisms of action.

Due to LDAEP’s presumed link with 5-HT activity, it is possible that LDAEP may be an effective tool as a differential biomarker. Hegerl and Juckel (1993) suggested that the LDAEP
slope is inversely correlated with serotonergic activity. That is, high levels of 5-HT in the central nervous system are related to suppression of ERP responsiveness to auditory tone intensity, whereas, low 5-HT levels facilitate it. Interestingly, the LDAEP slope has been shown to negatively correlate with plasma 5-HT concentration following administration of the SSRI, fluvoxamine in MDD patients but not controls (Hegerl et al., 2001). Keeping with this, individuals with steep baseline slopes who respond favourably to SSRI treatment are likely to have less efficient 5-HT neurotransmission. Conversely, individuals with shallow slopes who benefit from medications that do not directly target the 5-HT system are more likely to have normal or excessive 5-HT neurotransmission. However, in a recent review, O’Neill et al. (2008) concluded that LDAEP may not be a good index of central 5-HT but they still strongly supported the idea that LDAEP is a promising biomarker of antidepressant response.

2.4.8 Summary and Conclusion

Elevated parieto-occipital alpha power (less cortical activity) is evident in a subgroup of depressed patients who respond to antidepressant medication. Reports of scalp-indexed theta activity have yielded conflicting results with some studies reporting reduced pre-treatment levels to be associated with clinical response and other studies reporting the opposite. Discrepancies may arise from differences between wide-spread theta activity and theta activity that is localized to mid-frontal regions, thought to reflect ACC activity. Indeed, source localization methods that confine theta activity to the rACC have supported an association between elevated pre-treatment theta power and antidepressant treatment response. Studies investigating alpha asymmetry have also yielded conflicting results with opposing findings of left hypoactivation versus right hypoactivation in the occipital region of treatment responders and still, other studies failing to replicate either of these findings. Custom-defined EEG algorithms used to study treatment
response in MDD such as theta cordance and ATR have been shown to have an overall good sensitivity and specificity, however, it is unclear as to what exactly these novel algorithms truly mean and reflect at the level of the brain. Reports of ERP biomarkers of antidepressant treatment outcome have been consistent with findings of high P300 amplitude predicting response, and low P300 amplitude and delayed P300 latency predicting non-response. In addition, LDEAP has been shown to differentially predict response to antidepressants from different pharmacological classes.
Chapter 3

Research Hypothesis

3.1 EEG as a Biomarker of Antidepressant Treatment Outcome

Electroencephalography has been shown to have promise as a neurophysiological biomarker of antidepressant treatment response in MDD. Previous work suggests that early EEG measures at pre-treatment baseline, shortly after treatment onset and as early change variables may all be predictive of treatment response (Alhaj et al., 2011; Baskaran et al., 2012, Hunter et al., 2007, Jaworska & Protzner, 2013; Olbrich & Arns, 2013; Sayar et al., 2013). However, there is limited research regarding the utility of EEG indices in predicting response to escitalopram therapy, which has been show to have superior efficacy over other antidepressant medications (Ciprani et al., 2009; Kennedy et al., 2009; Montgomery et al., 2007; Sanchez et al., 2014). It is also unclear whether the predictive utility of some EEG indices is superior to others. To our knowledge, no previous study has looked at the comparative effectiveness of different EEG biomarkers towards escitalopram response prediction, in a multi-site initiative.

In the current study, we examined the utility of resting EEG activity at pre-treatment baseline, particularly frequency band power, alpha asymmetry and prefrontal theta cordance in predicting response to chronic (8 weeks) treatment with escitalopram therapy across multiple sites. Additionally, EEG biomarkers were also investigated at 2 weeks post-treatment and as an “early change” variable defined as change from pre-treatment baseline to 2 weeks post-treatment. The purpose was two-fold: 1) to replicate prior findings of pre-treatment differences between SSRI responders and non-responders. We hypothesized that responders would differ from non-responders in showing elevated alpha power at baseline. Given that there has been mixed results in studies investigating the predictive utility of alpha asymmetry and activity in
other EEG frequency bands, we did not have specific hypotheses regarding these parameters. We also hypothesized that acute treatment would reduce alpha and prefrontal theta cordance, in treatment responders. We did not have specific hypotheses regarding other parameters 2) to compare the predictive utility of EEG-derived biomarkers to probe for whether the utility of some indices is superior to others in predicting response to escitalopram therapy.

3.2 EEG as a Biomarker of Illness in Major Depressive Disorder

Previous research demonstrates that various EEG parameters have been shown to predict illness in MDD by differentiating MDD patients from healthy controls (Alhaj et al., 2011; Baskaran et al., 2013; Jaworska & Protzner, 2013; Olbrich & Arns, 2013). However, there is limited research regarding whether the predictive utility of some indices is superior to others. To our knowledge, this is the first study to investigate the comparative effectiveness of different EEG biomarkers towards prediction of MDD diagnosis, in a multi-site initiative.

The present study compared the utility of resting EEG frequency band power, alpha asymmetry and prefrontal theta cordance in differentiating patients with MDD from healthy controls, using data collected from multiple sites. Although prefrontal theta cordance has been shown to hold promise as an EEG biomarker of antidepressant treatment response prediction, to our knowledge, no previous study has examined the ability of prefrontal theta cordance in predicting MDD diagnosis.

The purpose was two-fold: 1) to replicate prior findings of EEG differences between MDD patients and healthy controls. We hypothesized that MDD patients would demonstrate elevated alpha power relative to healthy controls, as this has been one of the main and most consistent EEG biomarkers in MDD patients. We did not have specific hypotheses regarding power in the other frequency bands or alpha asymmetry, as there have been inconsistencies in
precedent research regarding these parameters in the context of predicting MDD diagnosis. Given that prefrontal theta cordance was examined as an exploratory measure, we also did not have specific hypotheses regarding this EEG parameter. A second goal of this study was to assess the predictive utility of these EEG parameters to probe for whether some indices are superior to others in predicting MDD diagnosis.
Chapter 4

Methods

4.1 Participants

55 participants across three study sites (The University Health Network and The Centre for Addiction and Mental Health in Toronto, Ontario, Canada, and The University of British Columbia in Vancouver, British Columbia, Canada) were recruited and signed written informed consent prior to participation, as part of the Canadian Depression Biomarker Network Study (CAN-BIND). Five participants were lost to attrition before study baseline. Two participants were lost to attrition after week 2. Four participants were not included in the analyses due to incomplete data collection. The remaining 44 participants were included in the analyses.

Participants were outpatients aged 18-60 years of age, met DSM-IV-TR (2000) criteria for MDE in MDD, confirmed by the Mini International Neuropsychiatric Inventory (MINI). Participants were experiencing a MDE duration ≥ 3 months at study enrollment with a MADRS score ≥ 24. Participants were free of psychotropic medications for at least 5 half-lives before baseline Visit 1. Participants were excluded if they had any Axis I diagnosis, other than MDD, that was considered the primary diagnosis or if they had a diagnosis of Bipolar Disorder Type I or II. Presence of a significant Axis II diagnosis (borderline, antisocial) was also exclusionary, along with high suicidal risk, substance dependence/abuse in the past 6 months, and presence of significant neurological disorders, head trauma or other unstable medical conditions. Female participants who were pregnant or breastfeeding were also excluded. Other exclusionary criteria included having failed four or more adequate pharmacological intervention, having started psychological treatment within the past 3 months with the intent of continuing treatment, previously having failed escitalopram treatment or showing intolerance to escitalopram, and
being at risk for hypomanic switch. (i.e. with a history of antidepressant induced hypomania).

20 healthy controls were also recruited across the three study sites. Healthy controls were aged 18 to 60 years of age and had no history of Axis I or Axis II disorders, as determined by the MINI. Non-depressed control individuals were not included in the analyses probing for EEG as a biomarker of antidepressant treatment outcome but were included in the analyses examining EEG as a biomarker of illness in MDD.

4.2 Clinical Measures

Participants were assessed at defined intervals throughout the study period including baseline (before administration of study medication), once during 2 weeks and once during 8 weeks after starting study medication (phase I). Clinical assessment consisted of the MADRS. Response was defined as a $\geq 50\%$ decrease in MADRS score from baseline to week 8 of the study.

4.3 Treatment Trial

Study medications were administered in an open-label manner. In phase I, patients received 10-20mg of escitalopram treatment. Medication dosing was started at 10mg escitalopram and increased to 20mg if clinically necessary. Those unable to tolerate the 20mg dose due to side effects had their dose decreased back to 10mg at the discretion of the treating psychiatrist. At the end of the first 8 weeks, which marked the beginning of phase 2, patients were assessed for treatment response. Those patients who achieved a 50% or greater reduction in baseline MADRS score were considered “responders” and remained on their effective dose of escitalopram for a further 8 weeks. Those who failed to demonstrate at least 50% reduction in baseline MADRS score were considered “non-responders” and received add-on aripiprazole treatment (2-10mg). Medication dosing was started at 2mg aripiprazole with a possible increase
to 5 mg or even 10 mg if clinically appropriate. Patients unable to tolerate the dose increases at week 10 and/or week 12 due to side effects had their dose reduced to 2 mg or 5 mg at the discretion of the treatment psychiatrist. Healthy controls had a total of 5 study visits: screening, baseline, week 2, week 8 and week 16 across both phases of the study. They received the same assessments as patients but did not receive any treatment. For this initial report, we present only the results for the escitalopram group and healthy controls through the primary endpoint of 8 weeks (phase I).

4.4 Procedures

Resting EEG was recorded while subjects sat quietly in a testing room. The EEGs were recorded during two 8-minute periods, one-half with eyes open, and one-half with eyes closed. During the eyes open condition, subjects were instructed to keep their eyes open while maintaining fixation on a cross presented centrally on a computer monitor. During the eyes closed condition, subjects were instructed to keep their eyes closed and to refrain from falling asleep. Subjects were asked to remain still and avoid blinks or eye movements during the entire recording period.

4.5 EEG Recording

Three mutually compatible EEG acquisition systems were used at each study site. At UHN, EEG was recorded using a Biosemi Active-Two amplifier system (Biosemi, Amsterdam, The Netherlands) from 64 scalp sites using Ag/AgCl electrodes (active electrodes) mounted on an elastic cap. In addition, eight additional electrodes were placed below the hairline (both mastoids, both pre-auricular points, outer canthus of each eye, and inferior orbit of each eye). Eye movements were recorded with the electrodes placed at the outer canthi (horizontal electrooculogram (EOG)) and at the inferior orbits (vertical EOG). Two additional electrodes
(Common Mode Sense [CMS] active electrode and Driven Right Leg [DRL] passive electrode) were used as reference and ground electrodes, respectively (cf. www.biosemi/faq/cms&drl.htm). Data were digitized at 512 Hz with a lowpass cut-off 102.4 Hz.

At CAMH, EEG was recorded with a 64-channel electrode cap with Ag/AgCl electrodes using a Neuroscan Synamps RT amplifier system (Compumedics Neuroscan USA, Ltd. Charlotte, North Carolina, USA). Data were digitized at 1000 Hz. Electrodes on the supra-orbital ridges and external eye canthi monitored EOG activity. The electrode posterior to Cz served as the reference electrode. Data was recorded with a digitized filter of 0.05 Hz – 100 Hz.

At UBC, EEG was recorded using a QuickAmp amplifier (Brain Products, Gilching, Germany) from a 64-channel electrode cap with Ag/AgCl electrodes. Data were digitized at 1000 Hz. Electrodes on the supra-orbital ridges and external eye canthi monitored EOG activity. A common average of electrodes was used as the reference. Data was recorded with a digitized filter of 0.01 Hz – 499 Hz.

For all sites, electrode placement was in accordance with the International 10–20 System. Impedance levels were set at less than 5 kOhm. When examining the electrode montages across data acquisition sites, there were 58 common electrodes (see Figure 1). In order to reduce the amount of data in summary statistical analyses of frequency band power and alpha asymmetry, four medial electrode sites, subdivided by hemisphere were chosen: frontal (left/right: F3/4), central (C3/4), parietal (P3/4) and occipital (O1/2) regions.
Figure 1. EEG Electrode Caps across Data Collection Sites.
EEG electrode caps depicting the 58 common electrodes across data collection sites (electrodes within red brackets were deleted channels)
4.6 EEG Data Analysis

Data pre-processing steps included the open source, MATLAB-based EEGLab suite of electrophysiological research tools. Channels other than the 58 common electrodes were deleted from all datasets. Data from CAMH and UBC were re-sampled to 512 Hz to match data collected from UHN. All data were then submitted to a zero phase shift Butterworth filter of order 2, and subsequently segmented into consecutive 2-sec epochs. Bad epochs and bad channels were excluded from analyses by direct visual inspection. Independent Component Analysis (ICA) was then conducted to remove data contaminated by eye blinks, eye movements, and movement-related artifacts. This was followed by a second round of visual inspection for bad epochs and bad channels. Deleted channels were interpolated and recordings were re-referenced to a common average. The EEG data were then subjected to a power spectrum analysis with a Fast-Fourier Transform for computation of absolute (μV²) and relative power (%) in each of four frequency bands: delta (1-3.5 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (12-30 Hz). Relative power was calculated using the following equation (Bian et al., 2014): 

\[ \text{RP}(f_1,f_2) = \frac{P(f_1,f_2)}{P(1,30)} \]

where \( P \) indicates the power, \( \text{RP} \) indicates the relative power, and \( f_1 \) and \( f_2 \) indicate the low and high frequency, respectively. The total power within the EEG spectrum ranged from 1-30 Hz. The output power values were log-transformed \([10 \times \log_{10}(x)]\) to normalize the power value distributions (John, Prichep, & Easton, 1987). Statistical analyses of frequency band power and alpha asymmetry were carried out using log-transformed values, however when reporting results, log-transformed values were converted back to original power values via inverse log transformation \([10^{(x/10)}]\), for ease of interpretation. For relative power, converted power values were multiplied by 100 to reflect values as percentages.
4.7 Statistical Analysis

4.7.1 EEG as a Predictor of Antidepressant Treatment Outcome

Analyses focused on resting frequency band power (absolute and relative), alpha asymmetry and prefrontal theta cordance. Responder and non-responder outcome groups were included in the analyses. EEG measures were analyzed (1) at pre-treatment baseline (2) at 2 weeks post-treatment and (3) as a “early change” variable defined as change in EEG from pre-treatment baseline to 2 weeks post-treatment \[\frac{(\text{week 2} - \text{baseline})}{\text{baseline}} \times 100\], for predictive utility towards treatment response. All analyses were performed using IBM SPSS Statistics version 23.0. Baseline sociodemographic comparisons, between outcome groups were analyzed using two-tailed independent sample t-tests. MADRS scores were evaluated using a two-way repeated measures analysis of variance (ANOVA) with time (baseline, week 2, week 8) as within- and outcome group (responder, non-responder) as between-subject factors.

Frequency band power was analyzed using mixed-model repeated measures ANOVA to examine the effects of region, hemisphere, condition and group, separately for absolute power and relative power in each frequency band. Each ANOVA model included three within-subject factors, region (frontal, central, parietal, occipital), hemisphere (left, right), and condition (eyes open, eyes closed) and one between-subjects factor, group (responder, non-responder). F ratios were evaluated using degrees of freedom computed using the Greenhouse-Geisser epsilon correction (Jennings & Wood, 1976) where appropriate to counteract heterogeneity of variance-covariance matrices associated with repeated measures. For frequency band power analyses, all significant main effects \(p<0.05\) were reported. Significant interaction effects \(p<0.05\) involving group were only reported if follow-up analyses of significant interactions revealed direct group differences.
Alpha asymmetry was analyzed using a one-way ANOVA to compare alpha asymmetry among outcome groups at each region, separately for eyes open and eyes closed conditions. Alpha asymmetry indices were calculated for each subject by computing the difference between the log absolute alpha power for the right and left hemispheres \([\log(\text{right hemisphere}) - \log(\text{left hemisphere})]\), separately for each region (Henriques & Davidson, 1991). Positive asymmetry scores indicate greater activation (less alpha power) over the left hemisphere than the right, and negative scores indicate greater activation over the right hemisphere relative to the left.

Group differences in prefrontal theta cordance were analyzed separately for eyes open and eyes closed conditions using two-tailed independent sample t-tests. Early differences (baseline to week 2) in prefrontal theta cordance within groups were analyzed using two-tailed paired-samples t-tests. Theta cordance was calculated according to the formula provided by Leuchter et al., (1994) which may be summarized as the following three steps. First, absolute power values were reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode. Relative theta power at each electrode was obtained by dividing absolute theta power by total power summed across the entire EEG spectrum. In the second step, normalized absolute \(ANORM(s,f)\) and relative \(RNORM(s,f)\) theta power were obtained by dividing the absolute and relative power values at each electrode site \(s\) and for each frequency band \(f\) by the maximum values of absolute and relative theta power \(AMAX_f\), \(RMAX_f\), respectively. In the final step, a half-maximal value \((0.5\) on the normalized scale) is subtracted from \(ANORM\) and \(RNORM\). Cordance is calculated by summing the absolute values of the above differences: \(CORDANCE(s,f) = |ANORM(s,f) - 0.5| + |RNORM(s,f) - 0.5|\). Average cordance values from three prefrontal electrodes \((\text{Fp1, Fp2 and Fz})\) in the theta frequency band \((4-8\text{ Hz})\) were subjected to statistical analysis.
Pearson’s correlations were carried out between all EEG parameters that resulted in significant group differences, and late clinical response rate defined as percent change in MADRS score from baseline to week 8 \[((\text{MADRS week8 } - \text{MADRS baseline})/\text{MADRS baseline}) \times 100\]. Prior to conducting correlation analyses, data resulting in significant hemispheric group differences in frequency band power were transformed into overall asymmetry scores derived by subtracting the average of left homologous sites over the frontal, central, parietal and occipital regions from the average of right homologous sites across regions. Significant correlations \((p<0.05)\) were followed up with ROC analysis which was used to model the sensitivity vs. \((1-\text{specificity})\) separately for each candidate EEG predictor of response. A threshold was chosen on the ROC curve that optimized the overall accuracy of each EEG candidate biomarker in predicting response versus non-response. Data for each candidate EEG predictor were divided into high/low split based on the chosen threshold. Chi-square statistics with the candidate EEG biomarker categories (high/low) as the independent variables and response category as the dependent variable, was used to probe for indices evaluating prediction of response including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), only if ROC analyses resulted in significant area under the curve (AUC). Sensitivity reflects the percent of responders predicted to be responders. Specificity reflects the percent of non-responders predicted to be non-responders. The PPV reflects the response rate for patients predicted to be responders and the NPV is the non-response rate for patients predicted to be non-responders.

### 4.7.2 EEG as a Biomarker of Illness in Major Depressive Disorder

Only pre-treatment EEG data were used to examine EEG as a biomarker of illness in MDD. The total MDD group (N=44) and healthy controls (N=20) were included in the analyses.
Analyses focused on resting frequency band power (absolute and relative) and alpha asymmetry because of prior findings of differences between MDD patients and healthy controls. Prefrontal theta cordance was examined as an exploratory EEG biomarker. All analyses were performed using IBM SPSS Statistics version 23.0. The differences between MDD patients and healthy controls in baseline sociodemographic data were assessed using two-tailed independent sample t-tests. Frequency band power and alpha asymmetry were analyzed using the same mixed-model repeated measures ANOVA, and one-way ANOVA analyses, respectively as outlined in Chapter 4.7.1 with the responder and non-responder outcome groups being replaced with the total MDD and healthy control groups. Group differences in prefrontal theta cordance were analyzed separately for eyes open and eyes closed conditions using two-tailed independent sample t-tests. For a detailed description of how to calculate theta cordance, please refer to Chapter 4.7.1. ROC analysis was used to model the sensitivity vs. \((1−\text{specificity})\) separately for each candidate EEG biomarker of illness (any parameter that resulted in a significant group effect). A threshold was chosen on the ROC curve that optimized the overall accuracy of each EEG candidate biomarker in predicting MDD diagnosis versus healthy control. Chi-square statistics with the candidate EEG biomarker categories (high/low) as the independent variables and group as the dependent variable, was used to probe for indices evaluating prediction of MDD diagnosis including sensitivity, specificity, PPV and NPV, only if ROC analyses resulted in a significant AUC.
Chapter 5

Results

5.1 EEG as a Predictor of Antidepressant Treatment Outcome

5.1.1 Demographics and Clinical Measures

Altogether, the data of 44 MDD patients were analyzed. The clinical response rate was (N = 18; 40.9%) and the non-response rate was (N = 26; 59.1%). The mean (± SD) age of the responder and non-responder groups was 35 ± 14 years and 36 ± 12 years, respectively with no significant difference between groups [t_{42} = -0.23, p = 0.82]. Table 1 gives the sociodemographic characteristics of the responder and non-responder groups. Groups did not differ significantly in education level, employment status or marital status, but responders and non-responders showed a trend level difference in gender. Group differences in frequency band power, alpha asymmetry and prefrontal theta cordance in the following text remained the same when gender was included as a covariate. A repeated measures ANOVA revealed a main effect of time for MADRS scores [F(2, 84) = 64.25, p < 0.001], with differences between all times (min p < 0.001); highest scores existed at baseline and lowest at week 8. A main effect of group was also noted [F(1, 42) = 15.90, p < 0.001] with lower ratings for responders relative to non-responders. A timexgroup interaction was also observed [F(2, 84) = 20.41, p< 0.001]; no difference between responders and non-responders in pre-treatment severity of depression on the MADRS was noted, however, responders had significantly lower MADRS scores than non-responders after 2 weeks (p = 0.012) and 8 weeks (p < 0.001) of escitalopram treatment (Figure 1).
### Table 1.

#### Sociodemographic Characteristics

<table>
<thead>
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<th>Characteristic</th>
<th>Responder Group (N=18)</th>
<th>Non-responder Group (N=26)</th>
<th>Between Groups</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
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<tr>
<td>Unemployed or Disabled</td>
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Figure 1. Mean MADRS Scores.
Mean ± standard error of MADRS scores for both responder and non-responder groups at pre-treatment baseline, 2 weeks post-treatment and 8 weeks post-treatment (*p < 0.05).

5.1.2 Pre-Treatment Frequency Band Power

Alpha Power

A mixed model ANOVA of baseline absolute alpha power revealed significant region [F(2.15, 90.31) = 83.72, p < 0.001] and hemisphere [F(1,42) = 11.76, p = 0.001] main effects. Absolute alpha power was maximal at occipital sites and over the right hemisphere. A main effect of condition [F(1,42) = 28.41, p < 0.001] also existed, with absolute alpha power reduced in the eyes open condition. There was a numerical trend for the predicted difference in alpha power with responders displaying greater absolute alpha power (7.11 ± 2.28 μV^2) compared to non-responders (5.04 ± 0.87 μV^2), however this difference did not reach statistical significance [F(1,42) = 0.06, p = 0.805]. A statistical trend towards group differences in hemispheric condition was observed [group by hemisphere by condition interaction, [F(1,42) = 3.70, p = 0.061]. This interaction is illustrated in Figure 2, which shows the mean absolute alpha power
by hemisphere (averaged over homologous sites of the frontal, central, parietal and occipital regions) for responders and non-responders in the eyes open and eyes closed conditions, at pre-treatment baseline. Follow-up analyses (separate mixed model ANOVAs for each condition) indicated that there was a significant hemispheric difference in mean absolute alpha power (regions collapsed) between responders and non-responders in the eyes open condition \( F(1,42) = 7.67, p = 0.008 \) but not in the eyes closed condition. In the eyes open condition, responders showed greater mean absolute alpha power over the left hemisphere \((4.50 \pm 1.43 \mu V^2)\), compared to the right \((4.47 \pm 1.39 \mu V^2)\) and non-responders showed the opposite with greater power over the right hemisphere \((4.81 \pm 1.26 \mu V^2)\), relative to the left \((3.95 \pm 0.10 \mu V^2)\).

**Figure 2. Mean Absolute Alpha Power by Hemisphere at Baseline.**
Mean ± standard error of absolute alpha power \((\mu V^2)\) by hemisphere (regions collapsed) for both responder and non-responder groups in the eyes open and eyes closed conditions, at baseline \((^*p < 0.05)\).
Relative alpha power at baseline was maximal at parietal sites and was reduced in the eyes open as opposed to the eyes closed condition. This was confirmed by significant region \( F(3,126) = 39.23, p < 0.001 \) and condition \( F(1,42) = 15.54, p < 0.001 \) main effects. No main effect of group or interactions involving group were noted for relative alpha power at baseline.

**Beta Power**

A mixed model ANOVA of baseline absolute beta power revealed significant region \( F(2.58, 108.74) = 41.06, p < 0.001 \), hemisphere \( F(1,42) = 4.3, p = 0.044 \) and condition \( F(1, 42) = 11.58, p = 0.001 \) main effects. Absolute beta power was maximal at occipital sites and over the right hemisphere, and reduced in the eyes open condition. Relative beta power at baseline was maximal at central sites and was reduced in the eyes closed as opposed to the eyes open condition. This was confirmed by significant region \( F(2.39, 100.29) = 23.47, p < 0.001 \) and condition \( F(1, 42) = 14.30, p < 0.001 \) main effects. No main effect of group or interactions involving group were noted for either absolute or relative beta power, at pre-treatment baseline.

**Theta Power**

A mixed model ANOVA of baseline absolute theta power revealed significant region \( F(3,126) = 87.43, p < 0.001 \), hemisphere \( F(1,42) = 5.67, p = 0.022 \) and condition \( F(1,42) = 33.80, p < 0.001 \) main effects. Absolute theta power was maximal at occipital sites and over the right hemisphere, and reduced in the eyes open condition. Relative theta power at baseline was maximal at frontal sites which was confirmed by a significant region \( F(3,126) = 20.25, p < 0.001 \) main effect. No main effect of group or interactions involving group were noted for either absolute or relative theta power, at pre-treatment baseline.
Delta Power

Absolute delta power at baseline was maximal at occipital sites and over the right hemisphere, and reduced in the eyes open condition. This was confirmed by significant region [F(3,126) = 100.87, p < 0.001], hemisphere [F(1,42) = 4.38, p < 0.042], and condition [F(1,42) = 7.75, p = 0.008] main effects. No main effect of group or interactions involving group was noted for absolute delta power, at baseline. A mixed model ANOVA of baseline relative delta power revealed significant region [F(2.59, 108.76) = 31.13, p < 0.001] and condition [F(1,42) = 7.02, p = 0.011] main effects. Relative delta power was maximal at frontal sites and in the eyes open condition. A significant group difference in hemispheric condition was observed [group by hemisphere by condition interaction, [F(1,42) = 7.95, p = 0.007]. Figure 3 shows the mean relative delta power by hemisphere (regions collapsed) for responders and non-responders in the eyes open and eyes closed conditions. Follow-up analyses indicated that there was a significant hemispheric difference in mean relative delta power (regions collapsed) between responders and non-responders in the eyes open condition [F(1,42) = 9.88, p = 0.003] but not in the eyes closed condition. In the eyes open condition, responders showed greater mean relative delta power over the right hemisphere (21.32 ± 2.51 %), versus the left (20.32 ± 2.53 %) and non-responders showed the opposite with greater power over the left hemisphere (19.78 ± 2.28 %), compared to the right (18.93 ± 2.19 %). No main effect of group was observed for absolute delta power, at baseline.
Figure 3. Mean Relative Delta Power by Hemisphere at Baseline.
Mean ± standard error of relative delta power (%) by hemisphere (regions collapsed) for both responder and non-responder groups in the eyes open and eyes closed conditions, at baseline (*p < 0.05).

5.1.3 Week 2 Frequency Band Power

Alpha Power

A mixed model ANOVA of absolute alpha power at 2 weeks post-treatment revealed significant region [F(2.08, 87.45) = 94.48, p < 0.001] and condition [F(1,42) = 24.59, p < 0.001] main effects. Absolute alpha power was maximal at occipital sites and in the eyes closed condition. Relative alpha power at 2 weeks post-treatment was maximal at occipital regions and reduced in the eyes open condition, confirmed by significant region [F(2.48, 104) = 49.48, p < 0.001] and condition [F(1,42) = 17.06, p < 0.001] main effects. No main effect of group or interactions involving group were noted for either absolute or relative alpha power, at 2 weeks post-treatment.
Beta Power

Absolute beta power was maximal at occipital regions and in the eyes closed condition at 2 weeks post-treatment, confirmed by significant region [F(2.43, 102.13) = 47.83, p < 0.001] and condition [F(1,42) = 14.87, p < 0.001] main effects in a mixed model ANOVA. While no significant main effect of group was observed, a significant group difference in hemispheric condition was noted [group by hemisphere by condition interaction, [F(1,42) = 7.02, p = 0.011]. This interaction is illustrated in Figure 4, which shows the mean absolute beta power by hemisphere (regions collapsed) for responders and non-responders in the eyes open and eyes closed conditions at 2 weeks post-treatment. Follow-up analyses indicated that there was a significant hemispheric group difference in mean absolute beta power (regions collapsed) between responders and non-responders in the eyes open condition [F(1,42) = 5.28, p = 0.027] but not in the eyes closed condition. In the eyes open condition, responders showed greater mean absolute beta power over the left hemisphere (0.34 ± 0.06 μV^2), compared to the right (0.33 ± 0.05 μV^2) and non-responders showed the opposite with greater power over the right hemisphere (0.37 ± 0.04 μV^2), relative to the left (0.34 ± 0.05 μV^2). A mixed model ANOVA of relative beta power at 2 weeks post-treatment revealed significant region [F(3,126) = 22.62, p < 0.001] and condition [F(1,42) = 8.69, p = 0.005] main effects. Relative beta power was maximal at central sites and in the eyes open condition. No main effect of group or interactions involving group were noted for relative beta power at 2 weeks post-treatment.
**Figure 4. Mean Absolute Beta Power by Hemisphere at 2 Weeks Post-Treatment.**
Mean ± standard error of absolute beta power (μV²) by hemisphere (regions collapsed) for both responder and non-responder groups in the eyes open and eyes closed conditions, at 2 weeks post-treatment (*p < 0.05).

**Theta Power**

Absolute theta power was maximal at occipital regions and in the eyes closed condition at 2 weeks post-treatment, confirmed by significant region [F(2.6, 109.06) = 117.16, p < 0.001] and condition [F(1.42) = 32.66, p < 0.001] main effects. A mixed model ANOVA of relative theta power at 2 weeks post-treatment revealed a significant region [F(2.54, 106.71) = 11.38, p < 0.001] main effect where relative theta power was maximal over frontal sites. No main effect of group or interactions involving group were noted for either absolute or relative theta power, at 2 weeks post-treatment.

**Delta Power**

A mixed model ANOVA for absolute delta power revealed a significant region main effect [F(2.46, 103.51) = 95.38, p < 0.001] demonstrating maximal power at occipital regions, at 2 weeks post-treatment. While no main effect of group was observed, significant group
differences in hemispheric condition were noted [group by hemisphere by condition interaction, \(F(1,42) = 5.32, p = 0.026\)]. Figure 5 displays this interaction by showing the mean absolute delta power by hemisphere (regions collapsed) for responders and non-responders in the eyes open and eyes closed conditions at 2 weeks post-treatment. Follow-up analyses indicated that there was a significant hemispheric group difference in mean absolute delta power between (regions collapsed) responders and non-responders in the eyes closed condition \([F(1,42) = 4.36, p = 0.043]\) but not in the eyes open condition. In the eyes closed condition, responders showed greater mean absolute delta power over the right hemisphere \((1.85 \pm 0.36 \, \mu V^2)\), versus the left \((1.72 \pm 0.32 \, \mu V^2)\) and non-responders showed the opposite with greater mean absolute delta power over the left hemisphere \((1.38 \pm 0.15 \, \mu V^2)\), relative to the right \((1.34 \pm 0.14 \, \mu V^2)\).

**Figure 5. Mean Absolute Delta Power by Hemisphere 2 Weeks Post-Treatment.**
Mean ± standard error of absolute delta power \((\mu V^2)\) by hemisphere (regions collapsed) for both responder and non-responder groups in the eyes open and eyes closed conditions, at 2 weeks post-treatment (*\(p < 0.05\)).
Relative delta power was maximal at frontal regions and reduced in the eyes closed condition at 2 weeks post-treatment, confirmed by significant region \([F(2.31, 97.06) = 27.97, p < 0.001]\) and condition \([F(1,42) = 15.95, p < 0.001]\) main effects in a mixed model ANOVA. A significant group by hemisphere interaction \([F(1,42) = 4.85, p = 0.033]\) was noted. This interaction is illustrated in Figure 6, which shows the mean relative delta power for responders and non-responders at 2 weeks post-treatment (averaged over eyes open and eyes closed conditions and regions). Responders showed greater mean relative delta power over the right hemisphere \((19.07 \pm 2.49 \%)\), compared to the left \((18.72 \pm 2.45 \%)\), and non-responders showed the opposite with greater power in the left hemisphere \((17.41 \pm 1.84 \%)\), versus the right \((16.97 \pm 1.93 \%)\). No main effect of group was noted for relative delta power at 2 weeks post-treatment.

*Figure 6. Mean Relative Delta Power by Hemisphere at 2 Weeks Post-Treatment.*
Mean ± standard error of relative delta power (%) by hemisphere (averaged over conditions and regions) for both responder and non-responder groups, at 2 weeks post-treatment (*\(p < 0.05\)).
5.1.4 Early Changes in Absolute and Relative Frequency Band Power

A mixed model ANOVA revealed a condition x group interaction for early changes in relative alpha [F(1,42) = 5.07, p = 0.030] and relative theta [F(1,42) = 4.42, p = 0.042] power. For early change in relative alpha power, responders showed a decrease (-5.92 ± 5.18 %) while non-responders showed an increase (9.15 ± 5.84 %), in the eyes closed condition. For early changes in relative theta power, responders showed a greater increase (9.12 ± 5.27 %) compared to non-responders (2.85 ± 6.41 %), in the eyes closed condition. Groups did not differ in relative alpha or theta power in the eyes open condition. No main effects of group or interactions involving group were noted for early changes in absolute power in any of the frequency bands or in relative power in the beta and delta frequency bands.

5.1.5 Alpha Asymmetry

One-way ANOVA indicated that there was a significant group difference in baseline alpha asymmetry between responders and non-responders in the parietal region, in the eyes open condition only [F(1,43) = 7.77, p = 0.008]. Responders showed a negative parietal asymmetry (-0.15 ± 0.36), and non-responders showed a positive asymmetry (1.17 ± 0.30) (Figure 7). No main effects of group or interactions involving group were noted for alpha asymmetry at 2 weeks post-treatment, or for early changes in alpha asymmetry.
Figure 7. Mean Alpha Asymmetry in the Eyes Open Condition at Baseline.
Mean ± standard error of the baseline alpha asymmetry scores by region derived by subtracting left from right log-transformed absolute alpha power at homologous electrodes, for both responder and non-responder groups in the eyes open condition. Positive scores indicate greater activation (less alpha power) over the left hemisphere than the right, and negative scores indicate greater activation over the right hemisphere (*p < 0.05).

5.1.6 Prefrontal Theta Cordance

Prefrontal theta cordance at baseline and week 2, as well as its early change, were not different between responders and non-responders (Table 2). However, when groups were analyzed alone for change over time, non-responders showed a significant increase in prefrontal theta cordance from baseline (0.62 ± 0.11) to 2 weeks post-treatment (0.66 ± 0.12), only in the eyes closed condition \([t_{25} = -3.07, p = 0.005]\). Responders failed to show any significant change over time (Figure 8).
Table 2.

**Prefrontal Theta Cordance Values during the Study**

<table>
<thead>
<tr>
<th></th>
<th>Eyes Open</th>
<th></th>
<th>Eyes Closed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responers N=18</td>
<td>Non-Responders N=26</td>
<td>P Value</td>
<td>Responers N=18</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.60 ± 0.12</td>
<td>0.63 ± 0.13</td>
<td>0.59</td>
<td>0.60 ± 0.13</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.60 ± 0.16</td>
<td>0.61 ± 0.14</td>
<td>0.96</td>
<td>0.61 ± 0.12</td>
</tr>
<tr>
<td>Early Change</td>
<td>-1.17 ± 0.19 %</td>
<td>-1.82 ± 0.19 %</td>
<td>0.91</td>
<td>2.56 ± 0.16 %</td>
</tr>
</tbody>
</table>

*Values are mean ± standard deviation

bIndependent Sample T-Test

---

**Figure 8. Early Change in Mean Prefrontal Theta Cordance over Time.**
Mean ± standard error of prefrontal theta cordance at baseline and 2-weeks post-treatment for both responder and non-responder groups, in the eyes closed condition (*p < 0.05).
5.1.7 Correlation Analyses

Prior to conducting correlation analyses, all data resulting in significant hemispheric group differences were transformed into overall asymmetry scores derived by subtracting the average of left homologous sites over the frontal, central, occipital, and parietal regions from the average of right homologous sites across regions.

At pre-treatment baseline, significant correlations between percentage change of MADRS at the end of treatment (week 8) and overall absolute alpha asymmetry in the eyes open condition \([r = -0.30, p = 0.048]\), parietal alpha asymmetry in the eyes open condition \([r = -0.31, p = 0.040]\), and overall relative delta asymmetry in the eyes open condition \([r = 0.41, p = 0.006]\), were observed for the whole sample. At 2 weeks post-treatment, a significant correlation was observed between percentage change of MADRS at the end of treatment and overall absolute delta asymmetry in the eyes closed condition \([r = 0.37, p = 0.013]\), for the whole sample. No significant correlations were noted between early changes in power and percentage change of MADRS at the end of treatment.

5.1.8 Examination of Predictive Utility

Receiver operating curve analysis (Leuchter et al., 2009) and follow-up chi-square tests were carried out to examine the predictive utility of EEG parameters that resulted in a significant correlation with clinical response at week 8: overall absolute alpha asymmetry, parietal alpha asymmetry, and overall relative delta asymmetry, all at pre-treatment baseline in the eyes open condition, along with overall absolute delta asymmetry at 2 weeks post-treatment in the eyes closed condition.

ROC analysis yielded significant AUC for baseline overall absolute alpha asymmetry \([AUC = 0.73 (95\% \text{ CI} = 0.57-0.89), p = 0.011]\), baseline parietal alpha asymmetry \([AUC = 0.76\]
(95% CI = 0.61-0.91), \( p = 0.004 \), baseline overall relative delta asymmetry [AUC = 0.74 (95% CI = 0.60-0.89), \( p = 0.007 \)], and overall absolute delta asymmetry at 2 weeks post-treatment [AUC = 0.70 (95% CI = 0.54-0.85), \( p = 0.034 \)] (see Figure 9).

Based upon the ROC analyses, a threshold value was selected for each parameter to maximize accuracy in classification of responders and non-responders to treatment. Optimal cut-off of baseline overall absolute alpha asymmetry and parietal alpha asymmetry for response prediction was 0.19 and 0.39, respectively. For baseline overall relative delta asymmetry, predictive optimal cut-off was -0.24 and for overall absolute delta asymmetry at 2 weeks post-treatment, predictive optimal cut-off was -0.03. For baseline overall absolute alpha asymmetry and parietal alpha asymmetry, values below threshold were designated as a positive biomarker, and above designated as a negative biomarker. For baseline overall relative delta asymmetry and 2-week post-treatment overall absolute delta asymmetry, values above threshold were designated as a positive biomarker, and below designated as a negative biomarker.
Figure 9. Receiver Operating Characteristic Curve for Prediction of Response to Escitalopram Treatment.
ROC area under the curve for baseline overall absolute alpha asymmetry, baseline parietal alpha asymmetry, baseline overall relative delta asymmetry and overall absolute delta asymmetry at 2 weeks post-treatment.
Follow-up chi square tests were conducted using threshold values resulting from ROC analysis in order to probe for indices of predictive utility including sensitivity, specificity, PPV and NPV (Table 3). A greater proportion of treatment responders exhibited low baseline overall absolute alpha power asymmetry (N = 13; 72.2%; sensitivity) compared to non-responders (N = 8; 30.8%), while more non-responders showed high baseline overall absolute alpha asymmetry (N = 18; 69.2%; specificity) compared to responders (N = 5; 27.8%) \(\chi^2(1) = 7.33, p = 0.007\]. PPV and NPV for baseline overall absolute alpha asymmetry were 61.9% and 78.3%, respectively.

A greater number of treatment responders displayed low baseline parietal alpha asymmetry (N = 16; 88.9%; sensitivity) versus non-responders (N = 9; 34.6%), while more non-responders exhibited high parietal alpha asymmetry at baseline (N = 17; 65.4%; specificity) compared to responders (N = 2; 11.1%) \(\chi^2(1) = 12.77, p < 0.001\]. PPV and NPV for baseline parietal alpha asymmetry were 64% and 89.5%, respectively.

A larger proportion of treatment responders showed high baseline overall relative delta asymmetry (N = 16; 88.9%; sensitivity) compared to non-responders (N = 11; 42.3%), while more non-responders displayed low baseline overall relative delta asymmetry (N = 15; 57.7%; specificity) versus responders (N = 2; 11.1%) \(\chi^2(1) = 9.73, p = 0.002\]. PPV and NPV for baseline overall relative delta asymmetry were 59.3% and 88.2%, respectively.

A greater number of treatment responders exhibited high 2 week post-treatment overall absolute delta asymmetry (N = 14; 77.8%; sensitivity) versus non-responders (N = 11; 42.3%), while more non-responders demonstrated low overall absolute delta asymmetry at 2 weeks post-treatment (N = 15; 57.7%; specificity) compared to responders (N = 4; 22.2%) \(\chi^2(1) = 5.45, p = 0.020\]. PPV and NPV for overall absolute delta asymmetry were 56% and 78.9%, respectively.
Table 3.

*Indices Evaluating Prediction of Treatment Response*

<table>
<thead>
<tr>
<th></th>
<th>Baseline Overall Absolute Alpha Asymmetry</th>
<th>Baseline Parietal Alpha Asymmetry</th>
<th>Baseline Overall Relative Delta Asymmetry</th>
<th>2 Week Overall Absolute Delta Asymmetry</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72.2%</td>
<td>88.9%</td>
<td>88.9%</td>
<td>77.8%</td>
</tr>
<tr>
<td>Specificity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69.2%</td>
<td>65.4%</td>
<td>57.7%</td>
<td>57.7%</td>
</tr>
<tr>
<td>Positive Predictive Value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61.9%</td>
<td>64.0%</td>
<td>59.3%</td>
<td>56.0%</td>
</tr>
<tr>
<td>Negative Predictive Value&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78.3%</td>
<td>89.5%</td>
<td>88.2%</td>
<td>78.9%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Sensitivity = percentage of responders who were predicted to be responders.
<sup>b</sup>Specificity = percentage of non-responders who were predicted to be non-responders.
<sup>c</sup>Positive Predictive Value = response rate for patients predicted to be responders.
<sup>d</sup>Negative Predictive Value = non-response rate for patients predicted to be non-responders.
5.2 EEG as a Biomarker of Illness in Major Depressive Disorder

5.2.1 Demographic Measures

Altogether, the data of 44 MDD patients and 20 healthy controls were analyzed. The mean (± SD) age of the MDD and healthy control groups was 35 ± 13 years and 34 ± 12 years, respectively with no significant difference between groups ($t_{62} = 0.25, p = 0.80$). Table 4 gives the sociodemographic characteristics of the groups. Groups did not differ significantly in gender, employment status or marital status, but groups showed a trend level difference for education with MDD patients showing somewhat less education than healthy controls. Group differences in frequency band power, alpha asymmetry and prefrontal theta cordance reported in the following text remained the same when education was included as a covariate.

Table 4.

Sociodemographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDD Group (N=44)</th>
<th>Healthy Control Group (N=20)</th>
<th>Between Groups</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>Gender</td>
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<tr>
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<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Education</td>
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<tr>
<td>High School Diploma or Less</td>
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<tr>
<td>Completed Some College</td>
<td>14</td>
<td>32</td>
<td>3</td>
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<tr>
<td>Technical Training</td>
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<td>Undergraduate Degree or More</td>
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<td>36</td>
<td>14</td>
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<td>Unknown</td>
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<td>0</td>
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<tr>
<td>Employment Status</td>
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</tr>
<tr>
<td>Employed (Full/Part-time)</td>
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<td>59</td>
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<td>32</td>
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<tr>
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<td>7</td>
<td>6</td>
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<tr>
<td>Unknown</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>Marital Status</td>
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<td>Married or Cohabiting</td>
<td>Separated or Divorced</td>
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</tr>
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<td></td>
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<tr>
<td></td>
<td>70</td>
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<td>5</td>
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</tr>
<tr>
<td></td>
<td>0.41</td>
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</tbody>
</table>

5.2.2 Absolute and Relative Frequency Band Power

**Alpha Power**

A mixed model ANOVA of absolute alpha power revealed significant region \( [F(2.28, 141.44) = 119.64, p < 0.001] \), hemisphere \( [F(1,62) = 18.88, p < 0.001] \) and condition \( [F(1,62) = 33.35, p < 0.001] \) main effects. Absolute alpha power was maximal at occipital sites and over the right hemisphere, and reduced in the eyes open condition. There was a numerical trend for the predicted difference in alpha power with the MDD group displaying greater absolute alpha power \( (5.89 \pm 1.06 \, \mu V^2) \) compared to healthy controls \( (3.63 \pm 1.33 \, \mu V^2) \), however this difference did not reach statistical significance \( [F(1,62) = 1.99, p = 0.164] \). Relative alpha power was also maximal over occipital regions and reduced in the eyes open condition. This was confirmed by significant region \( [F(2.47, 153.34) = 65.4, p < 0.001] \) and condition \( [F(1,62) = 8.7, p = 0.004] \) main effects. A numerical trend for the predicted difference in alpha power was also noted with relative alpha power with the MDD group displaying greater relative alpha power \( (41.62 \pm 2.47 \%) \) compared to healthy controls \( (31.46 \pm 3.41 \%) \), however the main effect of group did not reach statistical significance \( [F(1,62) = 2.06, p = 0.156] \). No interactions involving group were noted for either absolute or relative alpha power.

**Beta Power**

Absolute beta power was maximal at occipital sites and in the eyes closed condition. This was confirmed by significant region \( [F(2.69, 166.83) = 57.43, p < 0.001] \) and condition
[F(1,62) = 6.19, p = 0.016] main effects. A mixed model ANOVA of relative beta power revealed significant region [F(2.08, 128.64) = 29.24, p < 0.001], hemisphere [F(1,62) = 7.82, p = 0.007] and condition [F(1,62) = 9.89, p = 0.003] main effects. Relative beta power was maximal over the central region and over the left hemisphere, and reduced in the eyes closed condition. No main effect of group or interactions involving group were noted for absolute or relative beta power.

**Theta Power**

A mixed model ANOVA of absolute theta power revealed significant region [F(3,186) = 135.93, p < 0.001], hemisphere [F(1,62) = 4.29, p = 0.042] and condition [F(1, 62) = 23.47, p < 0.001] main effects. Absolute theta power was maximal at occipital sites and over the right hemisphere, and reduced in the eyes open condition. Relative theta power was maximal over the frontal region and over the left hemisphere. This was confirmed by significant region [F(3,186) = 26.82, p < 0.001] and hemisphere [F(1,62) = 4.55, p = 0.037] main effects. No main effect of group or interactions involving group were noted for either absolute or relative theta power.

**Delta Power**

A mixed model ANOVA of absolute delta power revealed significant region [F(3,186) = 143.99, p < 0.001] and hemisphere [F(1,62) = 7.17, p = 0.009] main effects. Absolute delta power was maximal at occipital sites and over the right hemisphere. While no main effect of group was noted, a condition x group interaction was observed [F(1,62) = 3.40, p = 0.070]. This interaction is illustrated in Figure 10, which shows the mean absolute delta power (averaged over left and right hemispheres and regions) for MDD patients and healthy controls by condition. In the eyes open condition, MDD patients showed less mean absolute delta power (1.48 ± 0.15 µV²), compared to healthy controls (2.81 ± 0.95 µV²). In the eyes closed condition, MDD
patients showed greater mean absolute delta power ($1.90 \pm 0.23 \mu V^2$), relative to healthy controls ($1.60 \pm 0.18 \mu V^2$). Relative delta power was maximal over the frontal region and in the eyes open condition. This was confirmed by significant region [F(3,186) = 36.23, $p < 0.001$] and condition [F(1,62) = 14.39, $p < 0.001$] main effects. No main effect of group or interactions involving group was noted for relative delta power.

![Figure 10. Mean Absolute Delta Power.](image)

Mean ± standard error of the absolute delta power ($\mu V^2$) (averaged over hemispheres and regions) for both MDD and healthy control groups, in the eyes open and eyes closed conditions (*$p < 0.05$).

**5.2.3 Alpha Asymmetry**

MDD patients did not differ significantly from healthy controls in alpha asymmetry, in the eyes open or in the eyes closed conditions (Figure 11).
5.2.4 Prefrontal Theta Cordance

Exploratory analyses of prefrontal theta cordance demonstrated no significant group differences between MDD patients and healthy controls, in eyes open or eyes closed conditions (Table 5).

*Figure 11. Mean Alpha Asymmetry.*
Mean ± standard error of the alpha asymmetry scores by region derived by subtracting left from right log-transformed absolute alpha power at homologous electrodes, for both MDD and healthy control groups in the eyes open and eyes closed conditions. Positive scores indicate greater activation (less alpha power) over the left hemisphere than the right, and negative scores indicate greater activation over the right hemisphere.
Table 5.

Prefrontal Theta Cordance Values$^a$

<table>
<thead>
<tr>
<th></th>
<th>Eyes Open</th>
<th>Eyes Closed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDD N=44</td>
<td>Healthy Controls N=20</td>
</tr>
<tr>
<td>$P$ Value$^b$</td>
<td>0.62 ± 0.12</td>
<td>0.66 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>Healthy Controls N=20</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>MDD N=44</td>
<td>Healthy Controls N=20</td>
</tr>
<tr>
<td>$P$ Value$^b$</td>
<td>0.61 ± 0.11</td>
<td>0.66 ± 0.44</td>
</tr>
</tbody>
</table>

$^a$Values are mean ± standard deviation

$^b$Independent Sample T-Test

5.2.5 Examination of Predictive Utility

ROC analyses were carried out to examine the predictive utility of absolute delta power in the eyes open and eyes closed conditions. ROC analysis yielded non-significant AUC curves for absolute delta power in both the eyes open [AUC = 0.62 (95% CI = 0.47-0.77), $p = 0.121$], and eyes closed [AUC = 0.50 (95% CI = 0.35-0.64), $p = 0.954$] conditions (see Figure 12). Due to non-significant results, follow-up chi square statistics were not performed.
Figure 12. Receiver Operating Characteristic Curve for Prediction of MDD.
ROC area under the curve for absolute delta power, in the eyes open (a) and eyes closed (b) conditions.
Chapter 6

Discussion

6.1 EEG as a Biomarker of Antidepressant Treatment Outcome

The present study examined the utility of EEG differences in frequency band power, alpha asymmetry and prefrontal theta cordance at pre-treatment baseline, at 2 weeks post-treatment and as an early change variable in predicting response to escitalopram treatment. At pre-treatment baseline, treatment responders showed elevated absolute alpha power in the left hemisphere (less cortical activity) versus the right while non-responders showed the opposite. Responders further exhibited a cortical asymmetry of greater right relative to left activity in parietal areas. Groups also differed in baseline relative delta power with responders showing greater power in the right hemisphere versus the left while non-responders showed the opposite. At 2 weeks post-treatment, responders exhibited greater absolute beta power in the left hemisphere relative to right and the opposite was noted for non-responders. The opposite pattern was noted for absolute and relative delta power at 2 weeks post-treatment (greater power in the right hemisphere versus the left). Responders exhibited early decrease in relative alpha power, while showing early increments in relative theta power. Groups did not differ in prefrontal theta cordance. However, non-responders demonstrated a significant increase in prefrontal theta cordance from baseline to 2 weeks post-treatment.

Correlational analyses suggested that hemispheric group differences in absolute alpha power and relative delta power at baseline, and in absolute delta power at 2 weeks post-treatment were all associated with percent MADRS reduction at week 8. Parietal alpha asymmetry was also associated with late clinical response. Baseline parietal alpha asymmetry predicted response with the greatest overall accuracy of 77%. This was followed by baseline relative delta power...
asymmetry and baseline absolute alpha asymmetry which demonstrated 73% and 71% overall accuracy, respectively. Absolute delta asymmetry at 2 weeks post-treatment had the lowest overall accuracy of 68%, which still showed reasonable predictive utility.

While there have been a number of studies that have investigated EEG alpha and theta power differences between responders and non-responders to antidepressant medication, only a handful of these studies have examined the predictive utility of regional and hemispheric differences in these frequency bands with conflicting findings. Moreover, to our knowledge, there have been limited studies reporting the use of regional hemispheric activity in the beta and delta frequency bands as predictors for treatment response to antidepressants. While two independent groups have probed for the predictive utility of prefrontal theta cordance towards antidepressant response across various clinical studies, none of them have focused on predicting response to escitalopram therapy. Lastly, a major pitfall of previous research studies is that not all studies have reported performance characteristics for their candidate biomarkers, specifically the sensitivity, specificity, positive and negative predictive values. To our knowledge, no previous study has compared EEG frequency band power, alpha asymmetry and prefrontal theta cordance for indices of predictive utility to escitalopram treatment in a single study for cross-comparison of effectiveness. Moreover, a multi-site initiative to undertake this task further adds to the novelty of this study. The goal of biomarker research is to identify reliable indicators early in the course of treatment that predict clinical response, regardless of what site the data is collected at.

Previous studies investigating the predictive utility of alpha power have indicated that elevated parieto-occipital alpha (less cortical activity) is evident in a subgroup of MDD patients who favourably respond to antidepressant medication (Bruder et al., 2001, 2008; Knott et al.,
In the present study, there was a numerical trend where responders exhibited greater absolute alpha power compared to non-responders but these differences did not reach statistical significance. This may be a reflection of our small sample size and perhaps with larger sample sizes, baseline alpha power differences in treatment responders and non-responders may emerge. Interestingly, early relative alpha power decreases were shown to be associated with treatment response while non-responders showed an increase, in the eyes closed condition. In responders, early alpha power decreases may reflect a positive response to SSRIs which is consistent with the purported arousing effect of antidepressants (Itil, 1983). While chronic antidepressant administration has been shown to not alter alpha power (Bruder et al., 2008), our findings of reduced early alpha power are supported by previous findings of early alpha power reductions (baseline to week 1) exhibited by escitalopram responders (Jaworska et al., 2014). Although outcome groups in the present study significantly differed in early alpha change, this finding failed to correlate with late clinical response and hence was not probed for indices evaluating predictive utility. Therefore, further research with larger sample sizes is warranted to probe for performance characteristics such as sensitivity and specificity of alpha power change with antidepressant treatment.

Studies investigating alpha asymmetry for predicting antidepressant response have yielded very different results with opposing findings of left hypoactivation (Ulrich et al., 1984) versus right hypoactivation (Bruder et al., 2001; 2008) in the occipital region of treatment responders and still, other studies have failed to replicate either of these findings (Jaworksa et al., 2014; Tenke et al., 2011). In the present study, outcome groups demonstrated hemispheric differences in absolute alpha power, and this was greatest in the eyes open condition with responders showing greater cortical activation (less alpha power) over the right hemisphere and
non-responders showing the opposite. When alpha asymmetry was further probed using asymmetry scores \([\log(\text{Right Hemisphere}) - \log(\text{Left Hemisphere})]\) for medial sites by region, responders exhibited parietal alpha asymmetry profiles reflecting increased right parietal activity (less alpha power) and non-responders displayed the opposite, only in the eyes open condition. Interestingly, the alpha asymmetry of escitalopram responders resembles the asymmetry seen in patients having MDD with comorbid anxiety disorder, and the alpha asymmetry of non-responders resembles what is normally observed in patients with “pure” MDD (Bruder et al., 1997). According to Clark and Watson’s (1991) tripartite model, symptoms of depression and anxiety are grouped into three subtypes: general distress and negative affect which are common to both MDD and anxiety, symptoms of somatic hyperarousal and tension that are specific to anxiety, and symptoms of anhedonia and absence of positive affect, which are specific to MDD. Frontal alpha asymmetry has been well documented to reflect affective behaviour, specifically with left frontal hypoactivation being associated with deficits in approach behaviours or positive affect and right frontal hyperactivation being associated with deficits in withdrawal behaviours or negative affect (Henriques & Davidson, 1990). Our findings of alpha asymmetry were not specific to the frontal region but outcome groups did differ in parietal alpha asymmetry. Heller et al. (1995) reviewed evidence demonstrating that somatic manifestations of anxious arousal, as observed in individuals with panic disorder, are associated with activation of the right parietal region. Conversely, Bruder and colleagues (1997) suggested that hypoactivation of right temporo-parietal regions could reflect emotional underarousal in MDD and perhaps features related to anhedonia. This has been supported by previous reports that MDD patients with melancholia, which involves the cardinal symptom of anhedonia, display alterations of perceptual asymmetry suggestive of right hemisphere dysfunction (Bruder et al., 1989). The
importance of arousal level is supported by our finding that hemispheric alpha power differences in responders and non-responders were less evident in the less arousing eyes closed condition. It is possible that responders and non-responders differed in overall anxious arousal, however we did not probe for this in the present study. Future EEG studies of depressed patients should include clinician administered or self-rating scales to measure trait anxiety or anxious arousal to further help understand differential patterns of alpha asymmetry. In addition, it has also been hypothesized that the 5-HT system, implicated in MDD may have a lateralized distribution in the brain and may be asymmetrically disrupted in a subtype of depressed patients (Bruder et al., 2001). This is important because the 5-HT system plays an important role in how antidepressant medication work, especially SSRIs. While some studies have supported the hypothesis that 5-HT pathways are asymmetric for opposite sides of the brain (Mandell & Knapp, 1979; Tucker & Williamson, 1984), other studies have failed to replicate this asymmetry (Arora & Meltzer, 1991, Arato et al., 1991).

Our report of parietal alpha asymmetry supports early findings of left lateralization of alpha power in the posterior region of antidepressant responders (Ulrich et al., 1984). However, our finding is in the opposite direction to more recent reports of right hypoactivation in antidepressant treatment responders (Bruder et al., 2001, 2008). Differences in findings could result from the heterogeneity of individuals with MDD, and/or from differences in design and study medication. In an early study conducted by Bruder and colleagues (2001), only three regions were included in their analyses examining regional hemispheric differences: frontal, central and posterior with two homologous pairs in each region: one medial and one lateral. In the present study, we examined differences in four regions including the frontal, central, parietal and occipital regions with only one medial homologous pair to each region. Perhaps, if we had
examined data across medial and lateral sites of the scalp, results may have differed. In a latter study conducted by the same group (2008) the design was more similar to the present study, however, control subjects were included with responders and non-responders in the data analyses. In addition, while both of these previous studies used a nose reference, our data were re-referenced to a common average during offline-analysis. Alpha asymmetry has been shown to be influenced by the location of the reference electrode (Hagemann, 2004), therefore study differences could be attributed to choice of reference electrode. Lastly, while Bruder and colleagues (2001, 2008) examined the predictive ability of EEG towards therapeutic response to fluoxetine, the present study examined response to escitalopram. Although fluoxetine and escitalopram can both be classified as SSRIs, escitalopram can further be classified as an ASRI due to its well-documented allosteric properties. Perhaps, positive and negative indices of alpha asymmetry differentially predict response to these antidepressants, however the evidence for this lacking. We must also address two recent studies that found no differences in alpha asymmetry between antidepressant responders and non-responders. Tenke and colleagues (2011) examined regional hemispheric differences using a high-resolution EEG method called current source density (CSD) which is a reference independent measure of the strength of extracellular current generators underlying the EEG (Tenke & Kayser, 2005). This is achieved by reducing volume conduction from distal sites and by sharpening spatial resolution in order to avoid problems associated with the recording reference (Kayser & Tenke, 2010). It is noteworthy that nose-referenced EEG power spectra were also analyzed at standard 10-20 system sites to provide a bridge to previous literature using conventional EEG, however no group differences in hemispheric alpha asymmetry were observed using either methods. Jaworksa and colleagues (2014) probed for mastoid-referenced frontal and posterior (difference between the average of
medial and lateral posterior sites plus medial occipital site) alpha asymmetry, however, power was assessed in the alpha2 (10.5–13.0 Hz) band, which is different from the alpha power range assessed in the present study (8-12 Hz). Although the exact reason for differences in reports of alpha asymmetry distinction between antidepressant responders and non-responders in the above mentioned studies is unclear, it is important to take into consideration the fact that alpha asymmetry may be influenced by a number of moderator or mediator variables (Reid et al., 1998). Future work, perhaps comparing different analytical and methodological approaches to study alpha asymmetry, may address these confounding results better. In the present study, baseline parietal alpha asymmetry predicted response with the greatest overall accuracy of 77%. This was closely followed by baseline overall absolute alpha asymmetry which had 71% overall accuracy. Hence, clinically, it may be useful to assess alpha asymmetry during pre-treatment stages. However, in order to alter antidepressant treatment regimens based on alpha asymmetry, our findings must be replicated with larger sample sizes.

Few studies have probed the utility of scalp-indexed theta power in antidepressant response prediction, with conflicting findings (Iosifescu et al., 2009; Knott et al., 1996, 2000; Spronk et al., 2011; Tenke et al., 2011). On the other hand, studies utilizing LORETA have consistently demonstrated elevated pre-treatment theta current density in the rACC to be associated with eventual response to antidepressant medications (Korb et al., 2009; Mulert et al., 2007; Pizzagalli et al., 2001). Theta band activity localized to the rACC has been shown to correlate with rACC metabolism (Pizzagalli, 2003). Therefore, elevated pre-treatment theta activity has been hypothesized to reflect increased activity in the DMN, in which the rACC is a main hub with involvement in self-focused processing (Buckner et al., 2008; Scheeringa et al., 2008). Pizzagalli (2011) proposed that elevated resting rACC activity may lead to treatment
response through adaptive self-referential functions such as mindfulness and non-evaluative self-focus, and via re-establishment of fronto-cingulate connections. In the present study, baseline theta activity did not differentiate between escitalopram responders and non-responders. Perhaps if we had examined theta power across the entire scalp or had used source localization methods such as LORETA as done in previous studies, significant treatment differences may have emerged. However, it is also possible that our small sample size was insufficiently sensitive in distinguishing antidepressant responders and non-responders in pre-treatment theta power. Interestingly, an increase in relative theta power was observed at 2 weeks into escitalopram treatment (early change) in treatment responders, in the eyes closed condition. Given the association between theta band activity and rACC activity, an early increase in theta activity may reflect rapid antidepressant-induced activity within the DMN. This in turn may indicate continued adaptive self-pondering and continued re-establishment of fronto-cingulate connections, which may be required for eventual favourable outcome. Previous findings have demonstrated inconsistencies in the predictive utility of early change in theta activity towards antidepressant treatment response. Knott and colleagues (1996) demonstrated that elevated theta to acute treatment (2 weeks) with imipramine was associated with eventual favourable treatment response. Contrary to this, reduced frontal theta relative power at 1 week post-treatment has been shown to predict clinical response to SSRIs or venlafaxine at 8 weeks, post-treatment (Iosifescu et al., 2009). Methodological differences may account for this directional discrepancy (i.e. short- versus long-term changes and differences in study medication). Early change in theta activity did not show a significant correlation with clinical change to end of treatment in the present study. Nonetheless, our results indicate that antidepressants may alter early theta activity in a specific manner, which appears to be associated with eventual response outcome. Further
research with larger sample sizes is warranted to examine change in theta activity with acute and long term antidepressant use.

Regional hemispheric power in the beta and delta bands have largely been unexplored for their predictive utility in antidepressant treatment outcome. In the present study, responders showed greater relative delta power in the right versus left hemisphere at pre-treatment baseline in the eyes open condition. At 2 weeks post-treatment, the same pattern was observed for both absolute and relative delta power in the eyes closed condition and conditions collapsed, respectively. Hemispheric group differences in absolute beta power were only observed with acute treatment with responders demonstrating left lateralization of beta activity and non-responders showing the opposite, in the eyes open condition. However, in relation to these findings, only overall relative delta asymmetry at baseline and overall absolute delta asymmetry at 2 weeks post-treatment were shown to be correlated with clinical response at end of treatment, both of which showed moderate predictive utility: 73% and 68% overall accuracy, respectively. The neurobiological basis of these findings in the context of antidepressant treatment response is poorly understood.

Higher frequency, lower amplitude EEG waves such as those seen in the beta frequency range are thought to reflect behavioral arousal and attentional processes (Nofzinger et al., 2000). EEG beta power has been shown to have a temporal association with cortisol secretion suggesting a mechanistic link between increased HPA function and higher frequency brain activation (Chapotot et al., 1998). Keeping with this, changes in beta asymmetry observed at 2 weeks post-treatment in the responder group may reflect antidepressant induced variations in arousal. However, this explanation warrants further scrutiny, and this finding requires further replication in larger studies. High frequency beta power is inversely related to power in the
lower frequency, higher amplitude delta band which is typically noted during reduced alertness and sleep (Hlinka, Alexakis, Duikova, Liddle, & Auer, 2010; Knyazev, 2012; Nofzinger et al., 2000). More recently, frontal delta band power in the DMN was shown to highly correlate with functional activity in the parahippocampal gyrus, suggesting that delta frequencies may play a role in memory processes (Neuner et al., 2014). In depressed individuals, right lateralized absolute and relative delta power have been shown to be elevated relative to controls (Knott & Lapiere, 1987; Kwon et al., 1996). Keeping with this, neuropsychological studies have reported that right hemispheric deficit in neuropsychological data on MDD patients and unilateral right hemisphere damage are associated with impaired emotional processing including the perception, comprehension and expression of emotional stimuli (Coffey, 1987). Hence, findings of right lateralization of delta in escitalopram responders are similar to reports of increased slow wave activity in the right hemisphere of MDD patients versus healthy controls. Perhaps, this trait-like feature reflects a subtype of MDD patients that respond well to antidepressants. Hemispheric group differences observed in beta and delta band activity after acute treatment may additionally represent the effects of the lateralized distribution of the 5-HT system, which may be asymmetrically disrupted in a subtype of MDD patients (Bruder et al., 2001). While interhemispheric differences in alpha power have been the focus of antidepressant response prediction research, it may be worthwhile to explore asymmetries in other frequency bands as well, especially in the delta band. However, further research with larger sample sizes is required to replicate our findings and also to further understand the meaning of such findings in the context of antidepressant treatment outcome. Additional research is also needed to interpret the significance of condition-dependent asymmetries in this context.
An early decrease in prefrontal theta cordance has been shown to predict antidepressant treatment response across various clinical studies (Cook & Leuchter, 2001; Cook et al., 2002; Bares et al., 2007, 2008, 2010). Contrary to previous findings and our hypothesis, outcome groups did not differ in prefrontal theta cordance. However, escitalopram non-responders did show a significant increase in prefrontal theta cordance measured from baseline to 2 weeks post-treatment. This finding is of interest as it is in the opposite direction of what is typically observed in antidepressant treatment responders. Hence, measures of early change in prefrontal theta cordance might be of value as predictors of clinical outcome to antidepressant medication. However, it remains unclear as to what theta cordance actually reflects at the level of the brain. Iosifescu (2011) interpreted early changes in theta cordance to be a reflection of early changes in brain activity caused by antidepressant medication. Moreover, considering that theta cordance is a measure that is based on theta band activity, the neurobiological mechanism proposed by Pizzagalli (2011) to explain the association between rACC activity and antidepressant treatment response may be useful here as well (Baskaran et al., 2012). However, no clear mechanisms have been proposed in support of this.

The results of this study should be interpreted within the context of four primary limitations, the most notable being sample size. When the depressed group was divided into responders and non-responders, sample sizes were further reduced. In particular, the failure to detect significant group differences in pre-treatment alpha power, and the limited correlation seen between EEG parameters and clinical response may be because of the small sample size of the study. For example, there was a numerical trend toward elevated baseline absolute alpha power in the responder group, and a larger study may have yielded statistically significant results. Secondly, the EEG findings were obtained during open-label treatment, and placebo
effects are unknown. A placebo arm should ideally be included in future work. Thirdly, patients receiving other psychotropic medications within 1 week of study baseline, with major psychiatric comorbidity, active substance dependence or abuse, or severe physical illness were excluded. The findings therefore may not generalize to less controlled treatment conditions or entirely naturalistic samples. Finally, there are a number of potential confounding factors associated with this study.

In the present study, EEG data for all participants were collected across three different sites. Although the parameters for EEG data collection were standardized across sites, the equipment used to collect data differed between sites (i.e. different amplifier systems, different EEG caps, etc.). For this reason, we repeated our statistical analyses with site as a covariate, and results did not differ. Therefore, it is unlikely that site differences in EEG data acquisition equipment, is a confounding factor in this study, however, the potential is present. Indeed, one of the major limitations of previous EEG work is a lack of standardization of EEG recording and analysis. Equipment used to record EEG activity has greatly varied from study to study. Differences exist in the number of electrodes used, type of montages used, and also in the placements of electrodes. These kinds of differences make it difficult to compare results from across studies. Recording, pre-processing parameters and analysis methods have also greatly varied from study to study. These parameters include length of recording, order of recording, reference electrode(s), length of used EEG epochs, etc. The issue of reference choice is of special importance as previous work indicates that it can greatly influence alpha power/asymmetry (Hagemann, 2004; Jaworska et al., 2012; Stewart, Bismark, Towers, Coan & Allen, 2010). In the present study, during data pre-processing, each channel was re-referenced to the average of all channels to avoid systematic effects that may arise from referencing to a particular channel.
(Alhaj et al., 2011). However, there are problems associated with this method too. An alternate approach is to use different reference montages for cross-comparison in a single study, but this is rarely feasible (Jaworska et al., 2014). A reference-free approach such as CSD analyses may be a better approach for future studies. The inclusion of elderly patients is another potential confound because aging is associated with EEG abnormalities, namely reduced alpha power and elevated slow wave activity (Babilono et al., 2006; Klimesch, 1999; Rossini et al., 2007). However, there was no significant difference between the responder and non-responders groups on mean age. For future studies, the exclusion of elderly participants may be useful.

In spite of these shortcomings, our results suggest that hemispheric asymmetries in the alpha and delta bands at pre-treatment baseline and at 2 weeks post-treatment have moderate to moderately strong predictive utility towards antidepressant treatment response. Such findings hold significant potential for improving clinical practice in psychiatry by eventually guiding clinical choice of treatments. Larger studies are required to validate our findings, and to understand the neurobiological basis of EEG biomarkers, which would help to further guide the classification of treatment outcome. Future multi-site research would benefit from standardization of EEG recording, pre-processing and analysis. For example, the International Pharmaco EEG Society (IPEG) recently released guidelines (Jobert et al., 2012) that help to make EEG results obtained from different recording sites and study centers comparable and the International Federation of Clinical Neurophysiology has released guidelines for ERP research (Duncan et al., 2009). In order to facilitate the use of EEG in the clinical management of MDD, EEG markers should be compared for their predictive power, and they should also be compared and integrated with biomarkers from other domains such as clinical, imaging, genetics,
proteomics, etc. The combination of parameters may further increase the accuracy of response prediction.

6.2 EEG as a Biomarker of Illness in Major Depressive Disorder

The present study additionally examined the utility of regional hemispheric differences in EEG frequency band power, alpha asymmetry and prefrontal theta cordance in predicting MDD diagnosis. MDD patients displayed reduced absolute delta power compared to healthy controls, in the eyes open condition. Groups also differed in the eyes closed condition with MDD patients demonstrating enhanced absolute delta power versus healthy controls. When probed for predictive utility towards MDD diagnosis using ROC analysis, absolute delta power in both the eyes open and eyes closed conditions, did not yield significant AUC curves. MDD and healthy controls did not differ in alpha asymmetry or prefrontal theta cordance.

Several studies have investigated EEG biomarkers of depression during resting state, namely frequency band power and alpha asymmetry, many of which have resulted in conflicting findings. Also, no previous study has examined the utility of prefrontal theta cordance towards MDD prediction. Lastly, a major limitation of prior research that mimics the pitfall of previous EEG response predictor studies is that not all studies have reported performance characteristics for their candidate biomarkers, specifically the sensitivity, specificity, positive and negative predictive values. To our knowledge, this is the first study, to date that compares frequency band power, alpha asymmetry and prefrontal theta cordance for predictive utility towards MDD diagnosis. Furthermore, a multi-site initiative to undertake this task adds to the novelty of this study.

Previous studies investigating the predictive utility of frequency band activity have indicated that elevated alpha activity during rest is one of the main and most consistent findings
in MDD patients (Jaworska et al., 2012; Pollock & Schneider, 1990; Possel et al., 2008; Prichep & John, 1992; Ricardo-Garcel et al., 2009; Roemer et al., 19992). Alpha activity has been shown to inversely correlate with functional cortical activation (Laufs et al., 2003). Therefore, elevated alpha power suggests that diffuse cortical hypoarousal may be a feature of MDD. In the present study, MDD patients exhibited a numerical trend of greater absolute and relative alpha power compared to healthy controls but these differences did not reach statistical significance. This may be a reflection of our small sample size and perhaps with larger sample sizes, significant alpha power differences between MDD patients and healthy controls may emerge.

Scalp-indexed beta and theta band activity have also been shown to be elevated in MDD patients relative to healthy controls (Flor-Henry et al., 2004; Grin-Yatsenko et al., 2010; Knott et al., 2000, 2001; Knott & Lapierre, 1987; Lieber & Prichep, 1988; Kwon et al., 1996; Suzuki et al., 1996). Beta excess has been hypothesized to reflect cortical excitation and increased metabolic activity in the brain (Grin-Yatsenko et al., 2010). In addition, a mechanistic link between HPA function and beta power has been proposed (Chapotot et al., 1998). Theta activity has been reported to positively correlate with glucose metabolism in the rACC, an area of the brain shown to be functionally abnormal in MDD patients (Mayberg et al., 1999; Pizzagalli et al., 2003). Activity in the theta band is further viewed as an EEG index of activity in the DMN, in which the rACC is a main hub with involvement in self-focused processing (Buckner et al., 2008; Scheeringa et al., 2008). Studies using source localization methods such as LORETA have indicated decreased theta activity localized to the rACC in MDD patients (Jaworska et al., 2013; Coutin-Churchman & Moreno, 2008; Saletu et al., 2010; Wienbrueh et al., 2003). However in the present study, we were not able to replicate previous findings of elevated beta activity in MDD patients or group differences in theta band activity. It is possible that our small
sample size may be insufficiently sensitive in distinguishing differences between MDD patients and healthy controls, in these frequency bands.

We did, however, observe group differences in overall absolute delta power that were condition dependent. In the eyes open condition, MDD patients demonstrated reduced absolute delta power relative to healthy controls while the opposite was observed in the less arousing eyes closed condition. These group differences did not, however, display significant predictive utility towards MDD diagnosis. Our findings of elevated delta power in MDD patients in the eyes closed condition support previous findings of elevated delta activity in MDD patients (also measured during eyes closed resting state conditions) (Knott et al., 2000; Knott & Lapierre, 1987; Kwon, Youn, & Jung, 1996; Ricardo-Garcell et al., 2009). However, our findings of reduced delta power in the eyes open condition, is opposite to previous reports. Although it is unclear what exactly may account for the discrepancy in the direction of delta activity in the eyes open versus eyes closed conditions, arousal level may explain these differences. Low frequency, high amplitude delta band activity is thought to characterize cortical deactivation and is thought to be associated with reduced alertness and deeper stages of NREM sleep (Hlinka et al., 2010; Knyazev, 2012; Merica & Fortune, 1997). This may explain why greater delta power was observed in the less arousing eyes closed condition while reduced delta power was noted in the more arousing eyes open condition. More recent research has indicated that delta power is not only observed during sleep, but that it also plays a crucial role during rest (Alper et al., 2006; Chen, Feng, Zhao, Yin, & Wang, 2008). Neuner and colleagues (2014) reported a strong correlation between frontal delta power and activity in the DMN, using simultaneous fMRI–EEG. Activity in the DMN is attenuated when the brain is task oriented, and the network is more active when the brain is at rest. Elevated resting state delta activity in MDD may reflect greater
activation of the DMN in the brains of these individuals, suggesting a persistent deficit in arousal. Interestingly, elevated delta band activity has also been reported with aging and other clinical populations. Aging has been associated with an overall “slowing” of EEG activity (Klimesch, 1999; Rossini et al., 2007). In order to avoid age as a confounding factor in EEG studies of MDD patients, it may be necessary to exclude elderly subjects from the study population. Pathologic increases in slow-wave EEG activity are also observed in clinical populations including schizophrenia, ADHD, and in subclinical cognitive deterioration such as mild cognitive impairment or Alzheimer’s disease (Hughes & John, 1999). This makes elevated delta activity an EEG abnormality that is equally common to disorders which raises questions about its clinical usefulness in MDD.

Studies investigating alpha asymmetry have demonstrated that MDD tends to be characterized by left frontal hypoactivation (greater alpha power over the left hemisphere in frontal regions) (Deslandes et al., 2008; Henriques & Davidson, 1990; Jaworska et al., 2012; Possel et al., 2008) and right posterior hypoactivation (greater alpha power over the right hemisphere in posterior regions) (Bruder et al., 2005; Kentgen et al., 2000). In the present study, MDD patients did not differ significantly from healthy controls in alpha asymmetry, in the eyes open or in the eyes closed conditions. Patient heterogeneity and methodological differences may account for these discrepancies. For example previous studies have greatly differed in reference choice and alpha asymmetry has been shown to be influenced by the location of the reference electrode (Hagemann, 2004; Jaworska et al., 2012; Stewart, et al., 2010). In the present study, while EEG data were collected from different sites using different reference electrodes, during offline data-analysis, cross-site data were combined and re-referenced to a common average during offline-analysis. Hence, it was not possible to compare the effects of reference choice on
alpha asymmetry. However, our negative findings are supported by previous studies that have failed to demonstrate alpha asymmetry in MDD patients (Carvalho et al., 2011; Gold et al., 2013; Price et al., 2008; Reid et al., 1998). Therefore, alpha asymmetry seems to be a problematic EEG biomarker that fails to consistently predict MDD illness which raises questions about its validity potential. Future studies with large sample sizes, perhaps using different reference montages in the same study, are required to address these inconsistencies, however this approach may not be feasible for translation to clinical practice. A reference-free approach such as CSD analyses may be a better approach for future studies.

Exploratory analyses of prefrontal theta cordance demonstrated no significant group differences between MDD patients and healthy controls, in eyes open or eyes closed conditions. These findings are novel as no previous study has explored this EEG parameter in the context of MDD illness prediction. Perhaps, the predictive utility of prefrontal theta cordance lies only in antidepressant response prediction and not in illness prediction of MDD, however this finding has to be replicated with larger sample sizes before we can draw definite conclusions.

The results of this study should be interpreted within the context of three main limitations, the most notable being sample size. For example, numerically, there was a trend of elevated absolute and relative alpha power in the MDD group versus healthy controls, and a larger study may have yielded statistically significant results. Secondly, the stringent exclusion criteria including no patients receiving psychotropic medications within 1 week of study baseline, with major psychiatric comorbidity, active substance dependence or abuse, or severe physical illness may hinder the generalizability of our study findings to less controlled treatment conditions or entirely naturalistic samples. Finally, there are a few potential confounding factors associated with this study.
In the present study, site differences primarily, variation in the equipment used to collect data differed (i.e. different amplifier systems, different EEG caps, etc.) may have been a confounding factor. For this reason, we repeated our statistical analyses with site as a covariate, and found that our results did not differ. Therefore, it is unlikely that site differences in EEG data collection, is a confounding factor in this study, however, the potential is present. Indeed, one of the major limitations of previous EEG work is a lack of standardization of EEG recording and analysis, as discussed in Chapter 6.1. The inclusion of elderly patients is another potential confound because aging is associated with EEG abnormalities, namely, reduced alpha power and elevated slow wave activity (Babilono et al., 2006; Klimesch, 1999; Rossini et al., 2007). However, there was no significant difference between the MDD and healthy controls groups on mean age. For future studies, the exclusion of elderly participants may be useful.

Our study demonstrates that absolute delta power may help differentiate MDD patients from healthy controls. The lack of EEG group differences between MDD patients relative to healthy controls in alpha asymmetry raises questions about its predictive utility as an EEG biomarker of illness in MDD. Lastly, our findings demonstrating that prefrontal theta cordance may not be an effective biomarker of MDD illness are novel to this field. However, given the relative small sample sizes, it is difficult to draw strong conclusions about these results. Larger studies are required to validate our findings, and to understand the neurobiological basis of EEG biomarkers in the context of depression. Future multi-site research may benefit from standardization of EEG recording, pre-processing and analysis, as set out by IPEG (Jobert et al., 2012).

Despite decades of research, EEG is not being used clinically in the management of MDD. One reason for this is because many researchers studying the same EEG parameters in
the context of MDD have reported conflicting results. This could be attributed to patient heterogeneity. While a single EEG biomarker may not identify all patients that are classified as having MDD, EEG abnormalities are more likely to identify subtypes within MDD. In order to better translate the use of EEG in the clinical management of MDD, EEG markers should be cross-compared for their discriminative power, and they should also be compared and integrated with other kinds of biomarkers from other domains such as clinical, imaging, genetics, proteomics, etc. Another important limitation to consider is that some EEG abnormalities are not unique or specific to MDD, as they have been reported elsewhere in different clinical populations. Therefore, the clinical utility of EEG can further be improved by not only demonstrating differences in EEG markers between MDD patients and healthy controls but also demonstrating differences between MDD patients and comparison groups, for predicting differential diagnoses.

6.3 Conclusion and Future Directions

The findings presented within this study are encouraging in several respects. First, they demonstrate that overall and regional hemispheric asymmetries in the alpha and delta bands at pre-treatment baseline and at 2 weeks post-treatment have moderate to moderately strong predictive utility towards antidepressant treatment response. Baseline hemispheric asymmetry differences are hypothesized to be vulnerability markers of MDD that may represent the underlying pathophysiology of depression. These trait-like markers may reflect a subtype of MDD patients that respond well to antidepressants. Baseline predictors are based on the information that is available to clinicians at the initiation of treatment. They are important because they could inform clinicians which treatment may be more effective than other
treatments and can aid in treatment choice. While less is known about hemispheric asymmetry differences that arise with acute treatment, such findings may represent the effects of the lateralized distribution of the 5-HT system, which may be asymmetrically disrupted in a subtype of MDD patients (Bruder et al., 2001). Process predictors are based on information that becomes available to the clinician during the process of treatment. Such predictors are also important as they can help determine whether continuation of the current therapy will lead to response or non-response. Second, it appears that baseline parietal alpha asymmetry is superior to other hemispheric asymmetry findings in predicting antidepressant treatment response. However, our results indicate that it may also be worth to focus attention on the predictive utility of delta asymmetry (as a baseline and process predictor) towards antidepressant treatment outcome. Such findings hold significant potential for improving clinical practice in psychiatry by eventually guiding clinical choice of treatments. This would greatly benefit patients awaiting relief from depressive symptoms as treatment optimization would help overcome the problems associated with delayed recovery. Moreover, information that arises during the early course of treatment which indicates the likelihood that a medication would be helpful could be used in making decisions about whether to continue or switch medications. In addition, information indicating that a medication is likely to prove effective eventually might help encourage adherence during the critical first weeks of treatment, when the risk of premature discontinuation is greatest. In order to aid early clinical decision making, future studies should examine EEG biomarkers using other antidepressants with different mechanisms of actions. Generalizability is also hampered by the fact that the majority of previous studies have focused on identifying EEG markers of treatment response to antidepressant medications. Hence, it is questionable whether results from these studies can generalize to patients receiving somatic treatments like repetitive
transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), or to those receiving psychotherapy such as cognitive behavioural therapy (CBT). Additionally, our study demonstrates that absolute delta power may help differentiate MDD patients from healthy controls while raising questions about the predictive utility alpha asymmetry and prefrontal theta cordance as EEG biomarkers of illness in MDD. The findings of this study must be interpreted with caution due to the small sample size. Larger sample sizes are required to validate our findings, and to more adequately understand the neurobiological basis of EEG biomarkers of illness prediction and treatment response prediction in MDD. Future studies may also benefit from combining various candidate EEG biomarkers together or by combining candidate EEG biomarkers with biomarkers from other domains including clinical, imaging, proteomics, genetics, etc. Such integration may better enhance the sensitivity and specificity of illness prediction and treatment outcome prediction. To further improve the clinical utility of EEG in the management of MDD, data collection and analyses need to be standardized in large multicenter clinical trials, and candidate EEG biomarkers should be compared for their discriminative and predictive power. The future of EEG for clinical application may also lie in the coupling of digital methods of signal analysis and of image processing, such as simultaneous EEG-fMRI, and in machine learning systems which have been shown to learn previously derived patterns to predict MDD diagnosis or to distinguish responders from non-responders to treatment, and to become progressively more accurate in their predication as more data are added to the system (Hosseinifard, Moradi, Rostami, 2013; Khodayari-Rostamabad et al., 2010).
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1. Introduction

Major Depressive Disorder (MDD) is a common and persistent psychiatric illness associated with personal suffering, and significant social and functional impairment (Lopez et al., 2006). The World Health Organization (WHO) ranks depression as the third leading cause of global disease burden and projects that by 2030, it will be the first leading cause worldwide (WHO, 2011). Tremendous societal costs are associated with the disability caused by depression (Greenberg et al., 2003). Higher medical costs, in particular, arise largely from non-response to treatment as initial treatments frequency do not lead to recovery (Simon et al., 2006).

Very few patients who receive adequate pharmacotherapy will achieve remission defined as absence or near absence of symptoms (Rush et al., 2006). The Sequenced Treatment Alternatives to Relieve Depression (START) study demonstrated that less than 50% of depressed patients respond (response is defined as 50% or more improvement in depressive symptoms) to the first antidepressant they try (Trivedi et al., 2006). Even less, that is, only 30% of patients achieved full remission. The probability that an individual will achieve remission decreased steadily with each new treatment failure. Patients who fail to achieve full remission have a more recurrent and chronic course of illness, increased medical and psychiatric co-morbidities, greater functional burden, and increased social and economic costs (McIntyre and O'Donovan, 2004). Hence, the management of depression and patient recovery both remain a challenge.

The majority of MDD patients experience lengthy trial-and-error periods with different antidepressant medications before a successful medication is identified. In practice, it has been well documented that approximately 6–8 weeks of “watchful waiting” are required to observe full recovery with a certain medication (Bauer et al., 2007; Fochtmann and Gelenberg, 2005). Moreover, delayed recovery leaves patients with a heightened risk of suicide (McIntyre and O'Donovan, 2004). Hence, the current treatment approach is seriously flawed leading to prolonged patient suffering and risk that patients will discontinue treatment efforts. Management of depression with antidepressant medication could be greatly improved with indicators early in the course of treatment that predict the likelihood of response, remission and non-response.

A promising area of research that has recently attracted great attention is the development and application of biomarkers that
are predictive of treatment response. According to Frank and Hargreaves (2003), biomarkers are objectively measured characteristics that indicate the intrinsically causative illness, the clinical course, and its modification by treatment. A more recent definition has been proposed by the "Biomarkers Definitions Working Group" in the context of drug discovery: biomarkers are objectively measured indices of pharmacological response or biological processes that are quantifiable, precise, and reproducible (Aitken et al., 2001). According to the latter definition, a biomarker may be used to predict clinical response to treatment. Identifying reliable biomarkers will not only aid clinicians in selecting antidepressant treatment for individual patients but also provide a critical step in drug discovery, both of which could have a significantly positive impact on patient suffering and economic burden by reducing or eliminating lengthy and ineffective treatment trials.

Several correlates of response to antidepressant treatment have been proposed but none have been validated as of yet. Various parameters of genetics, proteomics, metabolites, neuroendocrinology, neuroimaging, neurophysiology, and clinical characteristics have been suggested as potential biomarkers of antidepressant treatment outcome. For example, functional polymorphisms in genes of monoaminergic pathways such as those in the serotonin (5-HT) system have been shown to be predictive of outcome to selective serotonin reuptake inhibitor (SSRI) treatment (McMahon et al., 2006; Serretti et al., 2005). Recent studies employing the combined dexamethasone/corticotropin releasing hormone test have demonstrated that hypothalamic-pituitary-adrenal axis activity can also predict the efficacy of antidepressant medication in patients with MDD (Jiang et al., 2007; Pasakias et al., 2010; Schule et al., 2009). Functional neuroimaging studies have indicated a reduced alpha power in the posterior cingulate cortex (PCC) and response to various antidepressants (Chen et al., 2007; Davidson et al., 2003; Langmecker et al., 2007; Mayberg et al., 1997; Savina et al., 2003). However, many of these findings have not been consistently replicated or do not hold sufficient predictive value to be implemented in clinical settings. Moreover, the low prevalence of genetic and biochemical predictors and the high cost of neuroimaging make such predictors problematic for widespread clinical use (Lesesue, 2011).

Reliable predictors identified to date include physiological and symptomatic characteristics of patients that emerge early in the course of treatment (Leuchtler et al., 2000a). A neurophysiological biomarker that has promise as a predictor of treatment outcome is electroencephalography (EEG). EEG is a measure of the brain's spontaneous electrical activity acquired from electrodes placed on the scalp. Recorded activity at each electrode is the gross measure of electrical activity arising from a number of different neurons in cortical areas surrounding the electrode. The rhythmic EEG spectrum is categorized into various oscillation frequencies: delta waves (0-4 Hz) accompany slow wave sleep, theta waves (4-8 Hz) reflect a state of drowsiness, alpha waves (8-12 Hz) accompany a relaxed state, and beta waves (12-30 Hz) reflect an engaged or active brain. EEG signals are either described in terms of absolute or relative power. Absolute power is the measure of power in an EEG frequency band at a given electrode measured in microvolts (μV²). Relative power is the percentage of power in any frequency band compared with the total power of the entire EEG spectrum.

EEG has clear advantages over other proposed biomarkers as it is non-invasive, widely available, and has a relatively low cost. Furthermore, a more advanced form of EEG, called quantitative EEG (QEEG) now exists. In QEEG, electrical signals from the brain are converted to digital form, which allows patterns undetectable by the naked eye to be revealed. There are some limitations to consider with the use of EEG such as lower spatial resolution when compared to other neuroimaging techniques like functional magnetic resonance imaging (fMRI). However, source localization techniques have been developed in an attempt to overcome this problem.

A number of different EEG parameters have been considered as potential biomarkers of antidepressant response such as change in frequency band measures, alpha hemispheric asymmetry, theta coherence, antidepressant treatment response index (ATR), and evoked potentials. Although different reviews have focused on the evidence in support of these various techniques as potential biomarkers of antidepressant treatment response, none have thoroughly explored the neurobiological basis of these. For a detailed review of studies focusing on the utility of EEG as a biomarker of treatment outcome in depression, the reader is referred to other sources (Albacete et al., 2011; Bruder et al., 2011; Leuchtler et al., 2000a). We will not only review the literature pertinent to these EEG parameters, but we will also discuss biological mechanisms for each EEG-derived biomarker in the context of treatment response.

2. Change in EEG frequency band activity

Several studies have investigated the relationship between clinical outcome to antidepressants in patients with MDD and the change in EEG frequency bands, particularly in the alpha and theta bands.

2.1. EEG alpha band activity

Pre-treatment changes in the alpha band, that is increased alpha power has been shown to differentiate responders from non-responders anywhere from 3 to 6 weeks of treatment with tricyclic antidepressants (TCAs) such as clomipramine and imipramine, and with SSRIs such as paroxetine and fluoxetine (Bruder et al., 2001; Knott et al., 1996, 2000; Ulrich et al., 1988). However, there remains a question of what the change in alpha frequency in the treatment of depression actually means.

A possible mechanism involving the right temporo-parietal and subcortical regions was suggested by Bruder et al. (2008) to account for the increased alpha power seen in depressed patients who respond to SSRIs treatment. This hypothesis was based on the notion that increased pre-treatment alpha activity may be indicative of the correspondence between low serotonin activity and low arousal. It is known that 5-HT activity mediates behavioural arousal. Low serotoninergic activity could in turn be reflective of decreased activity of the mesencephalic raphe nuclei and cortical afferents (Bruder et al., 2000). Moreover, depression may be related to dysfunction of temporo-parietal mechanisms, which may mediate emotional arousal (Heller et al., 1995). This biological mechanism has been proposed to play a role in both increased alpha power and alpha asymmetry (see section 3) found in MDD responders.

2.2. EEG theta band activity

Studies investigating pre-treatment and early changes in the theta band have reported conflicting results. Decreased pre-treatment theta band activity associated with treatment response has been reported for the TCA, imipramine and more recently with open-label SSRIs at 8 weeks with 63% accuracy (Lesesue et al., 2009; Knott et al., 1996). The latter study also showed that reduced frontal theta relative power at 1 week post-treatment was predictive of treatment response at 8 weeks with 60% accuracy. Conversely, increased pre-treatment theta band activity has been shown to differentiate responders from non-responders at 6 weeks post-treatment with the SSRI, paroxetine (Knott et al., 2000). More recently, increased absolute theta power at baseline associated with treatment response was also demonstrated in MDD patients treated with a variety of antidepressants (Spronk et al., 2011). These studies
are limited due to the mixed results in terms of the direction of theta band activity associated with treatment response. Therefore, a more sensitive method may help in overcoming this limitation.

Other studies have utilized a sensitive source localization method called Low Resolution Tomographic Electromagnetic Analysis (LORETA) to examine change in theta band activity. LORETA is a technique used to create three-dimensional images to localize cortical and subcortical sources from where EEG signals generate. Elevated, pre-treatment theta current density, localized by LORETA to the rACC has been associated with response to nortriptyline, citalopram, reboxetine, fluoxetine, or venlafaxine, in depressed patients (Korb et al., 2006; Mulert et al., 2007; Pizzagalli et al., 2001).

In a recent review, Pizzagalli (2011) demonstrated that the strength of the link between resting rACC activity and antidepressant treatment response is quite robust. The review also proposed a neurobiological mechanism to explain this association. Specifically, the rACC is a main hub within the default network (DN) of the brain, which is involved in self-focused processing (Buckner et al., 2008). The DN also includes the ventromedial prefrontal cortex (vPFC), dorsal medial PFC, posterior cingulate, retrosplenial cortex, lateral parietal cortex, lateral temporal cortex, and hippocampal formation. Elevated resting activity in these brain regions is associated with focusing on reflexive thought or task-independent introspection such as rumination, remembering and planning (Simpson et al., 2001). Of particular interest is rumination, which is a mechanism of responding to distress by repetitively focusing on the symptoms, causes and consequences of the distress (i.e., depression) (Nolen-Hoeksema et al., 2008). According to a multidimensional view of rumination, it is comprised of two components: reflective pondering and brooding (Teyler et al., 2003). Reflective pondering is seen as an adaptive process by which, cognitive problem solving is achieved. Conversely, brooding involves analytic self-focus, which is ultimately destructive because it worsens depressive symptoms (Watts and Teasdale, 2004). Based on these findings, Pizzagalli (2011) proposes that elevated resting rACC activity may lead to treatment response through adaptive self-referential functions such as mindfulness and non-evaluative self-focus.

When processing external stimuli, DN regions show reduced activity lending the network an alternate name: the task-negative network (TNN) (Shulman et al., 1997). Conversely, engaging in goal-oriented tasks requiring attention and cognitive control activates the task-positive network (TPN). The TPN includes the dorsolateral PFC, dorsal ACC, the intraparietal sulcus, and the middle temporal area. In MDD, functional and structural abnormalities in frontocingular pathways may impair the relationship between the DN and TPN, which could lead to disrupted self-focus and maladaptive rumination such as brooding (Pizzagalli, 2011). This could be explained by impaired amygdalar activity as functional connections also exist between the DN and limbic/paralimbic regions (Schmitz and Johnson, 2006). Therefore, Pizzagalli (2011) further proposes that increased rACC activity associated with treatment response to antidepressants may play a key role in re-establishing the functional connections between the DN and TPN, indeed, several domains of research including neuropsychology, neurophysiology and neuroimaging have demonstrated significant frontocingular dysfunction in depression. The reader is referred to the review by Pizzagalli (2011) for a thorough review of the evidence in support of this.

3. Alpha hemispheric asymmetry

The majority of studies reporting increased alpha power in association with antidepressant treatment response in depressed patients also report hemispheric asymmetry. Asymmetry in the alpha band characterized by left lateralization has been demonstrated in treatment response with TCAs and the SSRI, fluoxetine (Bruder et al., 2001, 2008; Ulrich et al., 1984). In these studies, alpha asymmetry was a significant predictor of treatment outcome at 4 weeks and at 12 weeks post-treatment, respectively. Given the inverse relation between alpha power and cortical activity, increased alpha is reflective of reduced cortical activity whereas, decreased alpha reflects increased activity (Laufs et al., 2003). While greater left than right hemispheric activation at occipital sites was associated with treatment response, non-responders tended to show the opposite pattern of hemispheric activation (greater right than left) in frontal and posterior regions (Bruder et al., 2008).

Findings of left lateralization are in conflict with reports of reduced left frontal activity (increased alpha activity) in depressed patients (Henriques and Davidson, 1981). Bruder et al. (1986) approached the conflict in the directionality of hemispheric activation by suggesting that decreased left prefrontal activation in depression may disinhibit left temporoparietal regions, resulting in enhanced left hemisphere advantage in fluoxetine responders. Electrophysiological evidence supports this hypothesis as it demonstrates an inhibitory relationship between frontal and temporoparietal regions (Knight et al., 1986; Tucker et al., 1981). An additional explanation provided by Davidson and Henriques (2000) proposes that left frontal hypoactivation can be interpreted as a deficit in approach mechanisms, while right frontal hypoactivation can be interpreted as a deficit in withdrawal mechanisms.

Alpha asymmetry found in treatment responders may be trait-dependent as it has been demonstrated in depressed adolescents and adults; as well as in euthymic patients (Henriques and Davidson, 1980; Kortgen et al., 2000; Reid et al., 1998). It has also been found in both young and adult offspring of depressed parents (Bruder et al., 2005; Jones et al., 1997). Keeping with this perspective, it has been suggested that alpha hemispheric asymmetry may represent the underlying pathophysiology of depression as a trait marker of vulnerability to a familial form of depression that responds to serotonergic agents (Bruder et al., 2008).

While the meaning of alpha asymmetry in the context of treatment response remains unclear, attempts have been made to explain it. Bruder et al. (2001) hypothesized that the 5-HT neurotransmitter system may have a lateralized distribution in the brain and may be asymmetrically disrupted in a subtype of depressed patients. This is important because not only is 5-HT implicated in mood disruption; the 5-HT system is also affected by antidepressant medication. Although some studies have supported the hypothesis that 5-HT pathways are asymmetric for opposite sides of the brain (Mandell and Knapp, 1979; Tucker and Williamson, 1984), other studies have failed to replicate this asymmetry (Arico et al., 1991; Arco and Meltzer, 1991). Bruder et al. (2008) have also hypothesized that alpha asymmetry in SSRI responders may be reflective of low arousal associated with low serotonergic activity (see section 2.1).

More recently, in a review paper, Alhaj et al. (2011) discussed the evidence that suggests gene polymorphisms of the 5-HT1A receptor may be associated with trait EEG alpha asymmetry (Bismark et al., 2010). Not only are 5-HT1A receptor polymorphisms largely associated with the pathophysiology of depression, the 5-HT transporter of the brain provides one of the primary targets of antidepressant medication (Blier and de Montigny, 1994; Saitz et al., 2009).

4. Theta cordance

Theta cordance is a QEEG measure that combines information from both absolute and relative power from the EEG theta spectra according to a specific algorithm (Leuchter et al., 1994). The combined information has been reported to have a stronger
correlation with regional cerebral perfusion than other measure alone (Leuchter et al., 1999). Also, compared to standard spectral analysis, coherence is less influenced by age, gender and severity associated with baseline depression (Moran et al., 2005).

Increased frontal theta coherence was measured in depressed patients as early as 48 h (trend) to 1 week (significant) post-treatment has been shown to be predictive of treatment response with SSRI such as fluoxetine, and with the serotonin-norepinephrine reuptake inhibitors (SNRI), venlafaxine (Bares et al., 2008; Cook et al., 2002) and Cook and Leuchter, 2001). The early reduction in theta coherence has been shown to have an overall predictive accuracy of 90%.

It remains unclear as to what theta coherence actually reflects. Of interesting note, while other EEG derived biomarkers demonstrate differences in brain activity at baseline prior to treatment, frontal theta coherence does not. Instead, significant differences are seen 2–7 days post-treatment. Kaabouch (2011) interpreted this as a reflection of early changes in brain activity caused by antidepressant medication. However, no clear mechanisms have been proposed in support of this (see section 5). Moreover, since theta coherence is based on theta band activity, the neurobiological mechanism proposed by Pitsis et al. (2011) to explain the association between rACC activity and antidepressant treatment response may be useful here as well (see section 2.2).

5. Antidepressant treatment response index (ATR)

The antidepressant treatment response index (ATR) is a QEEG measure that integrates from baseline to post-treatment of the beta power extracted at pre-treatment baseline and at 1 week post-treatment. ATR was examined for the first time for its usefulness as a neurophysiological biomarker for treatment response in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression study (BRITE-MD) (Leuchter et al., 2009c). In BRITE-MD, patients were treated with escitalopram (ESC) for 1 week, after which time, they were randomized to continue on ESC, switch to bupropion (BUP) or augment with BUP. Overall, ATR had 74% accuracy in predicting both response and remission. The BRITE-MD study also showed that ATR is predictive of differential response to either ESC or BUP monotherapy. On a Receiver Operating Characteristic (ROC) curve for predictive accuracy of ATR with ESC, an optimal threshold of 58.6 was chosen. Patients with high ATR values (above the threshold value) were 2.4 times more likely to respond to ESC than those with low ATR values, below threshold (68% vs. 28%, p = 0.001). Furthermore, those with ATR values below threshold who were switched to BUP treatment were 1.9 times more likely to respond to BUP alone than those who remained on ESC treatment (53% vs. 28%, p = 0.034). Therefore, not only may ATR be a useful tool in predicting the effectiveness of antidepressant therapy, it may also be useful for guiding treatment decision.

Due to the complexity of ATR and even theta coherence, it is difficult to interpret results derived from these measures, in terms of biological mechanisms. Based on these limitations, Kuo and Tsai (2010) questioned the use of these measures as biomarkers of antidepressant response. Leuchter (2010) responded to the questions raised by Kuo and Tsai by explaining that coherence and ATR are largely related. He referred back to the BRITE-MD in which his team theorized that both biomarkers reflect activity arising from frontal rhythmic activity. Rhythmic frontal activity is thought to originate from regions in the ACC and PPC, regions implicated in the pathophysiology of depression (Aasland et al., 1991). Hence, it was hypothesized that theta coherence and ATR may reflect early functional changes in these areas of the brain. Since ATR is a combined measure of alpha and theta activity, mechanisms proposed for each of these frequency bands changes in the content of treatment response may be useful here as well (see section 2). However, how ATR is associated with differential response to antidepressant medication remains largely unexplained and merits further investigation.

6. Event-related potentials (ERPs)

Different from spontaneous EEG, evoked potentials represent electrical potentials recorded from the scalp following the presentation of a stimulus. Event-related potentials (ERPs) are a measure of change in voltage, which represent brain activity elicited in response to sensory stimulation (i.e., visual or auditory). Recorded ERPs comprise distinctive peaks and troughs reflective of positive and negative fluctuations in voltage and are referred to as 'components'. Different components have been identified and named based on the direction of the waveform deflection (P for Positive and N for Negative) and on the specific time course of the waveform at which it occurs post-stimulus (Picton et al., 2000). Mainly, two ERP components have been the focus of investigation in depression including the P300 (or P3) and the Loudness Dependent Auditory Evoked Potential (LDAEP).

6.1. The P300 component

The P300 component is measured at 300 msec after presenting an auditory stimulus. This ERP index is believed to reflect the cognitive processes of attention and auditory processing (Mulert et al., 2004; Volpe et al., 2007). In depressed patients, a delay in the latency of the P300 component has been reported (Bruder et al., 1991). This delay has been shown to normalize after 4 weeks of treatment with antidepressants (Herzog et al., 2005). Beyond this finding, only two studies have published data on the relationship between P300 and antidepressant treatment response. One study reported that higher amplitude of the P300 wave at occipital sites was associated with treatment response with fluoxetine and a TCA (Bruder et al., 1995). In a different study of elderly MDD patients treated with a variety of antidepressant medications over 6 weeks, patients who did not remit had longer P300 latency at baseline compared to those who did (Kalayam and Alesopulos, 1999).

The precise neurobiological basis of the P300 component in relation to treatment response is unknown. However, Alhaj et al. (2011) discuss in their review article an interesting finding: the P300 latency correlates with the prediction response to the 5-HT4A agonist fesoteron (Harmer and Anseau, 1999). This is interesting because as mentioned before, the 5-HT4A receptor plays an important role in the therapeutic action of antidepressants.

6.2. The loudness dependent auditory evoked potential (LDAEP)

The LDAEP is a measure of the ERP component N1/P2, taken 100–200 msec after presentation of an auditory stimulus. The amplitude of the waveform changes with increasing loudness of the stimulus. The LDAEP is thought to relate to the magnitude of 5-HT neurotransmission in the auditory cortex, particularly in the primary auditory cortex (Hegerl et al., 2001).

Faige et al. (1994) demonstrated that a larger slope of the P2 amplitude in response to stimulus intensity, at baseline was associated with response to SSRIs. In a subsequent study, they showed similar results for bupropion (Faige et al., 1995). The majority of other studies investigating LDAEP in antidepressant treatment response have divided their samples into a top 50% range (representative of higher slopes; "strong LDAEP") and bottom 50% range (lower slopes; "weak LDAEP") based on a median split midpoint. These studies found that strong LDAEP at baseline was associated with response to SSRIs such as fluoxetine, paroxetine, and citalopram (Gallinat et al., 2000; Buchel et al., 2007; Lee et al., 2005). In
contrast, weak rLDMP was found to be associated with response to the norepinephrine reuptake inhibitor (NRI), reboxetine (Jacobs et al., 2007; Linka et al., 2005; Muleri et al., 2007b). Hence, rLDMP may be a differential biomarker of response to antidepressant drugs with differing mechanisms of action (SSRIs vs. NRIs).

Due to rLDMP’s presumed link with 5-HT activity, it is possible that rLDMP may be an effective tool as a differential biomarker. Hegert and Juckel (1993) suggested that the slope of a plot of N1/P2 amplitude against loudness, the amplitude/stimulus intensity function (ASI-slope), inversely correlates with serotonergic activity: that is, high levels of 5-HT in the central nervous system are related to suppression of ERP responsiveness to auditory tone intensity, whereas, low 5-HT levels facilitate it. Interestingly, the ASI-slope has been shown to negatively correlate with plasma 5-HT concentration following administration of the SSRI, fluoxetine, in depressed patients but not controls (Hegert et al., 2001). However, in a recent review, O’Neill et al. (2008) concluded that rLDMP may not be a good index of central 5-HT but they still strongly supported the idea that rLDMP is a promising biomarker of antidepressant response.

7. Conclusion

The most significant challenge in managing depression lies in selecting effective antidepressant treatment for individual patients. Identifying reliable biomarkers may be useful in aiding clinicians with selecting medications that patients are most likely to benefit from. This can eliminate the current flawed treatment approach, which involves a long and ineffective medication trial. A number of different EEG derived techniques have been explored as biomarkers or predictors of antidepressant treatment response and a large body of evidence supports the clinical utility of many of them. This could lend way to a new paradigm under which medications could be prescribed based on the early response profile of each patient. This could optimize rates of response and remission leading to early recovery and tremendous health and economic benefits.

Neurology supports this paradigm because EEG techniques permit detection of cortical activity, which directly reflects neuronal activity. This allows EEG to be linked to the activity of subcortical neurotransmitter systems and antidepressant medications generally target these systems. Much of the evidence presented in this review (see Table 1 for a summary of our review) help in providing an explanation for the predictive property of EEG derived biomarkers for treatment response to serotonergic agents. However, predictive response or statistical association of EEG biomarkers with response to other types of antidepressants with differing modes of mechanistic action has also been demonstrated but no clear biological mechanisms have been proposed to explain such findings. Hence, the neurobiology of EEG biomarkers predictive of antidepressant treatment response remains largely unexplored and merits further investigation. For the future, it may be beneficial to investigate combinations of different EEG derived biomarkers and on a larger scale, combinations of EEG with other markers (e.g., genomics, metabolics, proteomics, imaging, etc.) should also be studied as done in the BRUTE-MD study. EEG may be a feasible predictor of antidepressant response in clinical practice allowing for the use of simple electrophysiological measures to be used in the future of personalized treatment for depression.

References


