ELECTROPHYSIOLOGICAL INDICES IN MAJOR DEPRESSIVE DISORDER AND THEIR UTILITY IN PREDICTING RESPONSE OUTCOME TO SINGLE AND DUAL ANTIDEPRESSANT PHARMACOTHERAPIES

by

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ABSTRACT

Certain electrophysiological markers hold promise in distinguishing individuals with major depressive disorder (MDD) and in predicting antidepressant response, thereby assisting with assessment and optimizing treatment, respectively. This thesis examined resting brain activity via electroencephalographic (EEG) recordings, as well as EEG-derived event-related potentials (ERPs) to auditory stimuli and facial expression presentations in individuals with MDD and controls. Additionally, the utility of resting EEG as well as auditory ERPs (AEPs), and the associated loudness-dependence of AEPs (LDAEP) slope, were assessed in predicating outcome to chronic treatment with one of three antidepressant regimens [escitalopram (ESC); bupropion (BUP); ESC+BUP].

Relative to controls, depressed adults had lower pretreatment cortical activity in regions implicated in approach motives/positive processing. Increased anterior cingulate cortex (ACC)-localized theta was observed, possibly reflecting emotion/cognitive regulation disturbances in the disorder. AEPs and LDAEPs, putative indices of serotonin activity (implicated in MDD etiology), were largely unaltered in MDD. Assessment of ERPs to facial expression processing indicated slightly blunted late preconscious perceptual processing of expressions, and prolonged processing of intensely sad faces in MDD. Faces were rated as sadder overall in MDD, indicating a negative processing bias.

Treatment responders (vs. non-responders) exhibited baseline cortical hypoactivity; after a week of treatment, cortical arousal emerged in responders. Increased baseline left fronto-cortical activity and early shifts towards this profile were noted in responders (vs. non-responders). Responders exhibited a steep, and non-responders shallow, baseline N1 LDAEP derived from primary auditory cortex activity. P2 LDAEP slopes (primary auditory cortex-derived) increased after a week of treatment in responders and decreased in non-responders. Consistent with overall findings, ESC responders displayed baseline cortical hypoactivity and steep LDAEP-sLORETA slopes (vs. non-responders). BUP responders also exhibited steep baseline slopes and high ACC theta.

These results indicate that specific resting brain activity profiles appear to distinguish depressed from non-depressed individuals. Subtle ERP modulations to simple

auditory and emotive processing also existed in MDD. Resting alpha power, ACC theta activity and LDAEP slopes predicted antidepressant response in general, but were limited in predicting outcome to a particular treatment, which may be associated with limited sample sizes.

PREFACE

Apart from Chapters 1 and 7, which comprise the General Introduction and Discussion, respectively, this thesis consists of manuscripts that have been published or are in the process of being reviewed in peer-reviewed journals (Chapters 2-6). The text of the original manuscripts comprising this thesis has been slightly modified to avoid redundancy. The authorship of the manuscripts comprising Chapters 2, 4 and 6 is as follows: Natalia Jaworska, Pierre Blier, Wendy Fusee and Verner Knott. The authorship of the manuscripts comprising Chapters 3 and 5 is: Natalia Jaworska, Pierre Blier, Claude Blondeau, Pierre Tessier, Sandhaya Norris, Wendy Fusee and Verner Knott.

Natalia Jaworska (M.Sc.) was implicated in the conceptualization of the research comprising this thesis work, carried out all the experiments, conducted data analyses and prepared all manuscripts.

Pierre Blier (M.D., Ph.D.) was the principal investigator of the clinical trial within which this thesis work was couched in, as well as one of the clinicians involved in patient assessment and treatment. He contributed to the conceptualization of this thesis research and edited manuscript drafts.

Claude Blondeau (M.D.), Pierre Tessier (M.D.) and Sandhaya Norris (M.D.) were clinicians implicated in patient assessment and clinical treatment.

Wendy Fusee (R.N.) was the clinical coordinator of the clinical trial within which this thesis work was couched in. She was responsible for assessing and recruiting patients.

Verner Knott (Ph.D., C.Psych.) was the principal investigator of the research comprising this thesis work. He was involved in the data analyses, and assisted in writing and editing all of the manuscripts.

Chapter 6 is a modification of the following published manuscript:

Jaworska N, Blier P, Fusee W, Knott V (2012). The temporal electrocortical profile of emotive facial processing in depressed males and females and healthy controls. *Journal of Affective Disorders*;136(3):1072-81.

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ABBREVIATIONS

5-HT	5-hydroxytryptimine (serotonin)
5-HTT/SERT	5-HT transporter/serotonin transporter
ACC	anterior cingulate cortex
AEP	auditory evoked potential
ANOVA	analysis of variance
ATD	acute tryptophan depletion
ATR	antidepressant treatment response index
BESA	brain electrical source analysis (software)
BDI-II	Beck depression inventory-II
BP	bipolar disorder
BUP	bupropion
CREB	cyclic AMP response element binding protein
CRN	caudate raphé nucleus
CSD	current source density
CSF	cerebrospinal fluid
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
DRN	dorsal raphé nucleus
DSA	dipole source analysis
EEG	electroencephalograph
EO/EC	eyes open/eyes closed
EOG	electrooculographic
EPQR-S	Eysenck personality questionnaire – short version
ERP	event-related potential(s)
ESC	escitalopram
FFG	fusiform gyrus
FH+	family history (of major depressive disorder)
FIGS	family interview for genetic studies
fMRI	functional magnetic resonance imaging

FST	forced swim test
$HAMD_{17/29}$	Hamilton rating scale for depression – versions 17/29
HVA	homovanillic acid (dopamine metabolite)
ICC	intra-class correlations
LC	locus coeruleus
LDAEP	loudness dependence of the auditory evoked potential
LPP	late positive potential
MADRS	Montgomery-Åsberg depression rating scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MEG	magnetoencephalography
MHPG	3-methoxy-4-hydroxyphenylglycol (noradrenaline metabolite)
mPFC	medial prefrontal cortex
MRN	median raphé nucleus
NA/NE	noradrenaline/norepinephrine
NET	norepinephrine transporter
OFC	orbitofronal cortex
PET	positron emission tomography
PFC	prefrontal cortex
Pla	placebo
POMS	profile of mood states
rmANOVA	repeated-measures analysis of variance
ROI	region of interest
SD	standard deviation
SEM	standard error of the mean
SCID-IV-I/P	structured clinical interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR diagnoses, Axis I, patient version
sg/pg/rACC	subgenual/perigenual/rostral anterior cingulate cortex
sLORETA	standardized low resolution brain electromagnetic tomography
SNpc	substantia nigra pars compacta

SNRI	serotonin and norepinephrine reuptake inhibitors
NRI	noradrenaline re-uptake inhibitor
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant
TRP	tryptophan
TST	tail suspension test
VMAT-2	vesicular monoamine transporter-2
VMPFC	ventromedial prefrontal cortex
VPP	vertex positive potential
VTA	ventral tegmental area

GENERAL INTRODUCTION

1.1 Overview of Thesis Aims

The research comprising this thesis aimed to assess if specific electroencephalographic (EEG) profiles and EEG-derived brain activity measures distinguish individuals with major depressive disorder (MDD) from non-depressed controls. Secondly, we probed the utility of these measures in predicting treatment outcome to one of three antidepressant regimens: escitalopram [ESC; a selective serotonin reuptake inhibitor (SSRI)] + placebo; bupropion (BUP; a non-SSRI antidepressant with an atypical mechanism of action) + placebo; ESC + BUP. EEG activity was measured during three experiments at three time points: baseline (pretreatment), 1 and 12 weeks post treatment. The first study, outlined in Chapter 2, assessed baseline resting electrocortical activity to probe if certain patterns of brain activity characterize MDD. The research presented in Chapter 3 examined treatment-induced alterations in these resting brain activity measures, and the utility of baseline and early (within a week) changes in resting EEG patterns as predictors of antidepressant treatment response. The study described in Chapter 4 was aimed at assessing whether the loudness dependence of auditory evoked potentials (LDAEP) slope, constructed from EEG-derived auditory evoked potentials (AEPs) elicited by auditory stimuli of increasing intensities, distinguished depressed from control individuals. The LDAEP has been suggested to be inversely correlated with central 5-hydroxytryptamine (5-HT/serotonin) activity, which is known to play a role in the etiology of MDD. The study comprising Chapter 5 examined the utility of baseline LDAEP slopes, and early slope changes (within a week) in predicting antidepressant response as well as whether the LDAEP is differentially influenced by the three antidepressant regimens. Finally, the work presented in Chapter 6 was spurred by evidence that MDD is associated with altered affective information processing. Thus, visual event related potentials (ERPs) to facial expressions of emotion were examined to determine if they differed between depressed from control individuals.

Several putative advantages exist with respect to using EEG/ERP as both a diagnostic aid in MDD assessment as well as in monitoring and predicting antidepressant treatment efficacy and response, respectively. The collection and analysis of EEG data is relatively easy, efficient and inexpensive and, thus, more likely to be used in psychiatric settings relative to some other neuroimaging techniques. However, the routine use of EEG in psychiatric practice is not possible until sufficient research is conducted regarding the reliability, sensitivity and specificity of selective electrophysiological markers in MDD assessment and in antidepressant treatment response prediction. The work presented within this thesis aimed to contribute to this goal.

1.2 Major Depressive Disorder (MDD): A Definition

One definition of major depressive disorder (MDD), or simply depression, is that it is an affective disorder wherein negative emotions and accompanying physiological, behavioral and cognitive effects become debilitating and interfere with daily functioning. This simple definition does not differentiate among the various MDD subtypes or acknowledge the frequent co-morbidity of other psychiatric disorders in depression. MDD (in its various forms) is the most common psychiatric disorder in adults, though it is approximately twice as common in females (Schloss & Henn, 2004), with a conservative lifetime prevalence of ~10% and high burden of disease (Mathers & Loncar, 2006). The diagnosis of MDD (and, thus, its operational definition) tends to be based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV). Briefly, MDD is diagnosed if at least one Major Depressive Episode (MDE) occurs. A MDE is defined as a two-week period of depressed mood and/or anhedonia nearly most of the day, every day, and a minimum of five other depressive symptoms.

1.2.1 An Overview of MDD Causes

Though the proposed causes of MDD are diffuse, they can broadly be categorized into social/environmental, cognitive-behavioral and biological determinants. Rearing, especially faulty or disturbed parent-child relationships, plays a dominant role in the

social/environmental determinants of MDD hypothesis. Social loss and emotional deprivation, particularly in early-life, are among the most powerful antecedents of clinical depression (Heim & Nemeroff, 2001; Gilmer & McKinney, 2003). Cognitive-behavioral theories of MDD propose that specific cognitive biases/schemas and consequential behaviors (which are intimately linked with specific personality traits) are risk factors for the disorder (Bradley & Power, 1988; Watson & Andrew, 2002). For instance, adopting a negative and passive coping style to adversity, representative of helplessness, hopelessness and an external locus of control (i.e., learned helplessness), is associated with MDD (Pryce et al., 2011). Finally, the neurobiological hypothesis of MDD indicates that specific genetic factors and a positive family history of the disorder are linked with its development. However, although the susceptibility for MDD development does appear to be heritable (to a certain extent), its manifestation tends to be elicited by psychosocial adversity/stress (Spijker & van Rossum, 2009). There is growing consensus that MDD likely arises from a complex interaction between several of the aforementioned factors. Considering this, as well as the heterogeneity of depression phenotypes, it is unlikely that a singular neurochemical/physiological correlate of the disorder exists. Nevertheless, certain dominant theories regarding neuronal activity and physiological changes in MDD have emerged.

1.2.3 Neurobiological and Physiological Correlates of MDD

The oldest theory regarding the neurobiological bases of MDD is the monoamine hypothesis, which proposes that the disorder is characterized by inefficient neurotransmission of monoamines, particularly 5-HT, noradrenaline (NA) and, to a lesser extent, dopamine (DA) in the brain. Although the monoamine hypothesis has been instrumental in guiding antidepressant drug development, as well as in providing a framework for continued research into the biological correlates of MDD, it is now regarded as too simplistic (Heninger et al., 1996). Nevertheless, the hypothesis continues to be endorsed as most antidepressants exert their action by either direct or indirectly modulating monoaminergic system activity (Section 1.5).

Two alternative explanations regarding the pathophysiology of MDD (though not discrepant with the monoamine hypothesis) include the neurotrophin dysregulation and abnormalities in stress hormone regulation hypotheses. Briefly, the neurotrophin dysregulation hypothesis posits that neurotrophins, such as brain derived neurotrophic factor (BDNF), which play a crucial role in neural survival, differentiation and in mediating synaptic plasticity and morphological maintenance, are altered in MDD (Coyle & Duman, 2003). Specifically, BDNF decreases have been noted in depression, while antidepressant interventions increase it (Russo-Neustadt & Chen, 2005; Aydemire et al., 2006). Central administration of BDNF has also been shown to induce antidepressant-like effects in animal depression models (Duman & Monteggia, 2006). Given BDNF's critical role in neuroplastic processes (i.e., ability to adapt with structural and functional changes to internal/external demands), inefficient/altered neuroplasticity has been proposed to be the core feature of MDD (Fossati et al., 2004).

The stress dysregulation hypothesis posits that MDD is associated with a hyperactive hypothalamic-pituitary-adrenal (HPA) axis and impaired negative feedback of the axis. While the consequences of a hyperactive stress response system are multifaceted, the one that has received greatest attention in the context of MDD is that persistently elevated coticosteroid levels can be neurotoxic and alter neuroplasticity in brain regions implicated in depression. Though the neurotoxic effects are unlikely to play a large role in the pathophysiology of MDD *in vivo* (Claes, 2004; Swaab et al., 2005), neuroplacticity alterations resulting from persistent corticosteroid elevations, likely by indirect BDNF expression modulations (Nibuya et al., 1999), are of concern.

Both neurotrophin and corticosteroid modulations ultimately affect monoaminergic activity. After all, BDNF up-regulation increases growth and survival of 5-HT and NA neurons (Coyle & Duman, 2003). Additionally, 5-HT stimulation appears to be implicated in controlling BDNF expression (Mattson et al., 2004). Conversely, decreased BDNF levels, resulting from excessive corticosteroids, for instance, can lead to disturbances in monoaminergic system activity. This simplified example of the interplay between neurotrophins, monoamines and corticosteroids indicates that the neurophysiological/chemical underpinnings of depression are multifaceted and complex. Thus, the disorder is regarded as stemming from interactions between multiple

neurochemical players constituting an integrated neuronal network implicated in affective and cognitive processing/regulation. Although the bulk of the evidence suggests impairments in monoamine system activity and neuroplastic processes in MDD, the nature and the extent of these neuromodulations will depend on depression phenotype and history.

The work comprising this thesis is predicated on the idea that MDD, particularly moderate-severe MDD, is associated with the aforementioned neurobiological correlates. As scalp-recorded electrocortical assessments result from underlying neural activity driven by chemical messengers (Section 1.7), any emergent differences in electrocortical indices between depressives and controls should be elicited due to differences in the neurochemical/physiological environment. This is not to say that *direct* inferences regarding the neurochemical correlates of MDD can be made from these scalp-derived measures. After all, the source-generators of ERPs and activity in specific EEG bands are crude and their neurochemical correlates are very poorly characterized (though it is assumed that they result from the summed activity of various excitatory and inhibitory neurotransmitters). Despite this limitation, electrocortical indices are a relatively inexpensive and convenient means of *indirectly* probing putative brain activity correlates in depression, thus, providing greater insight into the disorder.

1.2.4 Evaluating Antidepressant Pharmacotherapy Effectiveness

Despite extensive evidence for neurobiological and clinical changes with antidepressant drugs (though non-pharmacological interventions play a critical role in MDD treatment, they are not discussed in this thesis), some debate exists as to whether, given the heterogeneous nature of depression and typically subjective symptom measures, antidepressant drugs exert greater effectiveness than placebo in treating MDD. Recent meta-analyses suggest that antidepressants may not be more effective than placebo in treating mild MDD, though this is not true for moderate-severe depression (Fournier et al., 2010; Vöhringer & Ghaemi, 2011). Given that placebo treatment tends to represent everything (e.g. investigator-patient interactions, patient follow-ups etc.) apart from the psychoactive drug (Preskorn, 2011), this may be sufficient to induce positive

clinical effects in mildly depressed individuals. The effectiveness of antidepressants (versus placebo) increase with depression severity, presumably because severe MDD is associated with more pronounced neurobiological disturbances.

As the second major objective of this thesis was to examine the utility of electrocortical measures in predicating eventual response to antidepressant drugs, the assumption was accepted that the drugs exert neurochemical effects that would induce antidepressant mood and behavioral effects, at least in a portion of our moderate-severely depressed patients. The antidepressant regimens employed in this study have known actions on monoaminergic system activity (Section 1.5), thus, it was also assumed that any therapeutic effects would be associated with modulations in these systems (which may, however, spur alterations in other systems). Consequently, the assessed electrocortical indices should reflect neural activity patterns that emerge due to these changes. As mentioned, however, these electrocortical indices provide *indirect* insight into the neurochemical environment (in Chapters 4 and 5 we suggest a possible relationship between an auditory ERP and 5-HT activity, but, contend that this relationship is correlational, at best). Nevertheless, electrocortical measures of brain activity have previously been shown to be useful in tracking antidepressant treatment response - this thesis aimed to replicate and expand on these findings, and refine this relationship.

1.3 Serotonin (5-HT), Noradrenaline (NA) and Dopamine (DA) Systems

Despite the acknowledged involvement of non-monoaminergic factors in MDD, most antidepressant pharmacotherapies continue to be aimed at increasing the availability of the monoamines 5-HT, NA, and DA in central synapses. As this thesis research investigated the effects of antidepressant pharmacotherapies that modulate monoaminergic system activity on electrophysiological brain indices, a brief overview of these systems is warranted. Focus will be aimed at reviewing monoamine activity in the frontal lobes and in limbic structures, as these regions have received most attention with respect to MDD etiology and antidepressant drug action. However, one should keep in mind that EEG/ERP data only reflects cortical activity; thought activity in sub-cortical

limbic structures may certainly influence/drive cortical function, scalp-recorded EEG/ERP indices do not directly reflect this.

Serotonergic projections arise from nine 5-HT brainstem nuclei. Three of these, the caudal, dorsal and median raphé nuclei (CRN, DRN, MRN, respectively), constitute the rostral raphé complex, which sends 5-HT projections primarily to the forebrain (Hornung, 2003; Figure 1.1A). Serotonin is released as a result of primarily adrenergic excitatory action from neurons originating in other brainstem nuclei, the hypothalamus, limbic regions and from within 5-HT brainstem nuclei circuits (Jacobs & Azmitia, 1992), and exerts its actions via 5-HT receptors (Hoyer et al., 2002). The density of cortical post-synaptic 5-HT_{1A} receptors (5-HT_{1A}R), which play an important role in the mechanisms of action of many antidepressants, is greatest in the prefrontal cortex (PFC), though high densities also exist in the hippocampus (Marazziti et al., 1994). Pre-synaptic 5-HT_{1A}Rs, located on somatodendritic neural aspects, exert a large autoinhibitory function in regulating DRN 5-HT neuron firing. At the axon level, 5-HT_{1B}Rs as well as NA α_2 heteroreceptor are implicated in inhibiting 5-HT release (Harsing, 2006). The distribution of the lower affinity post-synaptic 5-HT_2Rs (also implicated in antidepressant actions) is similar to that of 5-HT_{1A}Rs, with greatest 5-HT_2R density in hippocampal regions (Jacobs & Azmitia, 1992). Serotonergic neurotransmission in the hippocampus and neocortex, facilitated mainly by 5-HT_{1A}R activation, appears to be primarily inhibitory, while 5-HT_2R activation is mainly excitatory. Finally, synaptic 5-HT clearance occurs via active reuptake by serotonin transporters (5-HTT/SERT). Similarly to other monoamines, 'stray' 5-HT is degraded by monoamine oxidase (MAO) enzymes (Figure 1.1B).

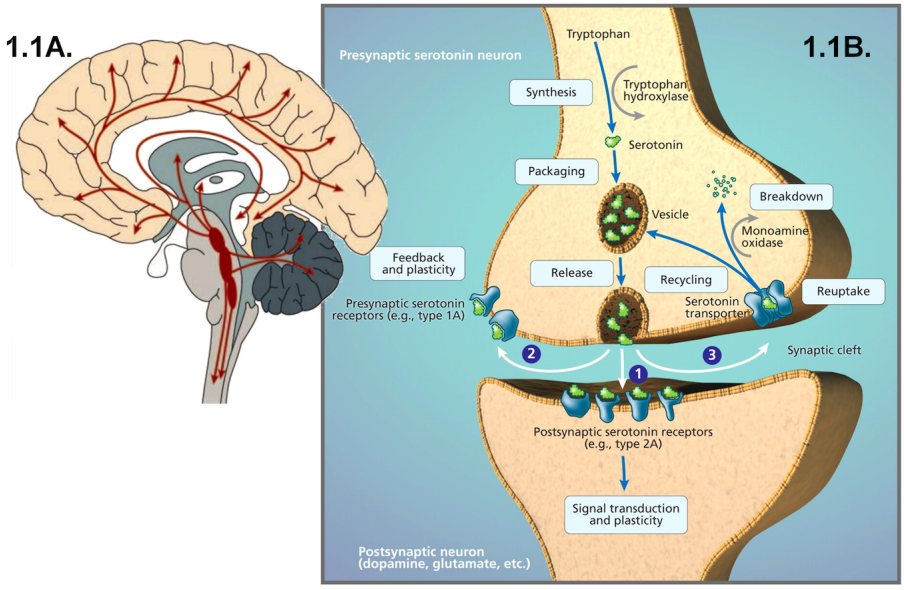
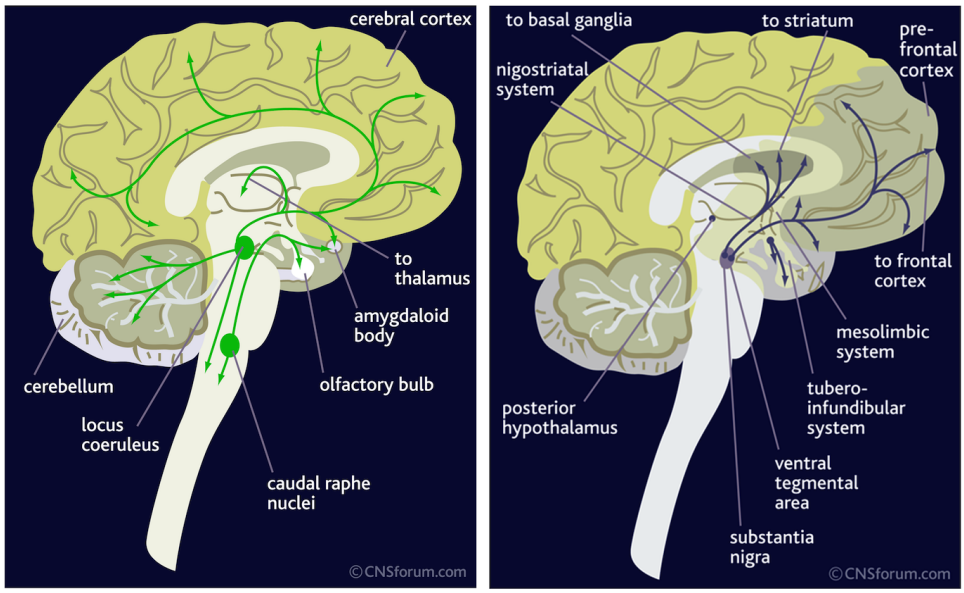


Figure 1.1A. Rostral raphé complex 5-HT projections. **Figure 1.1B.** 5-HT is packaged into vesicles and released into the cleft with neural activation. 1. Receptor binding induces signal transduction. 2. 5-HT also binds to autoinhibitory 5- HT_{1A} receptors. 3. Serotonin transporters take-up 5-HT into the neuron, where it is stored in vesicles or degraded by monoamine oxidase. Figures adapted from: aan het Rot M et al., (2009) CMAJ;180:305-313 & Berger M et al., (2009) Annu Rev Med;60:355-366

Noradrenergic neural projections originate for the locus coeruleus (LC), a dense cluster of cell bodies in the brainstem pons. Rostral NA projections are diffuse and terminate in various brain regions, including the PFC (Figure 1.2A). The LC, and thus NA neurotransmission, is primarily controlled by projections originating in the medulla and hypothalamus, though control from regions such as the PFC has also been noted (Jodo et al., 1998). NA exerts its actions on three families of adrenergic receptors, α_1, α_2 and β. It exhibits greatest affinity for the α_2 family (subtypes A, B, C), relatively low affinity for α_1 receptors (subtypes A, B, D) and lowest affinity for β adrenoceptors (three subtypes 1-3). While all three α_2 receptor subtypes are found post-synaptically, the α_{2A} subtype is also located pre-synaptically and functions as an NA inhibitory autoreceptor. Post-synaptic α_1 and α_{2A} receptors are most dense in superficial layers of the PFC, while β receptors are found in intermediate layers (Aoki et al., 1998). NA is cleared from the synapse by its reuptake transporter (NET) and degraded by MAO.

Rostral DA projections originate from clusters of neural cell bodies located in the brainstem, including the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA). Dopaminergic projections from the VTA to limbic regions, including the

nucleus accumbens, amygdala and hippocampus and aspects of the anterior cingulate cortex (ACC), comprise the DA mesolimbic pathway; VTA projections terminating in fonto-cortical regions, particularly the dorsolateral PFC (DLPFC) comprise the mesocortical pathway (Tzschentke, 2001; Figure 1.2B). DA receptor subtypes are clustered into two families: D_1-like receptors, which include the $DA_{1/5}$ subtypes, and D_2-like receptors, which consist of the $D_{2/3/4}$ subtypes (Gardner & Ashby, 2000). D_1 receptors are densely distributed in the caudate-putamen and amygdala, while low-moderate concentrations exist in the ACC and frontal cortex; D_2 receptors share a similar distribution. D_2 autoreceptors on the soma and axon terminals of DA neurons regulate its release. Much like 5-HT and NA, DA is taken up by its reuptake transporter (DAT), although it can also be taken up NET, especially in the PFC (Carboni & Silvagni, 2004).



1.2A. **1.2B.**

Figure 1.2A. Locus coeruleus NA projections. **Figure 1.2B.** DA projections originating from the substantia nigra pars comacta and ventral tegmental area. Figures adapted from: Lundbeck Institute CNSforum
http://www.cnsforum.com/imagebank/item/Neuro_path_DA/default.aspx
http://www.cnsforum.com/imagebank/item/Neuro_path_N/default.aspx

1.4 Monoamine System Involvement in MDD

The wealth of pre-clinical evidence implicating monoamine system dysfunction in MDD is immense and beyond the scope of this overview. After all, the vast majority of

antidepressants function by targeting aspects of monoaminergic neurotransmission. However, the following sections make little mention of pre-clinical work involving pharmacological modulations of monoamine system function as evidence of its involvement in depression-like phenotypes (i.e., pre-clinical antidepressant or putative antidepressant effects). Instead, the sections highlight research not involving antidepressant drug administration that also implicates monoamine system involvement/dysfunction in MDD. The mechanisms of antidepressant dug action and their influence on monaminergic transmission is presented in Section 1.5.

1.4.1 Evidence of Serotonin/5-HT System Implication in MDD

Accumulating clinical research has provided evidence for 5-HT system dysregulation in MDD. For instance, decreased plasma tryptophan (TRP; 5-HT precursor) levels have been noted in depressed individuals, suggesting altered 5-HT metabolism as lower peripheral TRP is thought to reflect decreased central 5-HT activity (Meltzer, 1989; Jans et al., 2007). Decreased corticospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA, primary 5-HT metabolite) levels have also been reported in MDD, perhaps indicating decreased/inefficient 5-HT metabolism. Further evidence for 5-HT system dysregulation in the disorder comes from acute TRP depletion (ATD) experiments, which reduce plasma TRP and subsequently decrease central 5-HT synthesis and levels (Bell et al., 2001). ATD has been found to induce transient depressive symptoms in remitted patients, in those with recurrent MDD, in non-depressed individuals with high sub-clinical depression scores and in individuals with a family history (FH+) of MDD (Delgado et al., 1990; Benkelfat et al., 1994; Leyton et al., 2000).

Positron emission topography (PET), post-mortem histological and genetic investigations in depressed individuals and in those vulnerable to MDD development have provided more direct evidence of 5-HT system disturbances in the disorder. PET studies in depressed individuals have documented elevated SERT binding as well as decreased pre- and post-synaptic 5-HT_{1A}R binding in various brain regions implicated in emotive and cognitive processing (Drevets et al., 1999; Sargent et al., 2000; Jans et al., 2007). Increased SERT may reflect compensatory up-regulation to decreased synaptic 5-

HT. These PET findings are consistent with some post-mortem studies of depressed individuals (Szewczyk et al., 2009).

Given that many antidepressants target SERT (Section 1.5), depressed individuals have been assessed for alterations in genes coding for the transporter, with focus directed at deletion/insertion polymorphisms in the transcriptional control region of the transcription initiation site (5-HTTLPR). Though some studies have noted associations between 5-HTTLPR polymorphisms and MDD susceptibility (Lotrich & Pollock, 2004), others have not (Lasky-Su et al., 2005). The most compelling evidence for an association between the s/s variant of the polymorphism, in particular, and increased MDD susceptibility indicates that the relationship may only be unmasked following stressful life events (Daniele et al., 2011). Genetic knockout (KO) mice have also been used to explore the contribution of specific 5-HT system components in depression-like phenotypes. Though such results must be interpreted with caution, SERT KO mice have been shown to display some depressinogenic-like behaviors/features as assessed by standardized laboratory tests (Lira et al., 2003; Wellman et al., 2007); similar findings have been noted with 5-HT_{1A}R KO mice (Klemenhagen et al., 2006; Savitz et al., 2009).

1.4.2 Evidence of NA System Implication in MDD

Urine and CSF 3-methoxy-4-hydroxyphenylglycol (MHPG; primary NA metabolite) levels have been proposed to index CNS NA function, with lower levels suggesting decreased NA turnover, thought to reflect synthesis rate (Barton et al., 2008). However, assessments of urinary and CSF MHPG levels in MDD have yielded inconsistent findings. A more complete index of NA turnover (assessment of several NA metabolites), however, indicated decreased turnover in depressed versus control individuals (Grossman & Potter, 1999). Similarly, venous NA and DA concentrations were decreased in depressed patients (Lambert et al., 2000). Thus, a handful of clinical evidence based on peripheral measures of NA and DA and NA metabolites suggests decreased central NA activity in MDD.

Catecholamine depletion and α-methylparatyrosine (AMPT) administration are experimental manipulations that decrease central catecholamine (i.e., DA and NA)

synthesis. As NA is produced from DA, it is difficult to selectively deplete the former. The functional consequences of NA/DA depletion in healthy controls are minimal, though, catecholamine depletion has been associated with mood decreases in MDD FH+ individuals (Ruhé et al., 2007). Some evidence also suggests that NA/DA depletion lowers mood in MDD patients who are treated with, and responsive to, NA system-targeting drugs (Berman et al., 1999; Delgado & Moreno, 2000). Nevertheless, such studies provide only indirect support for NA system impairments in MDD.

Research probing whether NET polymorphisms are associated with MDD (spurred by the fact that some antidepressants target NET) has been inconsistent. For instance, one group assessing NET gene T-182C polymorphisms, which can result in three allele variants (TT, TC or CC), found that the T/T variant was associated with increased MDD prevalence (Inoue et al., 2004), while another group noted the opposite (Ryu et al., 2004); yet others have found no associations between T-182C polymorphisms and the disorder (Zill et al., 2002; Chang et al., 2007). Investigations of G1287A NET polymorphisms have also yielded conflicting results (Yoshida et al., 2004; Zill et al., 2002; Chen et al., 2007; Inoue et al., 2007). As such, genetic evidence for an association between altered NET function and MDD is inconclusive. However, using rodent models of depression-like behaviors [e.g. forced swim test (FST), tail suspension test (TST)], several groups have noted antidepressant-like profiles in NET KO mice (Dziedzicka-Wasylewska et al., 2006; Perona et al., 2008). These findings suggest that increased synaptic NA levels, which could occur in NET KO mice due to limited clearance, decrease depression-like behaviors. However, this interpretation is tentative given that the functional consequences of NET KO are unknown (e.g. neuroadaptations could negate higher synaptic NA levels).

1.4.3 Evidence of DA System Implication in MDD

Specific symptoms such as psychomotor retardation suggest DA dysfunction in MDD. Similarly, since anhedonia and decreased motivation are core MDD features, and given that mesolimbic DA pathways are implicated in controlling pleasurable associations and motivation, this also suggests disturbed DA network activity in the

disorder (Nutt, 2006; Stein, 2008). Experimental assessments probing this relationship have reported decreased CSF homovanillic acid (HVA; DA metabolite) levels in MDD, especially in individuals with marked psychomotor retardation (Reddy et al., 1992; Brown & Gershon, 1993); similar results were noted in suicide attempters (Träskman et al., 1981; Engström et al., 1999). Post-mortem assessments in depressed suicide victims also found decreased dihydroxyphenylacetic acid (DA metabolite) in the basal ganglia (Bowden et al., 1997). PET studies have reported greater binding of exogenous ligands to $D_{2/3}$ receptors in MDD (D'Haenen & Bossuyt, 1994; Shah et al., 1997), which could reflect compensatory up-regulation to decreased DA levels, though others have noted no differences (Klimke et al., 1999; Parsey et al., 2001; Hirvonen et al., 2008).

Genetic work in humans and animal models has also provided support for DA system alterations in MDD. A meta-analysis probing putative genetic contributions in MDD indicated significant associations between the disorder and polymorphisms in both D_4 receptors and DAT (López-León et al., 2008), though research indicating no genetic variant differences between depressed and control individuals also exists (e.g., Pattarachotanant et al., 2010). Assessment of depression-like behaviors in DAT KO mice, with persistently elevated DA (Gainetdinov et al., 1999) and exhibiting hyperlocomotion (Haenisch & Bönisch, 2011), noted greater mobility in the FST and TST in KO mice. These antidepressant-like findings were unlikely to be confounded by locomotor hyperactivity as heterozygous DAT KO mice, which do not exhibit hyperlocomotion, also displayed such behaviors. Additionally, DAT KO mice had increased sucrose consumption in the sucrose preference test compared with wild-type mice (Perona et al., 2008). Thus, this evidence provides some support for DA system involvement in MDD pathophysiology.

1.5 Monoamine System Alterations with Antidepressant Pharmacotherapies

This section will briefly outline antidepressant mechanisms of action, with a primary focus on SSRIs, such as ESC, as well BUP, which were used in the experiments comprising this thesis. An overview of the mechanistic effects of ESC+BUP action will also be presented. The mechanisms of action of monoamine oxidase inhibitors (MAOIs)

and tricyclic antidepressants (TCAs) will not be directly discussed, as these drugs were not used in the research presented in this thesis.

Many commonly used antidepressants inhibit monoamine reuptake by blocking their reuptake transporters, particularly NET and SERT. Initially, SERT and NET inhibition [as occurs with SSRIs and selective NA reuptake inhibitor (NRI), respectively] induces a rapid decrease in 5-HT and NA neuron firing rates (Lenox & Frazer, 2002). With respect to 5-HT, this is thought to occur due to initially elevated DRN 5-HT levels that activate somatodendritic autoinhibitory 5-TH_{1A} receptors, thereby decreasing neuron firing (Blier et al., 1998; Figure 1.3A). A similar process is thought to occur with LC somatodendritic α_2 autoinhibitory receptor activation (Linnér et al., 1999). Prolonged transporter inhibition, as occurs with chronic ESC administration for instance, induces gradual desensitization of somatodendritic 5-HT_{1A} autoreceptors as well as terminal 5-HT_{1B} autoreceptors, and leads to increased 5-HT at terminal projection sites; this desensitization been associated with concomitant symptom relief (Blier & de Montigny, 1990; Figure 1.3B). Data on whether somatodendritic α_2 autoreceptor desensitization occurs with chronic NRIs administration is more mixed, with suggestions that terminal, rather than somatodendritic, receptors exhibit greater desensitization (Parini et al., 2005). Nonetheless, partial somatodendritic α_2 receptor desensitization appears to play a role in gradually enhanced NA neuron firing (Invernizzi & Garattini, 2004).

With respect to antidepressant effects on post-synaptic receptors, chronic administration tends to down-regulate post-synaptic receptors, especially β adrenoceptors and 5-HT_2Rs (Figure 1.3B), which may reflect a compensatory mechanism to excess stimulation (i.e., neuroadaptation to chronic antidepressant administration; Duman, 1999). Receptor down-regulation also follows a similar time course as the delay in symptom relief accompanying most antidepressants (Blier, 2003). Additionally, chronic antidepressant treatment has been associated with enhancing hippocampal post-synaptic 5-HT_{1A}R sensitivity (Stockmeier et al., 1992).

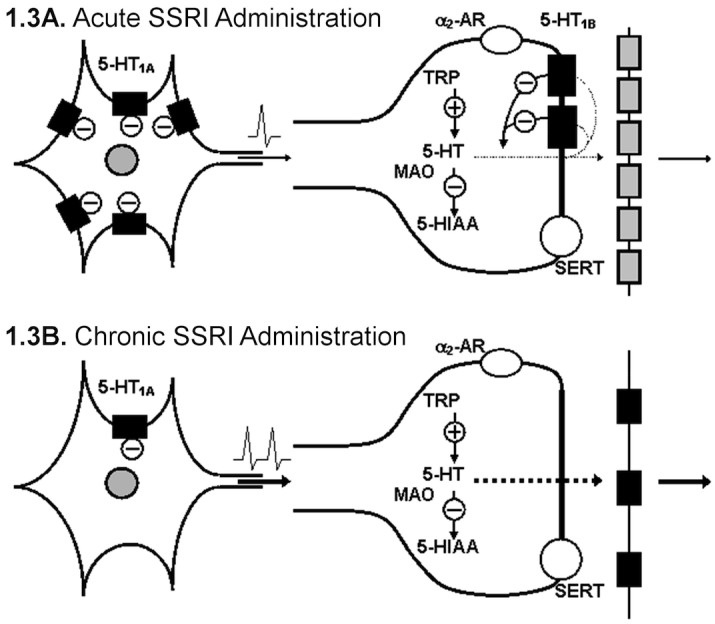


Figure 1.3A. Acute SSRI administration inhibits 5-HT reuptake by blocking SERT. 5-HT lingers in the synapse and acts on inhibitory receptors (somatodendritic: 5-HT_{1A}; pre-synaptic: 5-HT_{1B}). This decreases 5-HT neuron firing and levels at axon terminals. **Figure 1.3B.** Chronic SSRI administration down-regulates/desensitizes 5-HT_{1A}Rs, increasing 5-HT neuron firing and levels. Increased 5-HT at axon terminals induces down-regulation/desensitization of pre/post-synaptic receptors. Figures adapted from: http://www1.lf1.cuni.cz/~zfisar/bpen/psychopharmacology.htm

Chronic antidepressant (various classes) administration has been associated with inducing multiple intracellular modulations. For instance, altered activity of various kinases, including those implicated in signal transduction/transmitter release (Mann et al., 1995; Lenox & Frazer, 2001), has been reported. Chronic antidepressant treatment also activates the transcription factor cyclic AMP response element binding protein (CREB), which binds to specific promotor regions and influences gene expression, such as neurotrophin genes; neurotrophin up-regulation has been associated with antidepressant action (Schmidt & Duman, 2007). Activation of certain intracellular pathways and genes may also lead to neuronal restructuring (e.g., modulated microtubule assembly; Lenox & Frazer, 2001). Thus, in addition to long-term modulations in mechanisms implicated in monoaminergic neurotransmission (e.g. receptor down-regulation), further genetic and neuroplastic modulations may also underlie the time lag in symptom relief associated with antidepressant pharmacotherapy (Nemeroff, 2002).

The mechanisms of BUP action have yet to be fully elucidated. Though BUP tends to be referred to as a dual NA/DA reuptake inhibitor, its inhibitory action on

NET/DAT is relatively limited (Ghanbari et al., 2011) and it has virtually no SERT affinity (Foley et al., 2006). Additionally, BUP and its metabolites have minimal affinity for 5-HT, α and β receptors. However, preclinical evidence indicates that chronic BUP administration induces LC NA release and increases DRN 5-HT firing rates; the latter is likely mediated by activation of α_1 receptors located on DRN 5-HT neural cell bodies (Ghanbari et al., 2010). Chronic (14 day) BUP administration has been shown to increase tonic activation of post-synaptic hippocampal 5-HT_{1A}, which was also noted after 2 days, though to a lesser extent. Post-synaptic 5-HT level increases with BUP also appear to be mediated by desensitization of inhibitory α_2 heteroreceptors located on 5-HT terminals. Tonic activation of post-synaptic hippocampal α_2 and α_1 receptors was also enhanced with chronic (14 day) BUP treatment, while α_2 autoreceptor function (on pre-synaptic NA neurons) was attenuated, thus leading to increased post-synaptic NA with chronic BUP administration (Ghanbari et al., 2011). BUP does not appear to increase VTA DA neuron firing rates, though it is associated with increasing extracellular DA levels in the brain. BUP may enhance vesicular monoamine transporter-2 (VMAT-2) function, which is involved in pumping monoamines into vesicles; this mechanism could participate in its antidepressant effect (Foley et al., 2006).

Limited work exists examining the mechanisms of action underlying combined BUP and SSRI treatments. One preclinical study found that short (2-day) BUP administration did not alter firing rates of DRN 5-HT neurons to a large extent, while ESC administration decreased them. ESC+BUP co-administered, however, increased 5-HT neuron firing by day 2, which persisted for 2 weeks (Ghanbari et al., 2010). ESC+BUP co-administration leads to faster DRN 5-HT_{1A} autoreceptor desensitization, which may be driven by stimulation of α_1 receptors on 5-HT neural cell bodies (driven by BUP-mediated LC NA neuron activity), resulting in increased DRN 5-HT firing. Activation of excitatory D_2 receptors on 5-HT neuron cell bodies may also contribute to enhanced DRN 5-HT firing rates (Aman, et al., 2007). Based on this preclinical work, it is feasible that treatment with ESC+BUP may be associated with a faster clinical antidepressant response (and perhaps remission).

1.6 Neuroanatomical and Neural Network Disturbances Implicated in MDD

The neuroanatomy associated with affective processing is complex, implicating multiple neural networks and brain regions, and is not fully understood. This section provides a brief overview of the neural correlates (morphological and functional), specifically within fronto-cortical regions, which are associated with affective processing, and delineates how they are altered in MDD. The reason for specifically focusing this overview on frontal-cortical regions is that these areas are most consistently engaged during emotive information processing, and alterations in these regions have been noted in MDD with some consistency. Additionally, though sub-cortical structures (e.g. amygdala) are implicated in affective processing, the EEG/ERP measures used in this thesis work probe only cortical, not-subcortical, electrical activity.

1.6.1 Anterior Cingulate Cortex (ACC)

The anterior cingulate cortex (ACC), which is implicated in conflict monitoring, error detection and in evaluating the emotional significance of stimuli/events (Pizzagalli, 2011), has been frequently assessed in MDD, particularly the subgenual and perigenual ACC (sg/pgACC; Figure 1.4). The sgACC belongs to the ventral ACC while the pgACC (also part of the rostral ACC) makes up the dorsal ACC. The latter constitutes the 'cognitive' ACC subdivision as it is intimately connected with the dorsolateral prefrontal cortex (DLPFC), a region highly implicated in cognitive control (Section 1.6.2). The ventral ACC, known as the 'affective' subdivision, has extensive connections with several limbic and subcortical structures (e.g., amygdala, hippocampus, hypothalamus, brain stem nuclei) as well as the orbital prefrontal cortex (PFC; Ongür & Price, 2000). The sgACC has been implicated in the visceral responses associated with emotive processing and in emotive memory formation, and may thus play an important role in the hypersensitivity to negative information (i.e., negative processing bias) evident in MDD (Drevets et al., 2008). Additionally, given that the sgACC receives dense mesolimbic DA innervation, it is implicated in regulating reward contingencies. Disturbances in this network could account for the core MDD symptoms of apathy and anhedonia.

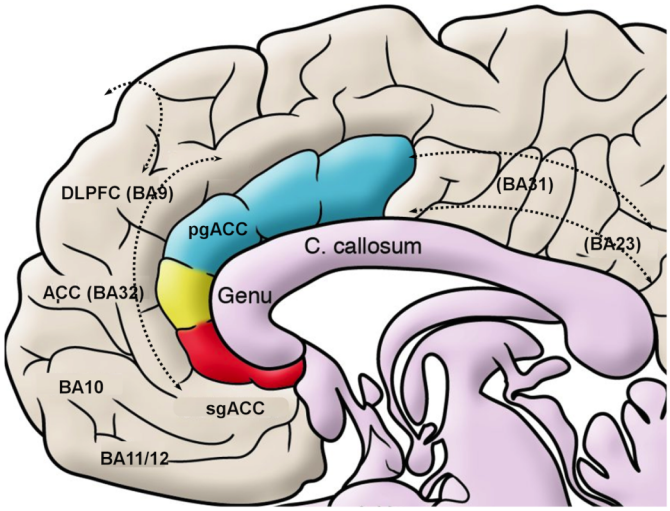


Figure 1.4. Subdivisions of the cingulate and prefrontal cortex (PFC). ACC: anterior cingulate cortex; pgACC: perigenual ACC; sgACC: subgenual ACC; DLPFC: dorsolateral PFC (BA9); BA10: frontopolar cortex; BA11/12: orbitofrontal cortex; BA31/23: posterior cingulate regions; BA: Broadmann area. Figure adapted from Mayberg HS (2009) J Clin Invest; 119(4):717-725

Decreased grey matter, brain volume and gyrification have all been documented in the ACC in MDD (Caetano et al., 2007; Koolschijn et al., 2009), though these changes may be mediated by factors such as age of illness onset, medication status and depression subtype. Individuals with more severe depression tend to be the ones who exhibit ACC grey matter decreases, especially in the sgACC (Vasic et al., 2008; Yucel et al., 2009; Zhang et al., 2009). These reductions have also been associated with specific cognitive and emotive alterations in MDD, such as enhanced attention to negative words (Leung et al., 2009) and altered negative emotion regulation (Mak et al., 2009). Assessment of resting ACC activity tends to indicate decreased perfusion/metabolism in MDD (Mayberg et al., 1994; Ito et al., 1996); though altered metabolism, particularly in the ventral ACC, may again be associated with specific MDD subtypes and severity (Skaf et al., 2002; Pizzagalli et al., 2004). Blunted ACC activity in MDD may reflect impaired conflict monitoring between internal affect and external cues (e.g. interpreting neutral cues as negative to decrease conflict between cue and negative mood; Davidson et al., 2002). Finally, accumulating evidence [functional magnetic resonance imaging (fMRI)-assessed] suggests that ACC activity to negative stimuli (e.g. expressions, images or words) is increased in MDD, perhaps representing increased processing of negative stimuli, and has been associated with greater depression symptoms (Fu et al., 2004;

Killgore & Yurgelun-Todd, 2006; Dichter et al., 2009; Keedwell et al., 2010; but see Chen et al., 2007).

Higher resting ACC metabolism, especially in the sgACC, and dorsal ACC activation to emotive processing (particularly of negative stimuli) have been, rather consistently, associated with better responses to various antidepressants (Mayberg et al., 1997; Smith et al., 1999; Davidson et al., 2003; Chen et al., 2007) as well as to cognitive behavioral therapy (CBT; Costafreda et al., 2009) and ketamine administration (Salvadore et al., 2009), though notable exceptions exist (e.g. Siegle et al., 2006). ACC hyperactivity may represent greater conflict monitoring between internal and external states, which may elicit greater activation and recruitment of other cortical regions for conflict resolution. Alternatively, ACC hyperactivity may represent more integrated activation of prefrontal networks; such enhancements may be a necessary pre-requisite for positive treatment outcomes (Davidson et al., 2002; Pizzagalli, 2011).

1.6.2 Prefrontal Cortex (PFC)

The PFC is highly implicated in regulating cognitive functions, such as planning and executing (or restraining from) specific actions, especially those guided by emotions (Fuster, 2001; Davidson et al., 2002), thus, its role in MDD has been a major focus of research. The PFC can be subdivided into two broad regions: medial and lateral PFC. The medial PFC (mPFC) includes the inferior PFC, frontopolar and orbitofrontal cortices, with the latter two constituting the ventromedial PFC (VMPFC), which has dense amygdalar connections. The mPFC receives projections from the hypothalamus and brainstem, implicating it in regulating emotion-associated autonomic activity, and the ventral striatum, which signals reward and motivational value. The DLPFC (part of the lateral PFC) receives input from sensory cortices and is interconnected with premotor areas, frontal eye fields and lateral parietal cortices (Figure 1.4). The DLPFC tends to be associated with ‘cognitive’ functions, whereas the VMPFC/mPFC is largely ascribed an ‘affective’ role (O’Doherty et al., 2001).

Orbitofrontal cortex volumes tend to be reduced in depressed individuals, as is PFC volume in general (Koolschijn et al., 2009). Decreased mPFC and DLPFC grey

matter concentrations have been associated with depression symptoms (Vasic et al., 2008; Li et al., 2010; Peng et al., 2010) while remission may be linked with decreased volume loss (Frodl et al., 2008). Assessment of resting metabolism has indicated decreased DLPFC activity in MDD (Kennedy et al., 2001; Kimbrell et al., 2002; Drevets et al., 2002; Hosokawa et al., 2009). A handful of studies also suggest simultaneously increased resting mPFC activity in the disorder (Biver et al., 1994; Drevets et al., 1992; 2002).

A meta-analysis assessing fMRI-indexed PFC activity (probed with various experimental paradigms) indicated that mPFC activity (especially orbitofrontal PFC), and to a lesser extent DLPFC, is most frequently reported as abnormal in diverse neuroimaging studies assessing depressed individuals (Steele et al., 2007). However, the directionality of these alterations is variable and task-specific. Tasks involving emotive information processing in MDD, however, tend to show decreased DLPFC activation (Kumari et al., 2003; Lawrence et al., 2004; Lee et al., 2008). Conversely, increased mPFC activity during emotive processing in MDD tends to be reported (Kumari et al., 2003; Mitterschiffthaler et al., 2003; Lee et al., 2007; Dichter et al., 2009). Many of these studies also noted specific asymmetric hemisphere increases/decreases in PFC activity according to stimuli valence (i.e., positive/negative; frontal hemispheric asymmetry according to valence and alterations in this asymmetry in MDD are discussed in Section 1.8.1 and Chapter 2).

Resting PFC activity and activation in this region to emotive tasks indicate different activity patterns in the mPFC and DLPFC in MDD. The mPFC plays a large role in emotion generation (Gillihan et al., 2010) and has been associated with self-awareness/introspection. The DLPFC is implicated in cognitive strategies related to emotive control, such as reappraisal or suppression (Herwig et al., 2007). Decreased DLPFC activity may thus be related to ineffective emotive coping, while mPFC hyperactivity could be associated with increased emotive reactivity it MDD. Preliminary work assessing resting PFC activity following antidepressant treatment suggests that successful treatment increases DLFPC (Mayberg et al., 2000; Kennedy et al., 2001) but decreases mPFC activity (Brody et al., 2001; Kennedy et al., 2007; Goldapple et al., 2004), although this clear-cut dissociation is rather rare.

1.7 Clinical Electrophysiological Measures

Though, in the previous section, evidence was presented regarding brain activity changes in MDD as assessed by PET, MRI and fMRI, electroencephalographic (EEG) recordings, and measures derived from it, namely event-related potentials (ERPs), are also useful indices of brain activity. Given that EEG/ERP activity as well source localization of this activity [by using standardized low resolution brain electromagnetic tomography (sLORETA), for instance; Pascual-Marqui, 2002] were used in this thesis research to describe electrocortical activity characterizing MDD as well as in antidepressant treatment response prediction, a brief explanation of EEG/ERP is warranted.

1.7.1 An Overview of Electroencephalographic (EEG) Activity

Spontaneous, scalp-recorded EEG activity reflects the summed voltage potential resulting from post-synaptic potentials occurring mainly at apical dendrites of pyramidal cortical neurons. Electrical activity associated with action potential propagation does not contribute substantially to the EEG signal as it occurs too quickly (Shibasaki, 2008). These resultant voltage potentials are amplified and, in quantitatively analyzed EEG, digitally sampled and then spectrally analyzed. This involves the decomposition of the EEG signal into specific frequency bands, with power or amplitude values estimated for each band at each recording site (Armitage et al., 1995).

The strength of a given frequency depends on the number of active oscillators (i.e., neural generators) belonging to a particular oscillatory system and on the degree of synchrony and reciprocal connections between them (Knyazev et al., 2004). Functionally, oscillatory activity at a specific frequency is thought to reflect resonant communication between/within neural networks involving large neural populations (Başar et al., 1999). Oscillations at specific frequencies are categorized according to bands: delta (< 3 Hz), theta (3.5-7.5 Hz), alpha (7.5-13 Hz), beta (14-30 Hz) and gamma (30+ Hz), though boundaries are flexible and bands can be further subdivided. The functional correlates of

each band may vary depending on where EEG is measured as its source generators may change with scalp location (Figure 1.5A).

Delta, which tends to be prominent in midline frontocentral regions, emerges in later stages of sleep. Theta oscillations, specifically at frontal-medial sites, originate from the rostral ACC (Pizzagalli et al., 2003) and hippocampus and tend to be evoked during mnemonic and emotive processing (i.e., cognitive functions; Mitchell et al., 2008). Alpha is maximal at posterior sites during resting, eyes-closed conditions and is thought to reflect cortical neuron inactivity or 'idling', though it may also be involved in actively inhibiting brain activity (Klimesch et al., 2007). Alpha is inversely related to arousal and its presence tends to index decreased activity in underlying generators. Conversely, beta is associated with alert/aroused states and tends to index cortical activation (Gevins et al., 1979). Finally, the functional correlates of gamma are the most elusive as it appears to be related to multiple functions (Başar et al., 1999). Due to the relative scarcity of studies probing gamma activity in MDD and antidepressant treatment, gamma power was not examined in this thesis work (Figure 1.5B).

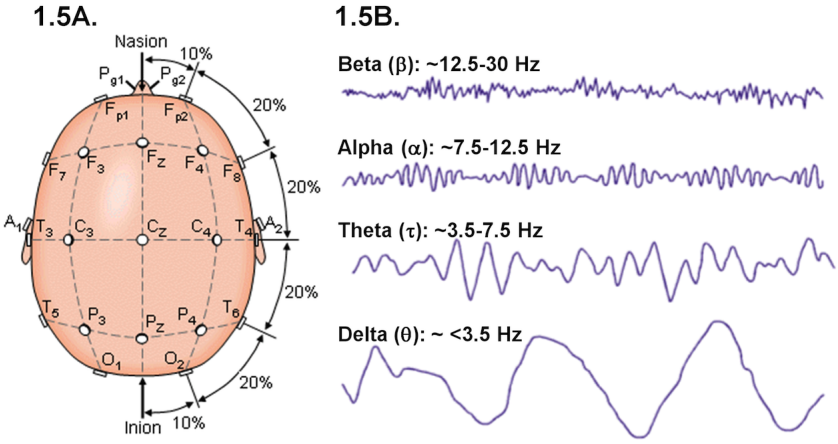


Figure 1.5A. An example of an EEG montage based on the international 10-20 system, which describes electrode placement at specific intervals along the head (Jasper, 1958). **Figure 1.5B.** A schematic of characteristic EEG frequency bands. Figures adapted from http://www.bem.fi/book/13/13.htm

1.7.2 An Overview of Event-Related Potentials (ERPs)

ERPs result from averaging EEG data typically time-locked to some event, such as the presentation of a stimulus. ERPs are embedded in the EEG signal and their extraction requires the processing of raw EEG data. ERPs are small, contaminated by

ongoing brain activity and, thus, rarely visible in a single measure, which is why signal averaging is necessary (Figure 1.6). Averaging unmasks a waveform/peak with a positive (P) or negative (N) deflection (i.e., the ERP). One theory posits that ERPs, much like the EEG signal, are a sum of cortical postsynaptic potentials, which lie 'on top' of EEG oscillations. Alternatively, ERPs may result from phase resetting of ongoing oscillations (i.e., stimulus presentation 'aligns' oscillations and these phase-coherent rhythms emerge as an ERP; Jansen et al. 2003). Regardless, ERPs can be thought of as on-line measures of brain activity in anticipation of and/or in response to stimuli (typically external).

Though not mutually exclusive, there are several means of classifying ERPs. Firstly, they can be classified according to the nature of the stimulus that elicits them (e.g. visual, auditory, somatosensory ERPs). Secondly, ERPs can be categorized according to their latency following stimulus presentation or evoking event. Broadly, short-latency ERPs occur within 100 ms, mid-latency ERPs occur 150-350 ms and long-latency ERPs emerge >350 ms following a stimulus/event, though these latency boarders are somewhat ambiguous. Finally, ERPs are grouped into exogenous and endogenous components. Exogenous ERPs are elicited during the sensory processing stages of stimuli and are highly determined by stimuli characteristics; shorter-latency ERPs are often exogenous. Exogenous components tend to be stable, unconscious/automatic and not highly influenced by cognitive processes. Endogenous components represent later cortical processing stages and are less dependent on stimuli characteristics. In fact, the absence of a stimulus (i.e., expectancy) can evoke them; longer-latency ERPs tend to be endogenous. Endogenous components are more variable than exogenous ones, and are influenced by factors such as attention, stimulus relevancy and resources required for stimulus processing (i.e., cognitive processes).

The utility of ERP probes in the context of MDD rests on their exquisite temporal resolution, on the order of milliseconds, which enables the assessment of dynamic patterns of brain activity, critical for better understanding the correlates (at both pre- and conscious levels) of sensory, cognitive and emotional disturbances in MDD. The use of ERPs has been extended to assessing the effectiveness of antidepressants and in predicting treatment outcome, consistent with the goals of this thesis work.

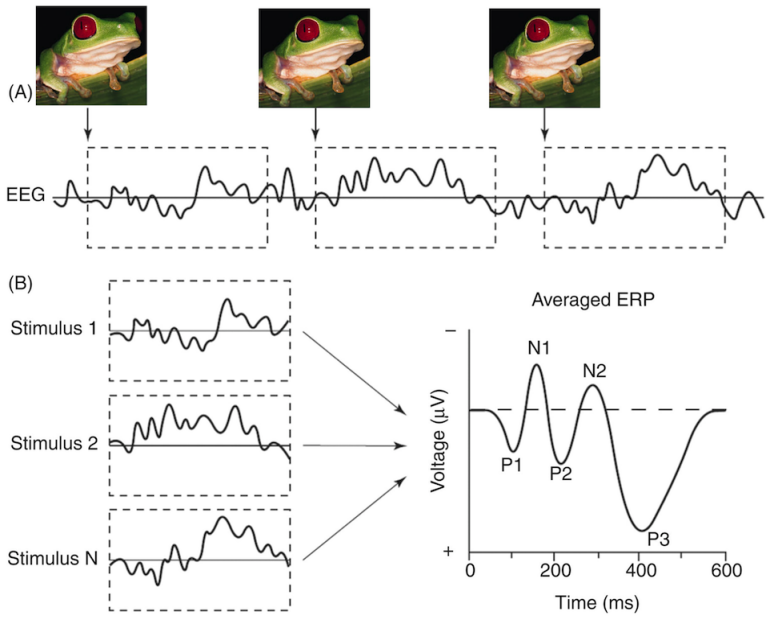


Figure 1.6. Schematic representation of ERP construction. ERPs are obtained by averaging EEG signals time-locked to a stimulus, in this case a picture of a frog. Figure adapted from Alhaj H et al., (2010) J Psychopharmacol;25:1175-1191

1.8 Overview of Electrophysiological Findings in MDD

Though the body of work on electrophysiological investigations in MDD is voluminous, a brief overview of the most pertinent EEG/ERP measures in MDD (i.e., those used in the experiments comprising this thesis), and what they suggest about the depressed brain, will be highlighted.

1.8.1 Alpha Asymmetry in MDD

A substantial number of studies have documented differential cerebral hemisphere activity during the processing and experience of positive versus negative emotive stimuli and emotions. Greater activity in right anterior regions tends to accompany the processing of negative emotions/stimuli while greater relative left anterior cortex activity emerges with the processing of positive ones (Ahern & Schwarts, 1985; Sobotka et al., 1992; Davidson et al., 1998; Kline et al., 2000). Furthermore, resting baseline frontal asymmetry profiles appear to be a trait-like feature biasing a person's affective style, such that individuals with high relative left anterior activity tend to exhibit increased positive

and decreased negative affect, and appraise their environment(s) in a manner that is consistent with this bias, compared to individuals with opposite resting asymmetry profiles (Tomarken et al., 1990; 1992a/b; Wheeler et al., 1993; Jacobs & Snyder, 1996; Davidson, 1998). This asymmetry tends to be probed with EEG alpha power/amplitude, which is inversely related to cortical activity. More recently, the frontal asymmetry model has been modified to account for EEG profiles associated with the processing of anger and cognitive dissonance (Wacker et al., 2003; Harmon-Jones, 2004), with anterior asymmetry models also encompassing the concepts of 'approach' and 'withdrawal' tendencies or motivational directions. Specifically, approach-eliciting tendencies (i.e., behavioral activation), typically elicited by positive stimuli/contexts, are associated with greater relative left anterior activity; withdrawal-eliciting tendencies (i.e., behavioral inhibition), as tends to occur with negative stimuli/contexts, are linked with relative right frontal activity (Davidson et al., 1998; 2004; Coan & Allen, 2003; Wacker et al., 2008; the asymmetry model is further discussed in Chapters 2 and 4).

As previously outlined, the PFC is extensively involved in affective information processing and in regulating emotion-driven motives (Section 1.6.2). The orbital and ventral aspects of the PFC may be especially important for representing reward and punishment. Specifically, the medial left OFC appears to be responsive to rewards whereas the lateral right OFC is implicated in processing punishment (O'Doherty et al., 2001); such evidence is consistent with frontal asymmetry profiles accompanying emotive processing/motivational tendencies. However, further work is needed to characterize the neural substrates underlying asymmetric EEG activity profiles associated with emotive processing/motivational tendencies.

Given that resting frontal asymmetry may reflect an affective processing bias, this could serve as a psychophysiological risk marker for MDD development (Towers & Allen, 2009). By extension, specific profiles may characterize individuals with MDD. Indeed, research suggests that MDD tends to be associated with relative left anterior hypoactivity (Henriques & Davidson, 1990; Davidson & Slagter, 2000; Deldin & Chiu, 2005; Deslandes, 2008; Pössel et al., 2008). Additionally, right parietotemporal hypoactivity has been reported in depressed individuals and in those vulnerable to its development (Henriques & Davidson, 1990; Heller et al., 1995; Bruder et al., 1997; 2005;

Kentgen et al., 2000), which may reflect impaired emotive arousal (Heller & Nitschke, 1997) and be related to symptoms of anhedonia. To date, few studies have investigated the reliability and stability of frontal or posterior asymmetry in MDD and whether stability is influenced by antidepressants (Allen et al., 2004; Vuga et al., 2006; Towers & Allen, 2009).

Finally, some preliminary evidence suggests that posterior alpha asymmetry may differentiate antidepressant treatment responders from non-responders, with eventual responders exhibiting less cortical activity over right (versus left) posterior regions, while non-responders showed the opposite asymmetry, though this effect appears to be stronger in females (Bruder et al., 2001; 2008). The utility of frontal alpha asymmetry in predicating treatment outcome and in guiding treatment selection has not, to our knowledge, been assessed.

1.8.2 Alpha and Theta Activity in MDD

Research probing electrocortical modulations in MDD, apart from alpha asymmetry, indicates that global activity in the alpha and theta bands tends to be altered in MDD. As evidence of modulated beta and delta activity in the disorder is less consistent, it will not be discussed in this overview, nor was activity in these bands explored in the studies comprising this thesis.

MDD tends to be associated with increased scalp-indexed EEG theta, especially in anterior regions (Nyström et al., 1986; Knott & Lapierre, 1987; Kwon et al., 1996; Knott et al., 2000; Fernández et al., 2005; Ricardo-Garcell et al., 2009), which may reflect modulated activity/disturbed coordination between networks, especially within the mPFC (Section 1.6.2). This interpretation is consistent with a handful of studies employing more complex EEG analyses approaches (e.g., temporal correlations in theta activity, connectivity and source analysis; Lieber, 1988; Pizzagalli et al., 2005; Linkenkaer-Hansen et al., 2005). Some studies have also documented alpha EEG alterations, apart from asymmetry, in MDD, with most work suggesting enhanced alpha power/amplitude in the disorder, especially at posterior sites (Pollock & Schneider, 1990;

Roemer et al., 1992; Ricardo-Garcell et al., 2009); this could represent an overall cortical hypoarousal in MDD.

A succinct summary regarding the effects of antidepressant pharmacotherapies on resting EEG alpha and theta is difficult as antidepressants from different classes may have varying effects on EEG activity (antidepressant influences on delta, theta and gamma will not be discussed). Interpretation of the literature is further complicated by whether drug administration was chronic or acute. Much of the work regarding alpha power/amplitude in the context of antidepressant treatment has focused on its utility in predicting outcome. Greater pretreatment alpha characterizes eventual responders (versus non-responders) to various antidepressant pharmacotherapies (Ulrich et al., 1984; 1988; Knott et al., 1996; Wiśniewski et al., 2002; Bruder et al., 2008), though the specificity of this effect should be further probed. Additionally, assessment of alpha power changes throughout the course of antidepressant treatment is lacking.

A handful of studies assessing chronic antidepressant treatment (various classes) effects have noted increased EEG theta power in MDD (Knott et al., 1996; 2002; Landolt & Gillin, 2002) and healthy controls (Siepmann et al., 2002); the opposite has been noted with acute drug administration (Leuchter et al., 2008). Additionally, greater early decreases in theta cordance, an index derived from frontal EEG theta, are evident in responders versus non-responders to several antidepressants (Cook & Leuchter, 2001; Cook et al., 2002; Bares et al., 2007; 2008). Positive antidepressant treatment outcome has also been linked with increased pretreatment theta activity localized to the ACC (Pizzagalli et al., 2001; 2005; Mulert et al., 2007; Narushima et al., 2010; Korb et al., 2011). However, the specificity of the predicative utility of baseline, ACC-localized theta or early theta changes to particular drug classes has been under-explored.

1.8.3 Resting EEG Activity and MDD: Summary and Research Aims

Individuals with baseline EEG-indexed relative right and/or decreased relative left frontal activity tend to exhibit a negative processing bias when appraising affective or ambiguous information. Such a profile has been noted in MDD, which is also associated with an opposite posterior asymmetry profile (i.e., right posterior hypoactivity). Posterior

alpha asymmetry, overall alpha power, as well as theta activity, especially ACC-localized theta, may serve as indices of treatment response. The work presented in Chapter 2 assessed if individuals with MDD are distinguished from controls on the basis of hemispheric asymmetry, alpha power and/or ACC theta activity. Analyses was carried out in depressed males and females as the role of sex has rarely been examined in comparable work, despite preliminary data indicating that sex may play an influential role on electrophysiological measures. In Chapter 4, the utility of baseline alpha power and asymmetry in predicting response to chronic treatment with ESC, BUP or ESC+BUP was assessed. The association between early (1 week) changes in alpha power/asymmetry and response outcome, and whether these indices change during the course of treatment, was also examined. Similar analyses were carried out on ACC theta activity. The stability of frontal asymmetry during antidepressant treatment (12 weeks) was also probed.

1.8.4 The Loudness Dependence of the Auditory Evoked Potentials (LDAEP)

Given that ERPs are averaged from EEG activity resulting from potentials triggered by neurotransmitter release into the synaptic cleft, ERPs (at least to a certain extent) indirectly index neurotransmitter activity. High 5-HT concentrations and synthesis rates exist in primary sensory cortices, including the primary auditory cortex (Berger et al., 1988). Thus, 5-HT neurotransmission is implicated in modulating auditory processing in the primary auditory cortex, which should be reflected (at least to a certain extent) in auditory ERPs (AEPs) evoked in this region. The N1 and P2 are two AEPs reliably elicited in response to auditory stimuli (Hegerl & Juckel, 1994). Their peak-to-peak amplitude (N1/P2) correlates with auditory intensity and is thought to index cortical processing strength. A loudness dependence of the auditory evoked potential (LDAEP) slope is constructed from plots of N1/P2 amplitude against tone intensity. The LDAEP slope has been proposed to be an inverse index of 5-HT activity.

DRN 5-HT neurons terminating in the primary auditory cortex are well suited for tonic, inhibitory modulation of primary auditory cortex activity, especially during intense auditory stimulation to guard against cortical over-excitation (Hegerl et al., 2001). Low tonic 5-HT activity, likely reflecting 5-HT system hypoactivity, should be associated with

a steep LDAEP. Conversely, a shallow LDAEP slope should reflect enhanced/normal 5-HT activity (Mulert et al., 2005; Figure 1.7). Though the evidence for this inverse relationship is robust pre-clinically (Mantz et al., 1990; Waterhouse et al., 1990; Juckel et al., 1999), clinical support is less consistent (Gallinat et al., 2000; Debener et al., 2002; Kähkönen et al., 2002; Massey et al., 2004; Segrave et al., 2006; Uhl et al., 2006; Norra et al., 2008), though some of these discrepancies could partially be accounted for by methodological factors. Depressed individuals, who tend to have dysfunctional 5-HT system activity, may exhibit an altered LDAEP compared with controls, though two known studies have probed this and found no group differences (Linka et al., 2007; Park et al., 2010).

However, certain caveats regarding the LDAEP and its putative relationship with central 5-HT activity must be pointed out. Firstly, as outlined (Sections 1.7 & 1.2.3), the neurochemical correlates of ERPs are ambiguous, and likely result from the summed activity of various interacting neurochemical systems. Consistent with this, LDAEP slope modulations have been associated with dopamine (DA) transporter availability (Lee et al., 2011), DA levels (Beucke et al., 2010) and DA receptor stimulation (Juckel et al., 1997). However, others examining the effects of altered DA levels and/or activation/antagonism of DA or noradrenaline (NA) receptors have found no associated LDAEP changes (O'Neill et al., 2006, 2008; Oliva et al., 2010). Thus, despite evidence for a link between central 5-HT activity and the LDAEP, the proposed exclusive 5-HT system influence on the LDAEP is unlikely.

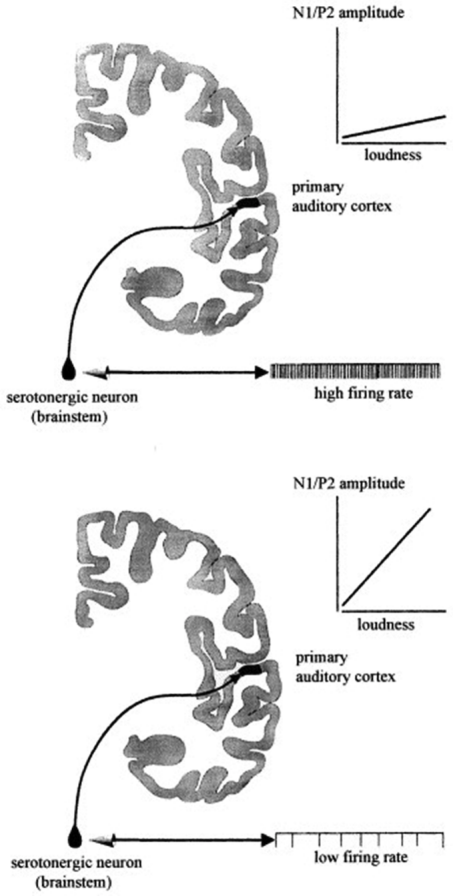


Figure 1.7. An illustration of the inverse relationship between the LDAEP slope and DRN 5-HT activity. Figure adapted from Hegerl et al., (2001) J Affect Disord;62(1-2):93-100

Increasing evidence suggests that the LDAEP may be a useful predictor of response to antidepressants targeting the 5-HT system (Mulert et al., 2002; Pogarell et al., 2007) as individuals with steep baseline slopes likely have less efficient 5-HT neurotransmission and should respond favorably to treatments that augment it, which indeed appears to be true (Paige et al., 1994; Mulert et al., 2002; Linka et al., 2004; Lee et al., 2005). Conversely, individuals with shallow slope may be more likely to benefit from drugs not directly targeting the 5-HT system (Juckel et al., 2007; Mulert et al., 2007). It is unclear whether chronic antidepressant administration alters the LDAEP, with only one known report indicating no alterations with SSRI treatment (Gallinat et al., 2000). LDAEP slope changes throughout the course of antidepressant treatment should be probed to determine if adaptations in 5-HT neurotransmission emerge at various stages of treatment.

1.8.5 LDAEP and MDD: Summary and Research Aims

Strong pre-clinical evidence exists in support of an inverse relationship between the LDAEP and 5-HT activity, though clinical support is less convincing. However, the utility of the LDAEP in predicating antidepressant outcome is compelling. The study presented in Chapter 3 examined if baseline LDAEP slopes differed between depressed versus control males and females. N1 and P2 LDAEP slopes, in addition to the N1/P2 LDAEP, were assessed as they may be more sensitive measures of 5-HT neurotransmission; precedent work has found differences only with the P2 LDAEP after monoamine system modulations (Paige et al., 1995). Given that the evidence for the influence of sex on the LDAEP is mixed (Linka et al., 2009; Park et al., 2010; Simmons et al., 2011; Oliva et al., 2011), this too was examined. The work presented in Chapter 5 assessed if the LDAEP is altered throughout the course of antidepressant treatment and probed the utility of baseline and early changes (1 week) in the LDAEP in predicting response to chronic treatment with ESC, BUP or ESC+BUP. One known study has examined the relationship between pretreatment LDAEPs with BUP outcome (Paige et al., 1995) and none exist with drug combinations, despite evidence of synergistic BUP+ESC effects on 5-HT an NA firing (Ghanbari et al., 2010). Due to high LDAEP variability, it has been difficult to establish slope cut-off values for classifying individuals as potential treatment responders/non-responders; this research, combined with other studies, may help establish such values.

1.9 Emotive Facial Processing

1.9.1 Emotive Facial Processing in MDD

The ability to meaningfully process facial expressions is critical in guiding appropriate social interactions (Gosselin et al., 1995). Negative expressions appear to most effectively recruit attention and interfere with on-going tasks (Pratto et al., 1991; Mathews et al., 2004). In accordance with the mood-congruent processing bias theory (Kovacs & Beck, 1978; Giesler et al., 1996), depressed individuals have been shown to

exhibit preferential processing of negative stimuli, including facial expressions, and interpret neutral information more negatively than non-depressed controls (Bouhuys, et al., 1999; Gotlib et al., 2004; Surguladze et al., 2004; Leyman et al., 2007; Gollan et al., 2008), though some evidence also suggests that MDD may be associated with blunted emotive facial processing in general (Gur et al., 1992; Rubinow & Post, 1992; Koschack et al., 2003; Leppänen et al., 2004). To reconcile these findings, it has been proposed that depressed individuals may exhibit reduced perceptual sensitivity to positive expressions, yet engage in more extensive negative expression processing (Gollan et al., 2008; Joormann & Gotlib, 2006), though evidence for such a clear double-dissociated is limited. As a final point, increased processing of negative, particularly sad, facial expression processing in MDD may be a trait-like feature of the disorder, as it has been noted in remitted patients and in those receiving treatment (Bhagwagar et al., 2004; Savaskan et al., 2008); it may also be associated with disorder severity and prognosis (Hale, 1998; Bouhuys et al., 1999).

The tendency for specifically enhanced sad expression processing appears to be somewhat MDD-specific. After all, bipolar disorder has been associated with blunted expression processing, regardless of valance (Bozikas et al., 2006; Schenkel et al., 2007; Brotman et al., 2008), though this is most apparent during mania (Lembke & Ketter, 2002; Getz et al., 2003; Summers et al., 2006). Anxiety, especially social anxiety, tends to be most consistently linked with altered processing (typically hypersensitivity) to expressions indicating threat, such as fear and anger (Horley et al., 2004; Leber et al., 2009; but see: Philippot & Douilliez, 2005). However, given that anxiety tends to be highly co-morbid in MDD, this should be kept in mind when interpreting emotive facial processing data in the context of MDD.

1.9.2 Neural Correlates of Emotive Facial Processing

Face processing elicits activation of the fusiform gyrus (FFG: 'face processing area'), particularly in the right hemisphere (Esslen et al., 2004). The FFG is implicated in coding static face features and, thus, in identifying a stimulus as a face, though evidence suggests that FFG activity can be modulated by facial expressions, especially intensely

negative ones (Fox et al., 2009). Facial expression processing also induces greater activation in the ventral occipitotemporal cortex and the calcarine fissure, which houses the primary visual cortex (Pessoa, 2002). The PFC and ACC are involved in affective, including facial expression, processing (Blair et al., 1999; Esslen et al., 2004). The sub-cortical amygdala is particularly relevant in processing fear and anger (Whalen et al., 1998; Morris et al., 1998), while the basal ganglia play a dominant role in processing positive expressions (Adolphs, 2002; Fu et al., 2007). Brainstem structures and the hypothalamus modulate automatic and endocrine responses associated with emotions, while the hippocampus plays a role in emotive memories (Kilts et al., 2003; Strauss et al., 2005).

Involvement of both cortical and sub-cortical structures in affective information processing has led to the development of a 'dual route' model of facial expression processing. The 'cortical stream' consists of reciprocal projections between the visual cortex, FFG, superior temporal sulcus and anterior cortical regions (e.g. ACC), with parallel projections to sub-cortical structures (e.g. amygdala; Calder & Young, 2005). It is implicated in detailed perceptual analysis necessary for facial expression discrimination (Adolphs, 2002). A parallel, 'subcortical stream' involves neural pathways through the superior colliculus and lateral pulvinar thalamus that project directly to sub-cortical structures. This route is thought to evaluate stimuli rapidly but crudely, thus allowing for automatic reactions to affective stimuli (Palermo & Rhodes, 2007; Hennenlotter & Schroeder, 2006).

1.9.3 ERPs and Emotive Facial Processing

The N170, emerging ~170 ms after a face is presented, reflects visual processing implicated in constructing a representation of a face (Eimer & Holmes, 2002; Vuilleumier & Pourtois, 2007); the FFG is its likely generator (Eryilmaz et al., 2007). Though it is regarded as being 'face-specific,' perceptual expertise with non-face stimuli (e.g. bird species in bird experts) can also elicit the N170 (Tanaka & Curran, 2001). Nevertheless, preferential facial processing is evident in infancy, indicating that face-tuned indices emerge early and may be somewhat innate (Peltola et al., 2008). Some

uncertainty exists as to whether the N170 is altered by facial expressions, with a substantial body of literature indicating that it is not (Ashley et al., 2004; Santesso et al., 2008; González-Garrido et al., 2009), though, a comparable amount of research indicates that it is (Eger et al., 2003; Stekelenburg & de Gelder, 2004; Krombholz et al., 2007).

Modulation by facial expressions of ERPs preceding the N170 suggests that affective information can be extracted even before face recognition occurs (Batty & Taylor, 2003; Brosch et al., 2008). ERPs elicited shortly after the N170 have also been shown to be modulated by facial expressions (Liddell et al., 2004; Williams et al., 2006; Eimer & Kiss, 2007; Pegna et al., 2008; Holmes et al., 2009). However, the directionality of these modulations to specific expressions is unclear given the large number of mid-latency visual ERPs, their dependency on the site of assessment and the experimental paradigm used in their elicitation (Carretié et al., 2001; Ashley et al., 2004; Schutter et al., 2004; Stekelenburg & de Gelder, 2004). Finally, a handful of studies investigating the effects of emotive face processing on late ERP activity, such as the late positive potential (LPP; peaks posteriorly at ~400-600 ms; Eimer & Holmes, 2002) indicate that it tends to be augmented by negative expressions (Schupp et al., 2004; Orozco & Ehlers, 1998).

1.9.4 ERP Correlates of Emotive Facial Processing in MDD

No published work has probed the effects of facial expressions on the N170, or on ERPs that precede it in MDD. The handful of studies using varying experimental paradigms (hampering direct study comparisons) have indicated decreased mid-latency ERPs to happy faces (Deldin et al., 2000; Cavanagh & Geisler, 2006), perhaps reflecting diminished processing of positive stimuli, though others noted the same findings with negative faces in MDD (Kayser et al., 2000). Yet other work probing mid-latency ERPs found evidence of increased processing and attention to emotive versus neutral faces in MDD, suggesting vigilance to emotive information (Rossignol et al., 2008). Finally, assessments of late ERPs indexing sustained processing revealed enhanced processing of negative and diminished processing of positive expressions in MDD, consistent with what would be predicted from behavioral research (Section 1.9.1). Given the scarcity of research, it is currently difficult to draw strong inferences regarding ERP modulations to

facial expressions in MDD; further work in this domain is required. To our knowledge, no research has examined the effects of antidepressants on the temporal (ERP-assessed) brain activity profile during facial expression processing in MDD, and whether it changes throughout the course of treatment.

1.9.5 Facial Processing and MDD: Summary and Research Aims

Behavioral evidence indicates that depressed individuals exhibit a bias for processing negative stimuli, including facial expressions, and seem to appraise neutral information more negatively than non-depressed controls. Due to their superior temporal resolution, ERPs are particularly appropriate for gaining insight into the temporal electrocortical activity profile associated with facial expression processing. The majority of the literature indicates that both early and late latency ERPs tend to be modulated by facial expressions, with intense negative expressions typically inducing the most robust modulations. The work presented in Chapter 6 probed the purported negative processing bias, and perhaps blunted positive information processing, in MDD using ERPs derived from a simple facial expression recognition task. Analysis was carried out in depressed males and females (and controls) to also probe the effects of sex on ERPs to facial expressions, as precedent literature indicates that females process faces more effectively than males (Lewin & Herlitz, 2002; Felmingham et al., 2010). This study was deemed a critical step for future research assessing whether antidepressants are associated with normalizing aberrant ERP patterns.

2. CHAPTER 2: ALPHA ASYMMETRY AND ANTERIOR CINGULATE CORTEX THETA ACTIVITY IN MDD (STUDY 1)

2.1 Introduction

As briefly discussed in Section 1.8.1, increased relative right fronto-cortical activity (probed with EEG alpha, which is inversely related to cortical activity) tends to emerge during the processing of negative information, including emotions, while greater relative left fronto-cortical activity is associated with positive information/affective processing (Davidson, 1998). However, electrocortical asymmetry profiles accompanying the processing of anger or cognitive dissonance have also been associated with increased relative left fronto-cortical activity (Wacker et al., 2003; Harmon-Jones, 2004). To account for this, current asymmetry models posit that approach tendencies and positive information/emotion processing are associated with greater left anterior activity while withdrawal tendencies and negative information/affective processing are linked with right frontal activity. In support of this, individuals with stable and extreme resting relative left anterior activity report increased positive and decreased negative affect compared to those with stable and extreme relative right anterior activity (Tomarken et al., 1992b). Resting frontal alpha asymmetry also predicted affective responses to emotive stimuli (Tomarken et al., 1990; Wheeler et al., 1993). Therefore, such resting anterior asymmetry profiles may be a trait-like feature biasing affective style (Jacobs & Snyder, 1996), though it is also plausible that asymmetry profiles reflect a motivational abnormality rather than an affective disposition (Pizzagalli et al., 2005).

Individuals with MDD tend to exhibit relative left frontal hypoactivity (Davidson & Slagter, 2000; Deldin & Chiu, 2005; Deslandes et al., 2008; Pössel et al., 2008; Kemp et al., 2010), which, along with right frontal hyperactivity, have been associated with greater depression scores (Saletu et al., 2010). Remitted depressives also exhibit decreased relative left frontal activity (Henriques & Davidson, 1990). Thus, left frontal hypoactivity (and/or right frontal hyperactivity) may be a risk marker for MDD. Individuals with this profile may be more likely to apply maladaptive coping strategies (e.g. rumination) especially with repeated stress, a known MDD precursor, increasing the

likelihood for MDD development compared with those displaying the opposite asymmetry.

Increased alpha power/amplitude over right parietotemporal regions has also been associated with MDD (Bruder et al., 2005; 2011; Kentgen et al., 2000). Right parietotemporal activity is involved in modulating emotion-related autonomic arousal (Heller & Nitschke, 1997); as such, decreased right parietotemporal activity may reflect diminished emotional arousal in the disorder. Some support for this comes from findings documenting that MDD patients with co-morbid anxiety, characterized by a hyper-aroused state, display right parietotemporal hyperactivity (Keller et al., 2000; Kentgen et al., 2000) while those without anxiety exhibit decreased activity in this region (Bruder et al., 1997). Accordingly, asymmetry models in the context of MDD are sometimes expanded to include two dimensions: the valance/motivation dimension involving anterior regions and the arousal dimension involving right parieto-temporal aspects.

However, certain caveats regarding the asymmetry model, particularly frontal asymmetry, must be pointed out. Firstly, when anterior asymmetry is examined in individuals without extreme/stable asymmetry, the relationship between asymmetry and dispositional affect weakens (Debener et al., 2000). Secondly, different methodological approaches (e.g. reference, sites assessed, alpha bands) in asymmetry assessments influence the relationship between frontal asymmetry and affective style/motivation (Thibodeau et al., 2006). Though factors such as age are also known to modulate frontal asymmetry, relatively little research has systematically assessed its influence by sex. One study unexpectedly found that males with childhood-onset MDD exhibited increased left frontal activity than controls (Miller et al., 2002). Another group, however, noted the expected relationship between left frontal activity and positive affective style in healthy males, though only at lateral sites (Jacobs & Snyder, 1996). Stewart et al., (2010) found that females with high depression symptoms exhibited decreased left frontal activity, which was less robust in males, suggesting that females are more likely to be characterized by left frontal hypoactivation. Lastly, several studies have noted no frontal asymmetry alterations in MDD, questioning its role as a marker in the disorder (Carvalho et al., 2011; Segrave et al., 2011).

As outlined in Section 1.8.2, theta activity has also been assessed in the context of MDD, with several studies indicating increased theta amplitude/power, typically in anterior regions and in the right hemisphere, in the disorder (Kwon et al., 1996; Knott et al., 2000; Ricardo-Garcell et al., 2009). On the other hand, neuroimaging or source localization methods [magnetoencephalography (MEG), LORETA (the older version of sLORETA)] have revealed decreased frontal/ACC theta activity in MDD, which has also been associated with increased depression scores (Wienbruch et al., 2003; Coutin-Churchman & Moreno, 2008; Saletu et al., 2010). Methodological differences may underlie these discrepancies, whereby EEG theta amplitude/power may stem from several neural generators while source localization and neuroimaging techniques allow assessment of activity in specific regions of interest (ROIs). Nevertheless, altered frontal theta activity may reflect disrupted functional connectivity in fronto-cingulate pathways in the disorder (Pizzagalli et al., 2005). Given that distinct information may emerge with scalp and source-localized theta, direct comparisons between the two in the same study are warranted. Finally, the influence of sex on theta activity has been under-explored, with one study reporting no sex differences in relative prefrontal theta power in MDD, though absolute power was higher in females (Morgan et al., 2005).

This study assessed resting frontal and parietal alpha asymmetry in MDD and examined the role of sex on asymmetry. Resting asymmetry was assessed using three reference montages, which have been shown to influence asymmetry (Stewart et al., 2010). Given evidence that lower and upper alpha bands reflect functional differences (Goncharova & Davidson, 1995) and that individual variability characterizes $alpha_{Total}$ (Segrave et al., 2011), $alpha_1$ and $alpha_2$ power was also assessed. It was expected that greater relative left frontal alpha power would emerge in MDD, and would be more pronounced in females. $Theta_{Total}$ as well as $theta_{1/2}$ activity using sLORETA in ACC ROIs were also examined; theta sub-frequencies were probed as preliminary evidence suggests that its subcomponent frequencies may provide increased insight into the electrocortical correlates of MDD (Fingelkurts et al., 2006). Given that past work suggests decreased anterior/ACC-localized theta activity in MDD, we expected similar results, though literature assessing scalp-recorded theta power/amplitude indicates the opposite. Finally, we carried out correlations between theta power and activity in ACC

ROIs to probe the relationship between the two. Similarly, correlations were carried out between the electrophysiological indices and clinical scores.

2.2 Methods

2.2.1 Participants

Fifty-three (N=53) adults with a primary diagnosis of MDD were recruited from the Mood Disorders Research Unit at the University of Ottawa Institute of Mental Health Research Center. Diagnoses were made by trained psychiatrists using the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR Diagnoses, Axis I, Patient Version (SCID-IV-I/P; First et al., 1997). The Hamilton Rating Scale for Depression [17 and 29 item versions ($HAMD_{17/29}$); Hamilton, 1960; Appendix A] and Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979; Appendix B) were used to index symptom severity. All patients had MADRS scores ≥ 22 at time of enrollment. Notable exclusion criteria were: Bipolar Disorder (I/II/NOS), psychosis history, current (within 6 months) substance abuse/dependence (except nicotine/smoking), history of seizures or increased seizure risk, unstable medical condition (unstabilized for ≥ 3 months), eating disorder history and significant suicide risk. Individuals with a secondary anxiety diagnosis were included in the study (Table 1).

Forty-three (N=43) non-depressed adult controls were also assessed (Table 1). Controls were screened to ensure the absence of a personal psychiatric history as well as alcohol/drug abuse or dependence (assessed with a modified non-patient version of the SCID [SCID-IV-I/NP]; Appendix C), history of seizures or brain trauma. Controls also completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Appendix D) to assess for the existence and severity of depression symptoms, and were included only if they scored ≤13. Only controls with no psychiatric history in first-degree relatives were included in this study (assessed with the Family Interview for Genetic Studies [FIGS]; Maxwell, 1992; Appendix E).

Table 2.1 Major Depressive Disorder (MDD) and control group characteristics & demographics (mean ± S.D.)

	MDD Females (N=29)	MDD Males (N=24)	Control Females (N=23)	Control Males (N=20)
Age	43.2 ± 11.6*	37.7 ± 11.6	37.2 ± 7.8	35.8 ± 11.9
Education Years	15.6 ± 2.4	16.5 ± 2.5	16.4 ± 2.0	16.4 ± 1.9
Smoker	4	7	1	2
$HAMD_{17}$	22.4 ± 5.1*	19.1 ± 4.7	-	-
$HAMD_{29}$	32.5 ± 5.4	29.5 ± 6.7	-	-
MADRS	30.8 ± 5.1	30.8 ± 5.4	-	-
BDI-II	-	-	4.4 ± 5.0	3.1 ± 4.8
Ethnicity	27 Caucasian; 1 Asian; 1 South Asian	21 Caucasian; 2 Asian; 1 African	20 Caucasian; 2 South Asian; 1 African	19 Caucasian; 1 Asian

$HAMD_{17/29}$: Hamilton Rating Scale for Depression, 29 & 17 item versions
MADRS: Montgomery- Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory-II
*p<.05, MDD females had higher HAMD-17 versus MDD males; MDD females were older than control females

2.2.2 Session Procedures

Prior to testing, participants abstained for >3 hr from caffeine and/or smoking/nicotine, as well as alcohol and drugs (other than oral contraceptives and medication required for a stabilized physical condition) beginning at midnight. Upon laboratory arrival, mood evaluations were carried out using the Profile of Mood States questionnaire (POMS; McNair et al., 1992; Appendix F) on which subjective state is rated on 65 mood adjectives, from which values are aggregated to form seven mood dimensions (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment, total mood disturbance: constructed from the other dimensions). Electrodes were applied and resting EEG was recorded. This study was approved by the Royal Ottawa Health Care Group and University of Ottawa Social Sciences and Humanities Research Ethics Boards; informed consent was obtained from all participants. Participants were compensated 30.00 CDN/session (patients participated in several sessions, this work is presented in Chapters 3 and 5).

2.2.3 Electrophysiological Recordings

EEG activity was recorded (500 Hz; mastoid referenced) for 3 min each during eyes-open (EO) and closed (EC) conditions (randomized), using a cap embedded with 32

Ag/AgCl electrodes (EasyCap, Herrsching-Breitbrunn, Germany) positioned according to the 10-10 system (Chatrian et al., 1985; Appendix G). Electrodes on the supra-orbital ridges and external eye canthi monitored electrooculographic (EOG) activity. An AFz electrode served as the ground. Impedance was maintained at ≤5 KΩ and recorded with amplifier filters set at 0.1-80 Hz (BrainVision Recorder, Richardson, TX, USA).

Off-line, EEG data was re-referenced using three montages: average of the left and right mastoids, Cz and average reference (BrainVision Analyzer, Richardson, TX, USA). Signals were filtered (0.1-30 Hz), ocular-corrected (Gratton et al., 1983) and segmented into 2 s epochs (50% overlap). This was followed by artifact rejection, which excluded epochs with signals exceeding +/-75 μV. A minimum of 100 s of artifact-free data for each condition were subjected to fast Fourier transformations (Hanning window; 5% cosine taper) for computation of absolute, ln-transformed power (μV^2) at $alpha_1$ (8.0-10.5 Hz), $alpha_2$ (10.5-13.0 Hz), $alpha_{Total}$ (8.0-13.0 Hz), $theta_1$ (4.0-6.0 Hz), $theta_2$ (6.0-8.0 Hz) and $theta_{Total}$ (4.0-8.0 Hz). Alpha power was assessed at $F_{3/4}$, $F_{7/8}$ and $P_{3/4}$. $Theta_{Total}$ power analysis was confined to Fz (EC, mastoid reference, as in Spronk et al., 2011). Asymmetry indices were calculated for each alpha band by subtracting power at left electrodes from homologous right electrodes (i.e., F_4-F_3, F_8-F_7, P_4-P_3). Only right-handers (Oldfield et al., 1971) were examined in the alpha EEG analysis (MDD females=27, males=22; control females=23, males=18). Power in each of the theta bands was used for analysis with standardized low-resolution electromagnetic tomography software (sLORETA; Pascual-Marqui, 2002).

2.2.4 Source Localization

EC $theta_1$, $theta_2$ and $theta_{Total}$ EEG was re-referenced to the average (as in Pizzagalli et al., 2001) and subjected to analysis with sLORETA (artifact- and ocular-corrected epochs, 60 s of data from 28 electrodes). sLORETA analysis estimates neuronal activity as current density based on the Montreal Neurological Institute 152 template creating a low-resolution activation image. The sLORETA solution space consists of 6239 voxels (5×5×5 mm^3/voxel) restricted to gray matter. Current source density is calculated from a linear, weighted sum of scalp potentials; this value is then squared for

each voxel yielding current density power measures (A/m^2). Its validation has been independently replicated (Phillips et al., 2002) and cross-validated (Pizzagalli et al., 2004; Mulert et al., 2005). sLORETA was used to estimate theta current source density at specific ACC ROIs. Consistent with precedent work (Mulert et al., 2007), ROIs were: BA 24ab (rostral ACC/rACC; 16 voxels, both hemispheres), BA 25 (sgACC; 12 voxels, both hemispheres) and BA 32 (pgACC; 54 voxels, both hemispheres; Supplementary Table 1 in Appendix H; Figure 2.1). Due to faulty channels, several participants were excluded from the sLORETA analysis, with 50 MDD (28 females) and 39 controls (23 females) included. Six left-handed and/or ambidextrous individuals (4 MDD; 2 controls) were included in the sLORETA analysis as hemispheric effects were not assessed (their inclusion did not alter the results, data not shown).

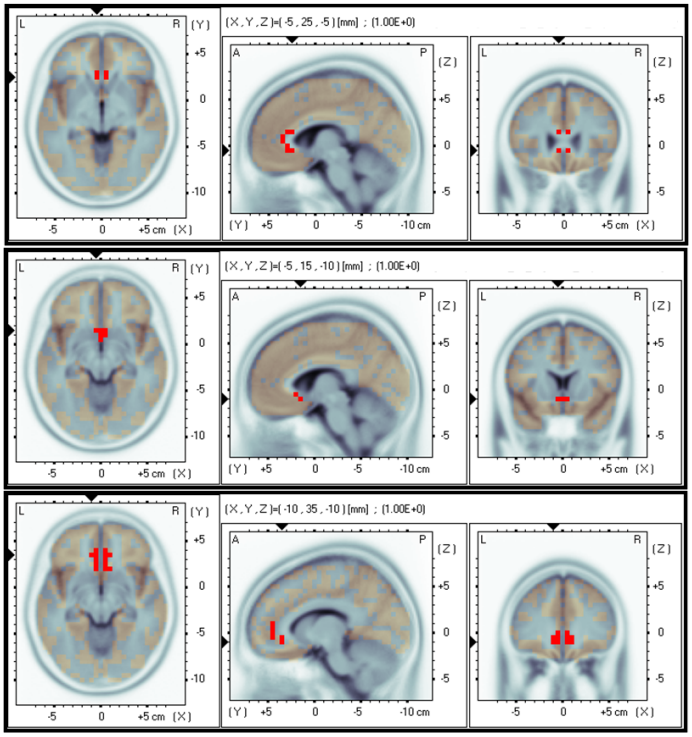


Figure 2.1. Anterior cingulate cortex (ACC) regions of interest (ROIs). Top panel: ROI consisting of voxels from BA 24 (part of the rostral ACC). Middle panel: ROI consisting of voxels from BA 25 (subgenual ACC). Bottom panel: ROI consisting of voxels in BA 32 (perigenual ACC)

2.2.5 Statistical Analyses

Analyses of variances (ANOVAs) were carried out (SPSS Inc., Chicago, IL, USA) on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. Repeated-measures ANOVAs (rmANOVAs) were carried out on ln-transformed absolute power in each alpha band with four within-subject factors: laterality (medial: $F_{3/4}$; lateral: $F_{7/8}$), condition (EC, EO), reference (average, Cz, mastoid) and hemisphere (left, right). Sex and group were between-subject factors. Similarly, rmANOVAs were carried out on each alpha asymmetry index (F_4-F_3, F_8-F_7, P_4-P_3) with reference and condition as within- and group and sex as between-subjects factors. Absolute EC $theta_{Total}$ power analysis (at Fz) was carried out with group and sex as between-subject factors. For alpha measures, only main effects are reported (p<.05). Significant interactions (p<.05) containing group, sex or both are only reported if follow-up comparisons of significant interactions revealed direct group or sex differences. For the ROI analyses, separate univariate, two-way ANOVAs were applied for each ROI in each theta band, with group and sex as between-subject factors. Greenhouse-Geisser corrections were applied to all significant main effects and interactions. To account for multiple comparisons, Tukey adjustments (built into SPSS) were applied to all pairwise comparisons. Correlations were carried out between EC F_4-F_3 asymmetry in the MDD group (sex collapsed) for each alpha band at all three reference montages and MARDS, $HAMD_{17}$ and $HAMD_{29}$ scores. Similarly, correlations were carried out between $theta_{Total}$ activity at the three ROIs (BA 25, 24ab, 32) and clinical scores for the MDD group (sex collapsed). Finally, correlations were conducted between $theta_{Total}$ power and $theta_{Total}$ activity at the three ROIs (groups collapsed). To adjust for multiple comparisons, significance was set at p<.01 for the correlations.

2.3 Results

2.3.1 Profile of Mood States (POMS)

POMS scores in Table 2 are collapsed across sexes, as no sex effects existed. A main group effect was noted for tension-anxiety [$F(1,91)=110.59$, $p<.001$], depression-dejection [$F(1,91)=243.47$, $p<.001$], anger-hostility [$F(1,91)=71.36$, $p<.001$], fatigue [$F(1,91)=216.76$, $p<.001$], confusion-bewilderment [$F(1,91)=155.18$, $p<.001$] and total mood disturbance [$F(1,91)=300.20$, $p<.001$] dimensions, with higher scores in MDD. Lower scores existed for the MDD group for vigour-activity [$F(1, 91) = 169.29$, $p<.000$].

Table 2.2 Profile of Mood States (POMS) in Major Depressive Disorder (MDD) and control groups (mean ± S.D.)

POMS Dimensions	MDD*** (N=53)	Control (N=43)
Depression-Dejection	35.4 ± 12.5	3.5 ± 4.8
Vigor-Activity	5.0 ± 4.2	19.4 ± 6.3
Confusion-Bewilderment	16.5 ± 5.8	4.1 ± 3.4
Fatigue-Inertia	20.2 ± 5.6	4.5 ± 4.7
Anger-Hostility	17.2 ± 9.6	3.8 ± 3.8
Tension-Anxiety	18.5 ± 7.5	5.1 ± 3.0
Total Mood Disturbance	103.2 ± 33.3	1.5 ± 19.8

***$p<.001$: All POMS dimensions differed between the MDD versus control groups

2.3.2 $Alpha_1$, $Alpha_2$ and $Alpha_{Total}$ Power: Effects of Laterality, Condition and Reference

A main effect of condition (EO/EC) existed for $alpha_1$ [$F(1,86)=130.57$, $p<.001$], $alpha_2$ [$F(1,86)=199.61$, $p<.001$] and $alpha_{Total}$ [$F(1,86)=213.40$, $p<.001$], with greater power in the EC condition. A main effect of reference was found for $alpha_1$ [$F(2,86)=170.97$, $p<.001$], $alpha_2$ [$F(2,86)=24.82$, $p<.001$] and $alpha_{Total}$ [$F(2,86)=142.55$, $p<.001$]. Power was different in all reference montages for $alpha_1$ and $alpha_{Total}$, (min $p<.001$), with smallest power in the average, intermediate in the Cz and greatest in the mastoid reference. For $alpha_2$, smaller power values existed in the average versus the Cz and mastoid references ($p<.001$ for both). A main effect of laterality (medial/lateral sites)

was found for alpha$_2$ F(1,86)=31.50, p<.001] and alpha$_{Total}$ [F(1,86)=11.35, p=.001], with greater power in the lateral versus medial aspect; a similar trend existed for alpha$_1$ [F(1,86)=3.71, p=.056].

2.3.3 Frontal Alpha$_1$, Alpha$_2$ and Alpha$_{Total}$ Power: Effects of Group and Sex

Alpha$_1$: A main effect of group existed [F(1,86)=5.44, p=.022] with greater alpha$_1$ power in the MDD (1.70 ± .12 μV^2) versus control (1.29 ± .13 μV^2) group (Figure 2.2).

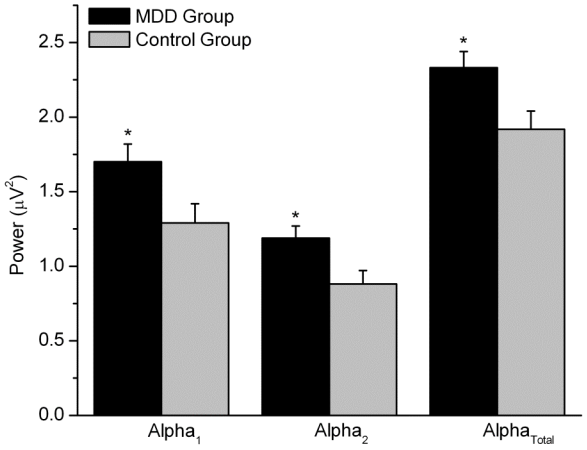


Figure 2.2. Frontal power (ln-transformed; collapsed across $F_{3/4}$ and $F_{7/8}$) in alpha bands in individuals with MDD and controls (*p<.05)

Alpha$_2$: A main effect of group [F(1,86)=6.80, p=.011], with greater fronal alpha$_2$ power in the MDD (1.19 ± .08 μV^2) versus control (.88 ± .09 μV^2) group existed (Figure 2.2). A reference×hemisphere×group×sex interaction [F(2,172)=8.36, p=.003] existed, with follow-up comparisons indicating group differences for the Cz reference in the left frontal hemisphere between MDD versus control males (p=.047), though a similar trend was noted in the right frontal hemisphere (p=.055). With the mastoid reference, the same difference existed in the left frontal hemisphere (p=.010), though the trend was again noted in the right hemisphere (p=.051). In both cases, MDD males had greater alpha$_2$ power than control males.

Alpha$_{Total}$: A main effect of group existed [F(1,86)=6.68, p=.011], with greater power in the MDD (2.33 ± .11 μV^2) versus control (1.92 ± .12 μV^2) group (Figure 2.2). A

reference×laterality×group×sex interaction [F(2,86)=3.99, p=.025] existed, with follow-up comparisons indicating a group difference in females in the lateral aspect ($F_{7/8}$) in the mastoid reference (p=.046), with greater $alpha_{total}$ in MDD versus control females. For males, in all reference montages, in both the lateral and medial aspects, MDD males had greater $alpha_{total}$ than control males (min. p<.05).

2.3.4 Frontal $Alpha_1$, $Alpha_2$ and $Alpha_{Total}$ Power Asymmetry (F_4-F_3)

$Alpha_1$: No specific group or sex differences were noted with $alpha_1$ asymmetry.

$Alpha_2$: A main effect of group existed [F(1,86)=4.87, p=.030], with a positive index in the control (.055 ± .025 μV^2) and a negative one in the MDD group (-.020 ± .023 μV^2; Figure 2.3). A condition×group interaction was noted [F(1,86)=6.14, p=.015], with a group difference in the EO condition (p=.007), with a positive index in controls (.091 ± .031 μV^2) and a negative one in MDD (-.025 ± .028 μV^2). A reference×group×sex interaction existed [F(2,172)=6.58, p=.006], with a group difference in $alpha_2$ asymmetry in females in the Cz reference (p=.010). In males, a group difference was noted in the mastoid reference (p=.009). In both cases, the index was negative in the MDD and positive in the control group. In controls, a sex difference was noted in the mastoid reference montage (p=.015), with a positive index in males (.12 ± .041 μV^2) and a negative one in females (-.013 ± .036 μV^2).

$Alpha_{Total}$: No group or sex differences were noted with $alpha_{Total}$ asymmetry.

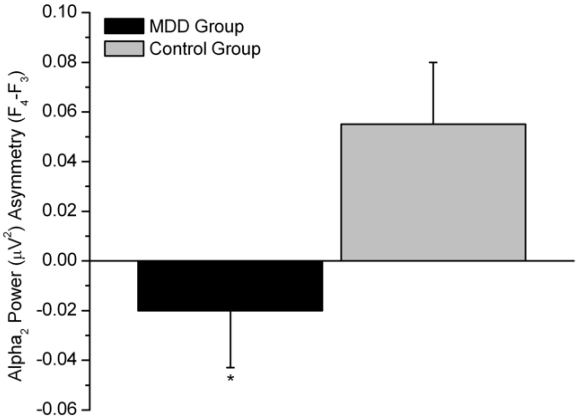


Figure 2.3. Midfrontal $alpha_2$ asymmetry, derived by subtracting left from right ln-transformed alpha power at homologous electrodes, in MDD and control groups (sex collapsed; *p<.05)

2.3.5 Frontal Alpha$_1$, Alpha$_2$ and Alpha$_{Total}$ Power Asymmetry (F_8-F_7)

Alpha$_1$: Only a main effect of reference was noted for alpha$_1$ F_8-F_7 asymmetry [F(2,172)=5.55, p=.012], with a difference between the average (-.077 ± .023 μV^2) versus the mastoid reference (-.008 ± .021 μV^2; p=.012)

Alpha$_2$: Follow-up comparisons of the reference×group×sex interaction [F(2,172)=6.69, p=.006] indicated a group difference in alpha$_2$ F_8-F_7 asymmetry in females in the Cz reference (p=.045); MDD females exhibited a more negative asymmetry index (-.095 ± .031 μV^2) than control females (-.001 ± .034 μV^2). In the MDD group, a sex difference existed in the Cz reference montage (p=.036), with a more negative index for females versus males (.004 ± .034 μV^2; Figure 2.4).

Alpha$_{Total}$: No direct group or sex differences were noted for alpha$_{Total}$ F_8-F_7 asymmetry.

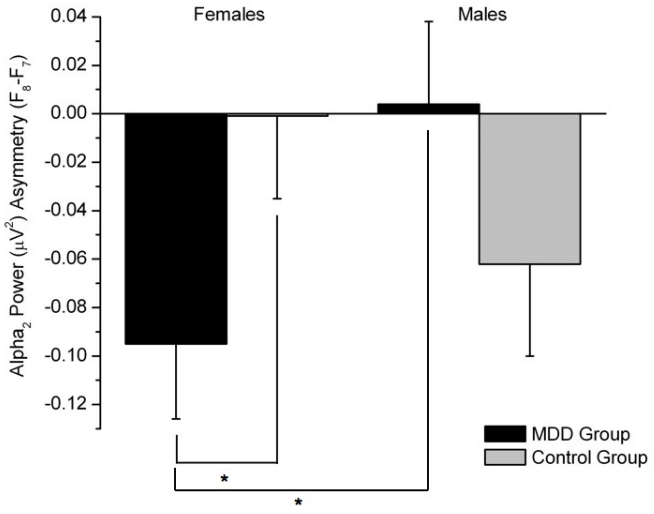


Figure 2.4. Frontolateral alpha$_2$ asymmetry, derived by subtracting left from right ln-transformed alpha power at homologous electrodes, in females and males with and without MDD (*p<.05)

2.3.6 Parietal Alpha$_1$, Alpha$_2$ and Alpha$_{Total}$ Power Asymmetry (P_4-P_3)

No effects were noted for alpha$_1$ or alpha$_{Total}$ parietal asymmetry. For alpha$_2$, a group×sex interaction existed [F(1,86)=6.41, p=.013], follow-up comparisons indicated a sex difference in the MDD group (p=.047), with a negative parietal asymmetry in MDD

females (-.041 ± .037 μV^2) and a positive one in MDD males (.071 ± .041 μV^2; Figure 2.5).

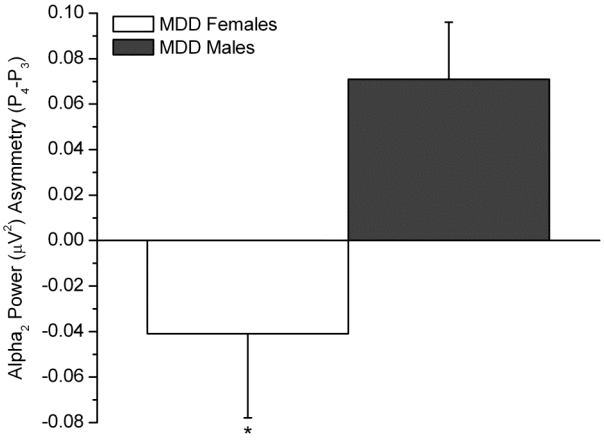


Figure 2.5. Parietal $alpha_2$ asymmetry, derived by subtracting left from right ln-transformed alpha power at homologous electrodes, in females and males with MDD (*p<.05)

2.3.7 $Theta_{Total}$ Power at Fz

No main effects of group, or sex or interactions between the two were noted.

2.3.8 $Theta_1$, $Theta_2$ and $Theta_{Total}$ Activity in Anterior Cingulate Cortex ROIs

BA 32 ROI: No group or sex effects existed for theta activity.

BA 25 ROI: For $theta_1$, a group trend was noted [F(1,85)=2.82, p=.097], with a tendency for greater $theta_1$ in the MDD (5.27 ± .066 A/m^2) versus control group (5.10 ± .076 A/m^2). A main effect of group [F(1,85)=4.90, p=.030] existed for $theta_2$, with greater activity in the MDD (5.36 ± .088 A/m^2) versus control group (5.07 ± .10 A/m^2). A main effect of group [F(1,85)=4.31, p=.041] also existed for $theta_{Total}$, with it being greater in the MDD (6.00 ± .075 A/m^2) versus control group (5.77 ± .086 A/m^2; Figure 2.6).

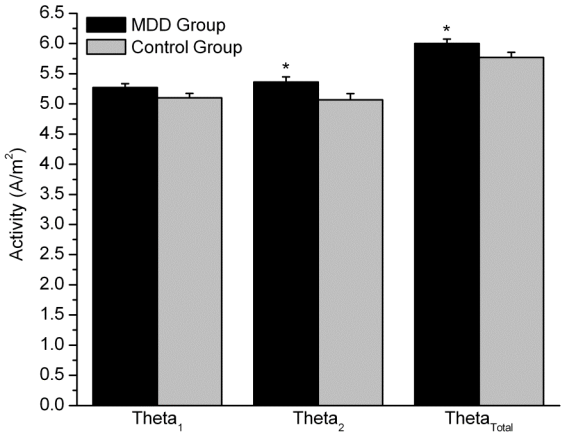


Figure 2.6. sLORETA-indexed theta activity localized to the sgACC/BA 25 in MDD and control groups (sex collapsed; *p<.05)

BA 24ab ROI: No main effects existed for theta activity.

2.3.9 Correlations

$Theta_{Total}$ power correlated with $theta_{Total}$ activity in BA 25 [r=.83, N=89, p<.001], BA 24ab [r=.76, N=89, p<.001] and BA 32 [r=.59, N=89, p<.001].

2.4 Discussion

This study probed frontal and parietal alpha asymmetry, using three reference montages, in MDD. Midfrontal theta power and activity in specific ACC regions was also assessed. Additionally, correlations were carried out between frontal alpha asymmetry as well as ACC theta activity and clinical ratings. Consistent with diagnoses, depressed versus control individuals were characterized by POMS-indexed mood disturbances. Greater anterior alpha power, reflecting hypoactivity, existed in MDD, which was especially evident in males. Group differences emerged in midfrontal $alpha_2$ asymmetry indicating left fontal hypoactivity in MDD. Finally, increased sgACC theta activity existed in MDD. These results and their implications are discussed below.

Although a main effect of reference was noted for alpha power in all bands, reference had a less substantial influence on alpha asymmetry indices, though the reference montage influenced $alpha_1$ F_8-F_7 asymmetry. This finding suggests that

comparisons between studies of midfrontal alpha asymmetry using different reference montages are possible, though should be made with caution. Furthermore, group effects on alpha power and asymmetry emerged only with certain references, highlighting the utility of assessing several montages in comparable future work (Stewart et al., 2010). Greater alpha power was evident in lateral versus medial aspects, which differs from what others have found (Deslandes et al., 2008). Nevertheless, these results suggest that different generators may contribute to alpha power measured at different frontal sites and should be taken into account when interpreting anterior asymmetry findings.

Though not a universal finding (Knott & Lapierre, 1987; Bruder et al., 1997; Mientus et al., 2002), which may be partially related to methodological factors, more work than not has documented enhanced EEG alpha in MDD (Pollock & Schneider, 1990; Roemer et al., 1992; Baehr et al., 1998; Kemp et al., 2010). Consistent with our findings, some work has noted increased anterior alpha power in MDD (Bauer & Hesselbrock, 2002; Ricardo-Garcell et al., 2009). However, it is possible that had alpha power been assessed across the scalp, these group differences would have also emerged and would thus reflect global cortical hypoactivity in MDD.

When frontal alpha activity was broken down by sex, MDD versus control males exhibited greater $alpha_2$ power in the left frontal region in both the Cz and mastoid reference montages, though a similar trend was noted in the right frontal region. Thus, although MDD males had increased anterior $alpha_2$ power in general, this was more pronounced in the left frontal region, consistent with precedent literature indicating left fronto-cortical hypoactivity in MDD (Davidson & Slagter, 2000; Deldin & Chiu, 2005; Kemp et al., 2010). Depressed males, in all reference montages and in both frontal aspects, exhibited greater $alpha_{total}$ power than control males, consistent with the group findings. Greater $alpha_{total}$ power was noted in MDD versus control females only in the fronto-lateral aspect in the mastoid reference montage. However, no direct sex differences were noted for frontal alpha power, inconsistent with previous work (Miller et al., 2002).

Alpha sub-frequencies were assessed because $alpha_{total}$ is susceptible to large variability (Segrave et al., 2011), and $alpha_1$ and $alpha_2$ have been associated with different cognitive processes. Specifically, $alpha_2$ has been linked with memory retrieval,

while $alpha_1$ is broadly associated with attention (Klimesch et al., 2007). Though the significance of these sub-frequencies at rest is unclear, and both are thought to reflect decreased cortical activity, inspection of sub-bands may enable greater specificity with respect to profiling the electrocortical correlates of MDD. In the current study, power in both sub-frequencies was greater in the MDD versus control group. However, only $alpha_2$ power was increased in left anterior regions in MDD versus control males, consistent with a previous study that found $alpha_2$-specific changes in depression (Lubar et al., 2003).

No midfrontal (F_4-F_3) $alpha_1$ or $alpha_{total}$ asymmetry index differences were noted between the groups, consistent with the findings of Segrave et al., (2011). Others, assessing $alpha_{total}$ frontal asymmetry, have also found no alpha power asymmetry differences in MDD (Kemp et al., 2005; Mathersul et al., 2008; Carvalho et al., 2011). However, a group difference, regardless of reference, existed for midfrontal $alpha_2$ asymmetry. Consistent with others' findings, a positive index existed in controls indicating increased relative left frontal activity, while a negative index was noted in the MDD group indicating the opposite. Further breakdown by sex indicated a group difference in midfrontal and frontolateral (F_8-F_7) $alpha_2$ asymmetry in females in the Cz reference montage; in males, a group difference in midfrontal asymmetry emerged in the mastoid reference montage, with the expected asymmetry in both cases. These findings further highlight the influential role of reference in frontal alpha asymmetry assessments.

Few further effects emerged for frontolateral alpha asymmetry. In the MDD group, a sex difference in $alpha_2$ asymmetry was noted in the Cz reference montage, with more negative indices in females versus males. This is consistent with predictions and previous work indicating greater asymmetry in depressed females than males (Stewart et al., 2010). However, given that this sex difference only emerged with the Cz montage, and because frontolateral asymmetry may be a less stable index of valence/motivation than the midfrontal asymmetry index (Pössel et al., 2008), the validity of these results is questionable. Thus, little evidence existed for pronounced sex effects on either frontal power or asymmetry.

For parietal $alpha_2$ asymmetry, a negative index was noted in MDD females and a positive one in MDD males, suggesting greater relative right parietal cortical activity in

females but reduced activity in males. Although no direct group differences emerged, the results in males are consistent with previous work indicating increased alpha power/amplitude in right parietotemporal regions in MDD (Bruder et al., 2005; 2011; Kentgen et al., 2000). Given that greater right parietal activity has been associated with anxious arousal (Kentgen et al., 2000; Manna et al., 2010), it is feasible that MDD females exhibited more anxiety symptoms than males, which could account for the reported findings, although state tension-anxiety scores did not differ between the sexes.

Midfrontal $theta_{Total}$ power did not differentiate MDD and control groups. Earlier work regarding scalp EEG theta assessments in MDD are somewhat mixed. For instance, Saletu et al., (2010) noted pronounced theta decreases across the scalp, while frontal (Ohashi et al., 1994) and prefrontal theta reductions in MDD have also been noted (Wienbruch et al., 2003). Others, however, have found increased slow-wave activity during late-life MDD (Roemer et al., 1992; Köhler et al., 2011) and increased posterior theta during the early stages of MDD (Grin-Yatsenko et al., 2010); increased frontal theta power was also associated with more severe depression (Knott et al., 2000). However, yet other groups report no theta power differences in MDD (Pollock & Schneider 1990), consistent with out work. It is feasible that had we examined theta power across the entire scalp (versus only at Fz), group differences may have emerged.

Though our primary interest was to assess theta activity in specific ACC ROIs, we measured midfrontal theta power to confirm reports of strong correlations between scalp and ACC-localized theta (Pizzagalli et al., 2003). $Theta_{Total}$ power was highly correlated with $theta_{Total}$ activity in BA 25, 24ab and 32, though the correlation was greatest in BA 25/sgACC. These results are consistent with work indicating that midfrontal theta power/amplitude reflects ACC-generated theta, as indexed by PET-assessed glucose metabolism (Pizzagalli et al., 2003). Nevertheless, correlations were not 100% (59-83%) indicating that other cortical regions likely contributed to scalp EEG theta power. Additionally, the spatial resolution limitations of sLORETA should be kept in mind, especially given that the 28-electrode montage used in this study is sub-optimal for source-localization of scalp rhythms with sLORETA.

Greater BA 25 theta activity was observed in the MDD group. Though this runs counter to some findings, documenting decreased ACC theta activity in MDD (Mientus

et al., 2002; Coutin-Churchman & Moren, 2008), these discrepancies may be accounted for by several aspects. Firstly, increased activity was primarily driven by high theta power, somewhat consistent with previous work indicating that antidepressant-associated modulations emerged only in specific theta bands (Pizzagalli et al., 2001; Narushima et al., 2010), thus, alterations in specific theta bands in MDD seem feasible. Secondly, theta activity increases in MDD emerged only in the sgACC, though the spatial limitations of sLORETA should again be considered. MDD tends to be accompanied by glial loss in the sgACC and (perhaps compensatory) increased metabolic activity, which may be reflected by increased theta activity. The sgACC and midline brain structures have been implicated in regulating emotional behavior and the stress response, which tend to be disturbed in MDD (Northoff et al., 2011). However, given that we noted no correlations between clinical symptoms and sgACC theta activity, increased theta may not be directly related to the clinical features of depression.

2.4.1 Limitations and Conclusion

Certain study limitations must be pointed out. Firstly, although different reference montages were compared, a current source density (CSD) approach was not, though recent work has highlighted its purported superiority given that it is a "reference-independent measure of the strength of extracellular current generators" underlying the EEG (Tenke & Kayser, 2005). Additionally, we did not assess whole scalp alpha or theta power, which may have further differentiated depressed individuals and/or revealed sex-specific differences. Posterior alpha, in particular, has been reported to be increased in MDD (Roemer et al., 1992; Ricardo-Garcell et al., 2009). Source localization of alpha bands in MDD should also be carried out in future investigations, as relatively scant literature exists regarding the asymmetric anterior generators of alpha power (Lubar et al., 2003). However, future work should consider using a montage with more electrodes, as sLORETA use with relatively few electrodes (i.e., 28 in this study) tends to bias source-localization. Finally, assessment of electrocortical activity during an emotional challenge may have resulted in more pronounced effects (Stewart et al., 2011). However, the utility of resting state assessments is particularly advantageous from a

clinical/diagnostic perspective.

In confirmation and extension of previous EEG literature, the MDD group was characterized by a general reduction in frontal cortical activity. Midfrontal $alpha_2$ power asymmetry indices indicated increased relative left frontal hypoactivity in the disorder, consistent with precedent work. Additionally, the MDD group was characterized by increased theta activity in the sgACC, a region implicated in affective regulation and stress response control, and which has been associated with morphological and functional alterations in the MDD. Only subtle sex effects of the probed electrophysiological measures emerged.

3. CHAPTER 3: RESPONSE PREDICTION TO SINGLE OR DUAL ANTIDEPRESSANT THERAPIES USING ALPHA POWER AND ASYMMETRY AS WELL AS THETA ACTIVITY IN THE ANTERIOR CINGULATE CORTEX (STUDY 2)

3.1 Introduction

In light of relatively high failure rates to initial antidepressant interventions, a need exists for biomarkers that could assist in predicating and optimizing treatment regimens. Regional EEG alpha power/amplitude and asymmetry are promising electrophysiological candidates. Bruder et al., (2008) found that responders (versus non-responders and controls) to chronic SSRI administration exhibited greater pretreatment occipital alpha power. This group also found that depressed non-responders to one of three antidepressant regimens [SSRI; SSRI + BUP; selective NA and 5-HT re-uptake inhibitors (SNRIs)] had less alpha power than responders or controls, especially at posterior sites; the authors found no predictive specificity to response with a particular treatment (Tenke et al., 2011). Though not statistically significant, another group noted that baseline alpha power was smaller in SSRI non-responders versus responders (Wiśniewski et al., 2002). Greater baseline occipital alpha has also been found in responders versus non-responders to non-SSRI antidepressants, such as chronic treatment with TCAs and MAOIs (Ulrich et al., 1984; 1988; Knott et al., 1996).

Though scant, some evidence indicates that specific alpha asymmetry profiles may distinguish antidepressant responders/non-responders. Depressed female non-responders to chronic SSRI treatment exhibited greater overall right versus left hemisphere activation (Bruder et al., 2001). A subsequent study indicated that SSRI responders had greater alpha power (i.e., decreased activity) over right versus left occipital regions, whereas non-responders tended to show the opposite asymmetry (Bruder et al., 2008); chronic treatment did not alter alpha power or asymmetry. The predictive utility of frontal alpha asymmetry in treatment outcome has not, to our knowledge, been directly assessed. However, one group noted that larger shifts toward relative right frontal activity with ATD were associated with decreased MDD development probability. Though these results were unexpected, it is possible that ATD

unmasked relative EEG asymmetry inflexibility in depression-susceptible individuals (Allen et al., 2009). On the other hand, antidepressants from various classes have been associated with greater relative right frontal $alpha_1$ power (i.e., decreased activity; Segrave et al., 2011). Similarly, cognitive therapy in individuals with a suicidal depression history was associated with more symmetric anterior EEG profiles compared with left frontal hypoactivity found in those not undergoing therapy (Barnhofer et al., 2007). Given that frontal asymmetry profiles may index MDD propensity and be altered with therapies (though others have demonstrated relative frontal asymmetry stability with antidepressants, e.g. Allen et al., 2004), they could be useful in predicting response.

As briefly discussed in Section 1.8.2, the utility of ACC-localized theta in predicting antidepressant response has also received attention. Evidence indicates that elevated pretreatment rACC and sgACC theta tends to index favorable treatment response (Pizzagalli et al., 2001, 2005; Mulert et al., 2007; Narushima et al., 2010; Korb et al., 2011). Similarly, Spronk et al., (2011) found that high baseline midfrontal EEG theta power predicted greater antidepressant outcome. On the other hand, a minority of studies have documented that responders exhibit lower pretreatment EEG theta power/amplitude (Knott et al., 1996; 2000) and that chronic antidepressant treatment increases it (Knott et al., 1996; Landolt & Gillin, 2002). Elevated resting ACC theta predicting favorable treatment outcome (and/or emerging with treatment) may reflect brain states permissive to adaptive modulations in regions implicated in cognitive control (Pizzagalli, 2011).

This study examined the utility of baseline frontal and parietal alpha power and asymmetry in characterizing and predicting response to chronic (12 weeks) treatment with one of three antidepressant regimens in depressed males and females: the SSRI ESC, the non-SSRI BUP, or their combination (ESC+BUP). Resting alpha asymmetry and power was assessed with three reference montages, as reference choice appears to influence asymmetry (Stewart et al., 2010). Given evidence of functional differences in alpha sub-bands (Goncharova & Davidson, 1995) and that variability characterizes $alpha_{Total}$ (Segrave et al., 2011), $alpha_1$ and $alpha_2$ power were also assessed. We also probed if early (at week 1) changes in alpha power/asymmetry would be associated with eventual response and be altered by antidepressants. Baseline sLORETA-indexed ACC

theta activity, and early theta activity changes, were also measured to probe if they predicted treatment outcome and were associated with clinical ratings; similar analyses were carried out on midfrontal theta power. We predicted that responders would have greater posterior alpha power, greater relative left frontal cortical activation, greater midfrontal theta power as well as ACC theta activity at baseline. Responders would also be characterized by larger early decreases in these measures. Given some clinical evidence for the superiority of combination therapies (Segrave & Nathan, 2005; Leuchter et al., 2008, but see Friedman et al., 2011; Rush et al., 2011), as well as pre-clinical evidence of synergistic mechanisms of action with BUP+ESC on 5-HT neuron firing (Ghanbari et al., 2010), we predicted more pronounced changes on the above measures (regardless of response) with combination versus monotherapy.

3.2 Methods

3.2.1 Patients

Please refer to Section 2.2.1, as the same patients were assessed. Non-depressed control individuals were not assessed.

3.2.2 Antidepressant Treatment Regimen

MDD patients were recruited from a clinical trial, wherein they were randomized to one of three antidepressant regimens (double-blind, randomized design): ESC + placebo, BUP + placebo or ESC+BUP. Previously medicated patients discontinued all other antidepressants prior to starting study medication; washout was 5× t½ of previously taken medication(s). Post-randomization, patients were assessed weekly for the first four weeks, then bi-weekly. Dosing followed the schedule outlined in Table 3.1 and was raised only if tolerated and remission not reached; final (week 12) average doses are presented in Table 3.1. Primary clinical measures of interest were: 1. Depression severity as assessed by the $HAMD_{17/29}$ and MADRS at baseline, weeks 1 and 12 post-treatment, and clinical rating changes between these times. 2. Treatment response (responder/non-

responder), a positive response (i.e., treatment responder) was defined as ≥ 50% decrease in baseline MADRS scores by week 12 (or last session carried forward; ratings were not carried forward if dropout occurred < 6 weeks). 3. Remission (remitter/non-remitter), a remitter was defined as persistent (over at least 2 consecutive visits) $HAMD_{17}$ scores ≤ 7.

Table 3.1 Antidepressant regimen dosing (mg) schedule

	ESC+BUP Dual Treatment		ESC or BUP Single Treatment	
Study Day	**ESC**	**BUP**	**ESC**	**BUP**
1-7	10	150	10	150
8-14	20	300	20	300
15-21	30	300	30	300
22-84 (week 12)	40	450	40	450
Week 12	**ESC**	**BUP**	**ESC**	**BUP**
Average dose (mean ± S.D.)	32.4	379.4	35	412.5

ESC: escitalopram; BUP: bupropion

3.2.3 Testing Procedures

Testing procedures were identical to those presented in Section 2.2.2, with the exception that patients in the current study were tested at baseline, 1 and 12 weeks after treatment initiation; clinical and subjective mood ratings as well as electrophysiological measures were obtained at each session.

3.2.4 Electrophysiological Recordings

Electrophysiological recordings were carried out in an identical manner as presented in Section 2.2.3. In the current study, alpha power was assessed at $F_{3/4}$, $P_{3/4}$, $P_{7/8}$ and $O_{1/2}$. Power at $P_{3/7}$ and O_1 was averaged to form a $Posterior_{Left}$ cluster; $P_{4/8}$ and O_2 sites comprised the $Posterior_{Right}$ cluster. $Theta_{Total}$ power analysis was confined to Fz (EC, mastoid reference, as in Spronk et al., 2011). Asymmetry was calculated for each alpha band by subtracting power at left from homologous right electrodes (F_4-F_3; $Posterior_{Right}$-$Posterior_{Left}$). Due to faulty channels, insufficient epochs and/or dropout, EEG data was available for N=52 at baseline, N=48 at week 1 and N=46 at week 12.

3.2.5 Source Localization

The source localization procedure was identical to that presented in Section 2.2.4. Please refer to Supplementary Table 1 in Appendix H and Figure 2.1 (Section 2.2.4) for information regarding the voxels used in constructing the three ROIs (rACC, sgACC, pgACC) and the sLORETA ROIs, respectively. Several participants were excluded from the sLORETA analyses, resulting in N=53 at baseline, N=48 at week 1, and N=44 at week 12.

3.2.6 Statistical Analysis of Clinical Response and Subjective Mood

Chi-square tests assessed the proportion of responders/non-responders per treatment (ESC+BUP, BUP, ESC). Clinical rating changes [$HAMD_{17/29}$ and MADRS response rates from baseline to weeks 1 and 12 ((week 1 – baseline)*100/basline; (week 12 – baseline)*100/baseline)), reflecting early and late changes, respectively] were assessed between treatments with independent samples t-tests.

$HAMD_{17/29}$, MADRS scores and POMS dimensions were evaluated using rmANOVAs with time (baseline, week 1, week 12) as within- and response status (responder, non-responder), treatment and sex as between-subject factors. Early and late changes in $HAMD_{17/29}$ and MADRS ratings were assessed with univariate ANOVAs with response, treatment and sex as fixed factors.

3.2.7 Statistical Analyses of $Theta_{Total}$ Power

Similarly to Spronk et al., (2011), baseline EC $theta_{Total}$ (Fz) was divided (median split) into high/low power. Chi-square tests were carried out (treatments collapsed/not collapsed) to assess if baseline $theta_{Total}$ (high/low) differed in treatment responders/non-responders. rmANOVAs probed if $theta_{Total}$ power changed with treatment [time as within-, response and treatment as between-subject factors; sex as covariate (COV)]. Univariate ANOVAs assessed if early $theta_{Total}$ power changes [((week 1 – baseline)/baseline)*100] were associated with response and altered by treatment

(response, treatment as fixed factors; sex as COV). Pearson's correlations probed if baseline and early changes in $theta_{Total}$ power correlated with late clinical response rates (MADRS, $HAMD_{17/29}$). Significant correlations ($p<.05$) were followed up with linear regressions to examine if baseline and early $theta_{Total}$ changes predicted late clinical response.

3.2.8 Statistical Analyses of sLORETA Theta ACC Activity

Chi-square tests were carried out on baseline sLORETA EC theta activity ($theta_{1/2/Total}$ in BA 24ab/25/32) divided into high/low activity (median split) to probe if the proportion of responders/non-responders differed on baseline theta (treatments collapsed/not collapsed). One-way ANOVAs assessed if high/low baseline theta activity was associated with early and late clinical response changes (treatments collapsed/not collapsed). Univariate ANOVAs assessed if early theta activity changes [((week 1 – baseline)/baseline)*100] were associated with response and altered by treatment (response, treatment as fixed factors; sex as COV). rmANOVAs examined if theta activity changed with treatment (time as within-, response and treatment as between-subject factors; sex as COV). Pearson's correlations were carried out between baseline theta activity as well as early theta activity changes and late clinical response rates. Correlations were followed up with linear regressions to probe the predictive utility of baseline and early theta activity changes on late clinical response rates. Analyses were conducted in each theta band and ROI.

3.2.9 Statistical Analyses of Alpha Power

Alpha power analyses were restricted to the EC condition, when it is greatest. Unless stated, analyses were carried out on power averaged over hemispheres, in all alpha bands, and the three reference montages. Chi-square tests (treatments collapsed/not collapsed) were carried out to assess if high/low (median split) frontal and posterior baseline alpha power was associated with response. One-way ANOVAs examined if baseline frontal or posterior alpha power, baseline or posterior frontal asymmetry, as well

as early changes (by week 1) in frontal or posterior alpha power and asymmetry were associated with response outcome (treatments collapsed/not collapsed). One-way ANOVAs were also carried out to assess if high/low baseline frontal and posterior alpha were associated with early and late clinical rating changes (treatments collapsed/not collapsed). Univariate ANOVAs probed if early changes in frontal and posterior alpha power were associated with response or influenced by treatment (treatment, response as fixed factors; sex, handedness as COVs). rmANOVAs on posterior alpha power, where it is maximal, were carried out with time as within- and response and treatment as between-subject factors (sex, handedness as COVs). Pearson's correlations were carried out between baseline frontal and parietal power as well as early changes in power and late clinical response rates. Linear regressions probed the predictive utility of baseline and early alpha power changes on late clinical response measures, if correlations ($p<.05$) between the factors existed.

Finally, exploratory correlations were carried out on EC $alpha_{Total}$ asymmetry (parietal and frontal, in each reference) between baseline, weeks 1 and 12, to probe asymmetry stability. Stability was further assessed with single-measure intra-class correlations (ICC) using a one-way random effects model (Allen et al., 2004).

For all analyses, main effects and interactions were Greenhouse-Geisser corrected ($p<.05$) and Tukey-adjusted (built into SPSS), when appropriate. Correlations were carried out with treatments and sexes collapsed; significance was $p<.01$ to account for multiple comparisons. Linear regressions were conducted on correlations of $p<.05$. Significant three-way (or greater) interactions are not reported or followed-up due to limited power. Unless stated otherwise, means ± S.D. are presented. Changes in measures between baseline and weeks 1 (early) and 12 (late) are expressed as percentages.

3.3 Results

3.3.1 Patients

Two patients dropped out before week 6 and could not be classified as responders/non-responders (N=51). Five dropped out before remission status could be established (N=47; Table 3.2). For patient characteristics please refer to Table 2.1.

Table 3.2 Number of patients per treatment group and the number of responders and remitters following chronic antidepressant treatment

	ESC+BUP	BUP	ESC
Baseline: N = Total (F/M)	17 (9/8)	17 (7/10)	19 (12/7)
Week 1: N = Total (F/M)	17 (9/8)	17 (7/10)	19 (12/7)
Week 12: N = Total (F/M)	17 (9/8)	16 (7/9)	18 (12/6)
N = Total (Responders/ Non-Responders)	17 (12/5)	16 (7/9)	18 (7/11)
N = Total (Remitters/ Non-Remitters)	17 (12/5)	14 (5/9)	17 (7/10)

F=Female; M=Male; ESC=escitalopram; BUP=bupropion

3.3.2 Treatment Response and Clinical Ratings

No difference in the proportion of responders/non-responders per treatment existed. T-tests indicated no treatment differences in late clinical response rates. A difference between ESC+BUP versus BUP existed for $HAMD_{17}$ [$t(32)=2.26$, $p=.031$; ESC+BUP: -25.6 ± 33.8; BUP: -2.1 ± 26.6] and $HAMD_{29}$ [$t(32)=2.67$, $p=.011$; ESC+BUP: -31.2 ± 27.9; BUP: -9.5 ± 17.7] response rates between baseline and week 1 (early response). A difference in $HAMD_{29}$ early response rates was noted between ESC+BUP versus ESC [-13.6 ± 21.2; $t(34)=2.15$, $p=.031$], with greater decreases for ESC+BUP.

rmANOVAs revealed a main effect of time for MADRS [$F(2,78)=94.34$, $p<.001$], $HAMD_{17}$ [$F(2,78)=53.09$, $p<.001$] and $HAMD_{29}$ [$F(2,78)=81.46$, $p<.001$] scores, with differences between all times (min $p<.01$); highest scores existed at baseline and lowest at week 12. A main effect of response was noted for all measures [MADRS: $F(1,39)=65.26$, $p<.001$; $HAMD_{17}$: $F(1,39)=35.71$, $p<.001$; $HAMD_{29}$: $F(1,39)=53.41$, $p<.001$], with lower

ratings for responders. A time×response interaction existed [MADRS: F(2,78)=50.44, p<.001; $HAMD_{17}$: F(2,78)=27.63, p<.001; $HAMD_{29}$: F(2,78)=33.58, p<.001]; responder/non-responder differences emerged at weeks 1 and 12 (min p<.001; limited to responder/non-responder comparisons; Table 3.3). For $HAMD_{17}$, a main effect of sex existed [F(1,39)=5.16, p=.029], with higher scores in females (18.3 ± 5.0; males: 15.7 ± 5.1). A sex×response interaction emerged for $HAMD_{29}$ [F(1,39)=4.64, p=.038], with higher scores in female (22.2 ± 8.5) versus male responders (17.1 ± 8.8).

Univariate ANOVAs indicated a main effect of response on early $HAMD_{17}$ score changes [F(1,39)=4.79, p=.035], with greater decreases in responders. A main effect of response status was noted on late $HAMD_{17}$ [F(1,37)=102.02, p<.001], $HAMD_{29}$ [F(1,37)= 96.90, p<.001] and MADRS [F(1,37)= 133.95, p<.001] response rates, with greater decreases in responders.

Table 3.3 Clinical ratings in individuals with MDD at baseline, weeks 1 and 12 post-treatment, collapsed across treatments (mean ± S.D.)

Clinical Measures	Baseline	Week 1	Week 12
	Overall (N=52)	**Overall (N=52)**	**Overall (N=49)**
$HAMD_{17}$	20.9 ± 5.2	18.0 ± 7.2	10.6 ± 8.3
$HAMD_{29}$	31.1 ± 6.2	25.6 ± 8.9	16.0 ± 11.5
MADRS	30.9 ± 5.4	26.6 ± 8.7	15.5 ± 12.6
	Responder (N=26)	**Responder (N=26)**	**Responder (N=26)**
$HAMD_{17}$	19.6 ± 5.9	14.7 ± 5.6	4.4 ± 3.2
$HAMD_{29}$	29.4 ± 7.3	21.7 ± 8.0	7.0 ± 5.6
MADRS	29.4 ± 4.5	22.9 ± 8.0	5.9 ± 4.9
	Non-Responder (N=24)	**Non-Responder (N=24)**	**Non-Responder (N=23)**
$HAMD_{17}$	21.6 ± 3.5	21.2 ± 7.2	17.7 ± 6.5
$HAMD_{29}$	32.63 ± 4.3	29.5 ± 8.3	26.0 ± 7.2
MADRS	31.9 ± 5.8	30.2 ± 7.8	26.5 ± 9.1

$HAMD_{17/29}$: Hamilton Rating Scale for Depression, 29 & 17 item versions
MADRS: Montgomery-Åsberg Depression Rating Scale

3.3.3 Subjective Mood Measures

rmANOVAs indicated a main effect of time for all POMS dimensions [tension: F(2,68)=17.31, p<.001; depression: F(2,68)=29.66, p<.001; anger: F(2,68)=8.782,

p<.001; vigor: F(2,68)=13.33, p<.001; fatigue: F(2,68)=12.87, p<.001, confusion: F(2,68)=15.97, p<.001, total mood disturbance (TMD): F(2,68)=25.67, p<.001]. A difference between all time points existed for tension, fatigue, depression and TMD scores (min p<.05). For anger and vigour scores, a difference emerged between baseline and weeks 1 and 12 (min p<.001); for confusion scores, a difference existed between baseline and week 12 (min p<.001; Table 3.4). A main effect of response was noted for all POMS dimensions but anger [tension: F(1,34)=12.99, p=.001; depression: F(1,34)=10.41, p=.003; vigor: F(1,34)=18.33, p<.001; fatigue: F(1,34)=10.00, p=.008, confusion: F(1,34)=13.95, p=.001, TMD: F(1,34)=17.29, p<.001], with responders having lower scores, with the exception of higher vigor. A time×response interaction existed for all dimensions, but anger [tension: F(2,92)=3.51, p=.039; depression: F(2,92)=5.60, p=.006; vigor: F(2,92)=8.96, p=.001; fatigue: F(2,92)=3.91, p=.026, confusion: F(2,92)=3.70, p=.045, TMD: F(2,68)=5.981, p=.005]. Follow-up comparisons (of responders/non-responders only) indicated TMD score differences between responders/non-responders at all times (p<.05). For tension, depression, vigour, fatigue and confusion, a difference existed between responders/non-responders at week 12 (min p<.001). A difference also emerged between the two for baseline tension (p=.004) and confusion scores at week 1 (p=.013).

Table 3.4 Profile of Mood States (POMS) in individuals with MDD at baseline, weeks 1 and 12 post-treatment, collapsed across treatments (mean ± S.D.)

POMS Dimensions	Baseline N=52	Week 1 N=49	Week 12 N=46
Depression-Dejection	35.4 ± 12.6	28.5 ± 12.1	19.0 ± 15.5
Vigor-Activity	5.1 ± 4.2	5.9 ± 4.9	10.7 ± 8.0
Confusion-Bewilderment	16.4 ± 5.8	14.9 ± 5.1	11.4 ± 6.4
Fatigue-Inertia	20.2 ± 5.6	17.4 ±6.1	14.2 ± 7.6
Anger-Hostility	17.4 ± 9.6	13.4 ± 10.1	9.4 ± 8.6
Tension-Anxiety	18.5 ± 7.5	15.0 ± 6.8	11.8 ± 8.5
Total Mood Disturbance	103.6 ± 33.5	84.4 ± 35.1	55.8 ± 46.8

3.3.4 $Theta_{Total}$ Power Results

No effects emerged for any of the analyses on Fz $theta_{Total}$ power.

3.3.5 sLORETA Theta ACC Activity Results

3.3.5.1 Non-Treatment Specific sLORETA Theta ACC Activity Results

No differences in the proportion of responders/non-responders based on high/low baseline theta activity were noted when treatment groups were collapsed.

One-way ANOVAs indicated a main effect of high/low baseline BA 25 $theta_1$ activity [$F(1,51)=4.93$, $p=.031$] on early $HAMD_{17}$ response rates. Greater early decreases existed in those with high baseline BA 25 $theta_1$ than those with low activity (Figure 3.1).

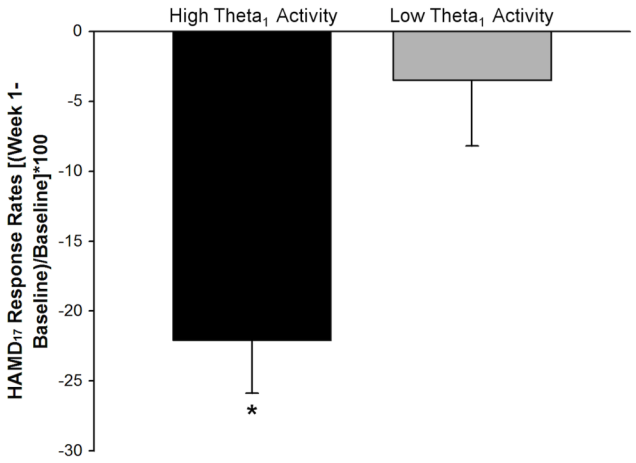


Figure 3.1. Early decreases in $HAMD_{17}$ response rates in patients with high and low baseline $theta_1$ activity in the sgACC (BA 25; $p<.05$)

rmANOVAs revealed a main effect of time on BA 24ab $theta_2$ activity [$F(2,72)=3.96$, $p=.029$], with lower values at week 1 (5.1 ± .08) versus baseline (5.3 ± .09; $p=.004$). A main effect of time also existed for BA 25 $theta_{Total}$ [$F(2,72)=4.26$, $p=.022$], with lower activity at week 1 (5.9 ± .08) versus baseline (6.0 ± .1 $p=.048$).

No correlations existed between baseline or early changes in theta activity and late clinical responses.

3.3.5.2 Treatment Specific sLORETA Theta ACC Activity Results

More BUP non-responders had low baseline BA 24ab activity in all theta bands ($theta_1$: 87.5%, N=7; $theta_{2/Total}$: 88.9%, N=8; i.e., specificity) versus responders ($theta_1$:

12.5%, N=1; $theta_{2/Total}$: 11.1%, N=1). Conversely, more BUP responders ($theta_1$: 75%, N=6; $theta_{2/Total}$: 85.7%, N=6; i.e., sensitivity) had high baseline BA 24ab theta activity than non-responders [$theta_1$: 25%, N=2; $\chi^2(1,16)=6.35$, p=.041; $theta_{2/Total}$: 14.3%, N=1; $\chi^2(1,16)=8.91$, p=.009]. More BUP non-responders also had low baseline BA 32 $theta_{Total}$ activity (87.5%, N=7; i.e., specificity) than responders (12.5%, N=1), while more BUP responders (75%, N=6; i.e., sensitivity) had high BA 32 $theta_{Total}$ activity than non-responders (25%, N=2: $\chi^2(1,16)=6.35$, p=.041].

Univariate ANOVAs indicated a response×treatment interaction in early changes in $theta_2$ activity in all three ROIs [BA 24ab: $F(2,40)=5.26$, p=.009; BA 25: $F(2,40)=4.85$, p=.013; BA 32 $F(2,40)=5.32$, p=.009]. A difference existed between ESC+BUP responders and non-responders (BA 24ab: p=.029; BA 25: p=.05; BA 32: p=.03), with greater early decreases in $theta_2$ activity in non-responders (BA 24ab: -9.1 ± 2.6; BA 25: -8.7 ± 3.0; BA 32: -9.0 ± 2.8) versus responders (BA 24ab: -2.0 ± 1.7; BA 25: -1.6 ± 2.0; BA 32: -1.5 ± 1.8). A difference in early changes in $theta_2$ activity between BUP responders and non-responders in all ROIs was noted (BA 24ab: p=.027; BA 25: p=.022; BA 32: p=.024), with greater decrease in responders (BA 24ab: -6.8 ± 2.2; BA 25: -6.6 ± 2.5; BA 32: -7.7 ± 2.3) versus non-responders (BA 24ab: .3 ± 2.2; BA 25: 1.8 ± 2.5; BA 32: -.05 ± 2.3). Further comparisons indicated a difference between ESC+BUP versus both BUP (BA 24ab: p=.008; BA 25: p=.009; BA 32: p=.017) and ESC (BA 24ab: p=.005; BA 25: p=.005; BA 32: p=.014) non-responders, with greater early decreases in $theta_2$ activity for ESC+BUP versus BUP and ESC non-responders (BA 24ab: .4 ± 1.8; BA 25: 2.1 ± 2.1; BA 32: -.3 ± 1.9). A difference in early changes in $theta_2$ activity in BA 25 and BA 32 also existed between BUP and ESC responders (BA 25: p=.039; BA 32: p=.042), with greater decreases in BUP (BA 25: -6.6 ± 2.5; BA 32: -7.7 ± 2.3) versus ESC responders (BA 25: 1.0 ± 2.5; BA 32: 1.3 ± 2.3).

For early $theta_{Total}$ activity changes in all ROIs, a responder×treatment interaction existed [BA 24ab: $F(2,40)=4.47$, p=.018; BA 25: $F(2,40)=4.43$, p=.018; BA 32: $F(2,40)=3.962$, p=.027]. Greater early $theta_{Total}$ activity decreases (BA 24ab: p=.035; BA 25: p=.033; BA 32: p=.039) existed in BUP responders (BA 24ab: -5.0 ± 1.9; BA 25: -4.2 ± 1.9; BA 32: -6.1 ± 2.2) versus non-responders (BA 24ab: .8 ± 1.9; BA 25: 1.6 ± 1.9;

BA 32: .6 ± 2.2). A difference in early changes in $theta_{Total}$ (all ROIs) existed between ESC+BUP versus BUP (BA 24ab: p=.014; BA 25: p=.007; BA 32: p=.033) and ESC non-responders (BA 24ab: p=.017; BA 25: p=.007; BA 32: p=.036), with greater decreases in ESC+BUP (BA 24ab: -6.6 ± 2.2; BA 25: -6.6 ± 2.2; BA 32: -6.9 ± 2.6) than BUP (BA 24ab: .8 ± 1.9; BA 25: 1.6 ± 1.9; BA 32: .6 ± 2.2) and ESC non-responders (BA 24ab: .2 ± 1.6; BA 25: 1.2 ± 1.6; BA 32: .2 ± 1.9).

Univariate ANOVAs indicated a main effect of treatment [$F(2,40)=3.87$, p=.029] on early changes in BA 25 $theta_2$ activity, with a decrease in $theta_2$ with ESC+BUP (-5.2 ± 1.8) versus a slight increase with ESC (1.5 ± 1.6; p=.009).

3.3.6 EEG Alpha Power Results

3.3.6.1 Non-Treatment Specific EEG Alpha Power Results

A greater proportion of treatment non-responders exhibited low baseline frontal $alpha_2$ power (N=17; 68%; i.e., specificity) versus responders (N=8; 32%), while more responders had high baseline frontal $alpha_2$ power (N=18; 69.2%; i.e., sensitivity) than non-responders [N=8; 30.8%; $\chi^2(1,51)=7.07$, p=.012, mastoid and average references].

A difference in early changes in frontal $alpha_2$ power (mastoid reference) existed between responders/non-responders [$F(1,44)=4.87$, p=.033], with smaller decreases in non-responders (-.2 ± 5.7) than responders (-15.3 ± 3.4). Similar results were noted for early changes in posterior $alpha_2$ power [mastoid: $F(1,44)=4.96$, p=.031; Cz: $F(1,44)=6.69$, p=.013], with increases in non-responders (mastoid: 7.7 ± 9.2; Cz: 5.7 ± 8.4) and decreases in responders (mastoid: -12.8 ± 3.4; Cz: -17.6 ± 4.2). Differences between responders/non-responders also existed in early changes in $alpha_2$ power frontal asymmetry (Cz reference) [$F(1,44)=6.36$, p=.015], with increased asymmetry in non-responders (214.0 ± 102.4) and a decrease in responders (-104.0 ± 77.4).

A main effect of high/low baseline frontal $alpha_1$ power (average reference) on early changes in $HAMD_{17}$ ratings [$F(1,51)=6.03$ p=.018] was found, with greater decreases in those with high (-23.0 ± 5.6) versus low (-2.6 ± 6.2) power. Similar results were observed for baseline posterior $alpha_1$ power (average reference) [$F(1,51)=4.75$,

p=.034], with greater decreases in those with high (-22.0 ± 5.5) versus low (-3.7 ± 6.4) power. One-way ANOVAs also revealed a main effect of high/low baseline posterior alpha$_2$ power (average reference) on late MADRS respose rates [F(1,49)=5.77 p=.02], with greater decreases in individuals with high versus low baseline power (Figure 3.2A). Similar results were noted for frontal alpha$_2$ power (mastoid reference) [F(1,49)=4.95, p=.031], with greater late MADRS rating decreases in those with high versus low baseline posterior alpha$_2$ power (Figure 3.2B).

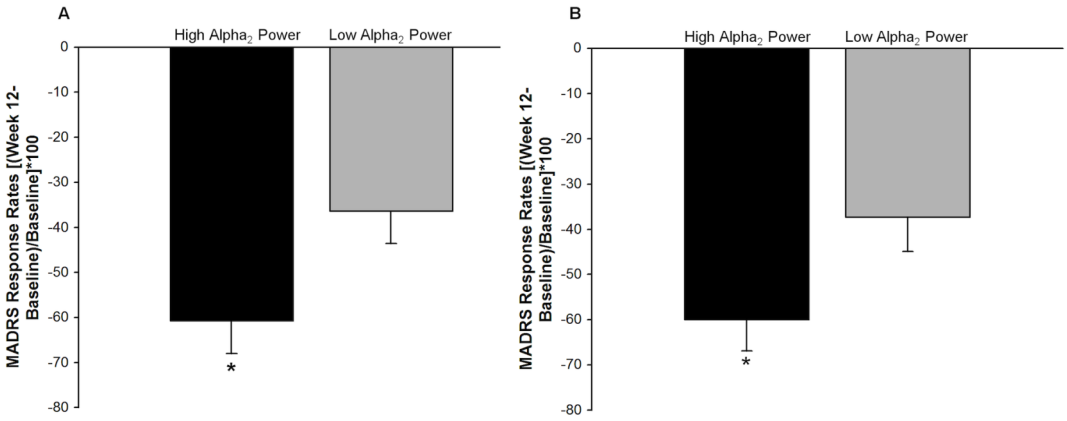


Figure 3.2A. Late decreases in MADRS response rates in patients with high and low baseline posterior alpha$_2$ power (average reference; p<.05). **Figure 3.2B.** Late decreases in MADRS response rates in patients with high and low frontal alpha$_2$ power (mastoid reference; p<.05)

rmANOVAs indicated a main effect of time for posterior alpha$_2$ power (average reference) [F(2,72)=3.25, p=.049], with greater power at baseline (2.1 ± .2) versus weeks 1 (1.8 ± .2) and 12 (1.6 ± .2; p<.001). A time×response interaction was noted [average: F(2,72)=3.63, p=.031; Cz: F(2,70)=3.93, p=.027]; greater posterior alpha$_2$ power existed at baseline (Cz: 2.6 ± .2) versus weeks 1 (Cz: 2.3 ± .2) and 12 (Cz: 2.0 ± .2; min p<.01) only in responders (Figure 3.3; average reference).

No correlations between baseline or early changes in alpha and late clinical response rates were noted. Linear regressions revealed no predictive utility of alpha on late clinical response measures.

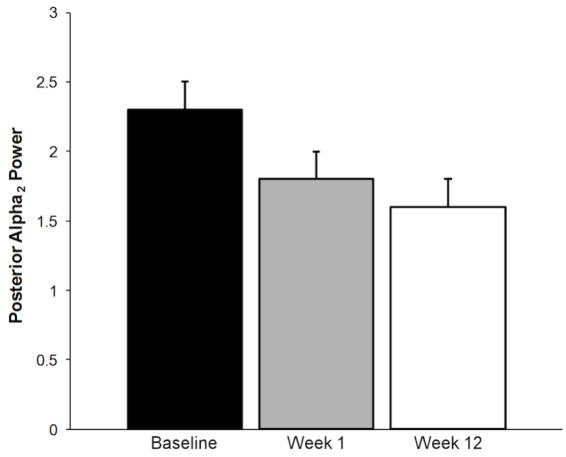


Figure 3.3. Posterior alpha$_2$ power across time in antidepressant treatment responders (average reference; differences existed between all times, min $p<.05$)

3.3.6.2 Treatment Specific EEG Alpha Power Results

A greater proportion of ESC non-responders had low frontal alpha$_2$ power in all reference montages (average: N=9; 90%; Cz: N=8; 88.9%; mastoid: N=10; 76.9%; i.e., specificity) versus ESC responders (average: N=1; 10%; Cz: N=1; 11.1%; mastoid: N=3; 23.1%). Conversely, more ESC responders exhibited high baseline frontal alpha$_2$ power (average: N=6; 75%; Cz: N=6; 66.7%; mastoid: N=4; 80%; i.e., sensitivity) than non-responders [average: N=2; 25%; Cz: N=3; 33.3%; mastoid: N=1; 20%; average: $\chi^2(1,18)=7.90$, $p=.013$; Cz: $\chi^2(1,18)=5.84$, $p=.05$; mastoid: $\chi^2(1,18)=4.92$, $p=.047$].

One-way ANOVAs revealed a difference between ESC responders/non-responders (average reference) in baseline frontal [$F(1,16)=9.11$, $p=.008$] and posterior alpha$_2$ power [$F(1,16)=15.34$, $p=.001$], with lower alpha$_2$ in non-responders (frontal: .7 ± .2; posterior: 1.5 ± .2) versus responders (frontal: 1.7 ± .3; posterior: 2.8 ± .3). Similarly, for the mastoid and Cz references, lower baseline posterior alpha$_2$ power existed in ESC non-responders (mastoid: 1.8 ± .2; Cz: 1.9 ± .2) versus responders [mastoid: 3.0 ± .3; $F(1,16)=15.37$, $p=.001$; Cz: 3.1 ± .3; $F(1,16)=14.30$, $p=.002$]. Additionally, a difference between ESC responders/non-responders (mastoid reference) was noted in early changes in frontal alpha$_2$ power [$F(1,14)=18.82$, $p=.001$], with power increases in non-responders (16.2 ± 5.9) and decreases in responders (-16.1 ± 3.6).

A main effect of high/low baseline posterior alpha$_2$ power (average reference) on late changes in MADRS ratings was found for ESC [F(1,16)=13.31, p=.002], with greater decreases (-74.7 ± 9.7; N=8) in those with high versus low (-18.0 ± 11.5) baseline posterior alpha$_2$ power.

Univariate ANOVAs indicated a main effect of treatment on early changes in frontal alpha$_1$ (average reference) [F(2,39)=4.31, p=.02] and alpha$_{Total}$ (mastoid reference) power [F(2,38)=3.78, p=.031]. Early decreases in frontal alpha$_1$ power were noted with ESC+BUP (-39.2 ± 18.1) versus an increase with ESC (30.4 ± 16.5; p=.007). For frontal alpha$_{Total}$, an early increase in power existed with ESC (4.8 ± 3.1) versus a decrease with ESC+BUP (-6.6 ± 3.4; p=.019) and BUP (-5.7 ± 3.4; p=.03). A treatment×responder interaction existed for early changes in frontal alpha$_2$ power (mastoid reference) [F(2,38)=3.29, p=.048], with a difference between ESC versus ESC+BUP (p=.003) and BUP (p=.015) non-responders; increases in frontal alpha$_2$ power existed in ESC non-responders (15.7 ± 6.8) versus decreases in ESC+BUP (-20.1 ± 9.0) and BUP (-10.4 ± 7.6) non-responders. For early changes in posterior alpha$_{Total}$ power (all references) a main effect of treatment existed [average: F(2,38)=4.80, p=.014; mastoid: F(2,38)=7.83, p=.001; Cz: F(2,38)=3.86, p=.030]. A greater early decrease in posterior alpha$_{Total}$ power existed with BUP (average: -12.6 ± 4.9; mastoid: -9.3 ± 3.5; Cz: -7.6 ± 3.5) versus an increase with ESC (average: 8.1 ± 4.6; p=.004; mastoid: 9.2 ± 3.3; p=.001; Cz: 5.4 ± 3.2; p=.01). Additionally, a difference in early changes in posterior alpha$_{Total}$ power (mastoid reference) existed between ESC+BUP (-4.1 ± 3.5) and ESC (9.2 ± 3.3; p=.01).

3.3.7 EEG Alpha Asymmetry Stability

Baseline EC frontal alpha$_{Total}$ asymmetry (average reference) correlated with asymmetry at week 1 (r=.39, p<.005, N=49) only; the single-measures ICC was .18. Baseline EC frontal alpha$_{Total}$ asymmetry (Cz reference) also correlated with asymmetry at week 1 (r=.40, p=.006, N=47) only; ICC=.019. Finally, baseline EC frontal alpha$_{Total}$ asymmetry (mastoid reference) correlated with asymmetry at weeks 1 (r=.41, p=.004, N=48) and 12 (r=.31, p=.037, N=46); ICC=.39.

Baseline EC parietal $alpha_{Total}$ asymmetry (average reference) correlated with asymmetry at weeks 1 (r=.50, p<.001, N=49) and 12 (r=.33, p=.024, N=46); the single-measures ICC was .40. Baseline EC parietal $alpha_{Total}$ asymmetry (Cz reference) also correlated with asymmetry at weeks 1 (r=.66, p<.001, N=47) and 12 (r=.57, p<.001, N=46); ICC=.64. Finally, baseline EC parietal $alpha_{Total}$ asymmetry (mastoid reference) correlated with asymmetry at weeks 1 (r=.67, p<.001, N=48) and 12 (r=.59, p<.001, N=46); ICC =.61.

3.4 Discussion

This study examined the utility of Fz theta power, ACC theta activity as well as alpha power and asymmetry in predicting response to chronic treatment with one of three antidepressant regimens, ESC, BUP or ESC+BUP, in depressed males and females. No treatment response differences emerged at week 12, though certain clinical ratings decreased more with ESC+BUP by week 1. Clinical ratings decreased with treatment, and treatment responders had lower ratings by week 1, which persisted into week 12. Mood disturbances stabilized within a week and this was more pronounced in treatment responders. No predictive utility for treatment response existed with theta power. Regarding ACC theta activity, more BUP responders had high baseline theta while more non-responders had low theta. Theta activity decreased in specific ACC regions and theta bands within a week of treatment and greater early decreases in $theta_{2/Total}$ activity existed in BUP responders versus non-responders. Conversely, greater early decreases in ACC $theta_2$ activity existed in ESC+BUP non-responders versus responders. This may be due to the number of responders/non-responders in the dual treatment group or may reflect different early electrocortical alterations to various treatments. Regarding alpha, more responders had high baseline $alpha_2$ power (sensitivity: 69.2%), while more non-responders had low power (specificity: 68%). Greater early power decreases were associated with a favorable treatment response. Responders exhibited frontal $alpha_1$ asymmetry profiles reflecting increased left frontal activity and early shifts towards this profile; non-responders exhibited opposite early asymmetry shifts. ESC responders versus non-responders had high baseline frontal and parietal $alpha_2$ power and early

decreases in frontal alpha$_2$. Finally, weak frontal and moderate posterior alpha asymmetry stability existed throughout the course of antidepressant treatment. The implications of these results are discussed below.

As no antidepressant treatment differences emerged in late clinical response rates (by week 12), the regimens had comparable long-term efficacy. Early HAMD$_{29}$ response rates (by week 1) were greater with ESC+BUP versus monotherapies, suggesting that dual treatment hastened initial response. Although some evidence indicates that combination treatments expedite response (Nelson et al., 2004; Segrave & Nathan, 2005) a recent clinical trial has not indicated superior BUP+ESC efficacy to BUP or ESC alone, though the combination was superior in alleviating suicidal ideation (Rush et al., 2011), contrasting with some preliminary clinical work (Leuchter et al., 2008). Expectedly, clinical ratings decreased with treatment, and responders had lower clinical ratings than non-responders, which emerged with one week of treatment, consistent with previous reports (Posternak & Zimmerman, 2007; Leuchter et al., 2008). Females had higher scores on certain clinical measures, in line with reports of greater depression symptom severity in females (Smith et al., 2008).

With the exception of increased vigour, mood disturbances decreased with treatment. Most ratings changed within a week of treatment, indicating that mood can improve relatively rapidly. Apart from anger, responders differed from non-responders on all mood dimensions. Responders also demonstrated somewhat more stable mood profiles even at baseline, indexed by lower pretreatment total mood disturbance and tension scores, consistent with past research (Mandelli et al., 2006).

Few studies have probed the utility of scalp theta power/amplitude in antidepressant response prediction. Though Spronk et al., (2011) found that high baseline theta power predicted better response rates, others noted the opposite (Knott et al., 1996; 2000). Chronic antidepressant treatment has also been associated with increased frontal theta power/amplitude (Knott et al., 1996; Landolt & Gillin, 2002). It is feasible that had we examined theta power across the entire scalp, treatment differences may have emerged. However, it is also possible that midfrontal theta amplitude/power is insufficiently sensitive in distinguishing antidepressant responders/non-responders.

Inconsistent with hypotheses, baseline ACC theta activity did not differentiate responders/non-responders when treatments were collapsed. When not collapsed, more BUP non-responders exhibited low baseline BA 24ab theta activity while more responders had high activity; similar findings existed with baseline BA 32 $theta_{Total}$ activity. These results are consistent with other LORETA findings albeit with different antidepressants (Pizzagalli et al., 2001; Mulert et al., 2007; Korb et al., 2011). However, PET studies have reported more mixed results, with some groups indicating that greater baseline rACC metabolism indexes positive outcome (Mayberg et al., 1997; Saxena et al., 2003), similarly to the LORETA work, while others have reported the opposite (Brody et al., 1999; Konarski et al., 2009). The relationship has also been explored with fMRI studies using tasks that engage the ACC. For instance, increased pretreatment BOLD signals in the rACC during the Stroop task were associated with greatest clinical rating decreases with SSRI and NRI treatments (Wagner et al., 2010). High baseline ACC activity to fearful faces (MEG-assessed) was positively correlated with a rapid antidepressant response to ketamine (Salvadore et al., 2009). Thus, most evidence indicates that higher baseline ACC activity predicts favorable outcome. Given that the ACC, particularly the r/sgACC, is implicated in emotive processing and cognitive control, elevated ACC activity in MDD, as indexed by ACC-localized theta, may reflect compensatory activity in ACC networks, which may be a prerequisite for positive treatment response (Pizzagalli et al., 2011).

While it is possible that increased baseline theta activity may specifically characterize BUP response, this seems unlikely as previous work has indicated its predictive utility to outcome with antidepressants from various classes (Pizzagalli et al., 2001; Mulert et al., 2007; Korb et al., 2011). One explanation for these BUP-specific results may be related to sample size. Though not statistically significant, unequal numbers of responders/non-responders existed in the ESC+BUP group (theta data available for 11 responders/5 non-responders). However, the number of responders/non-responders in the ESC group (8 /7) was comparable to the BUP group (7/7). Thus, it is curious that results comparable to those with BUP did not emerge with ESC, as previous work with similar samples (Pizzagalli et al., 2001; Mulert et al., 2007) noted predictive utility of baseline ACC theta activity to outcome with antidepressants, including SSRIs.

Greater early decreases in $HAMD_{17}$ ratings existed in those with high versus low baseline BA 25 (sgACC) $theta_1$ activity. This indicates that early clinical rating changes are also associated with baseline theta activity. Korb et al., (2011) recently found that individuals with early (2 week) responses to SSRIs or NRIs demonstrated almost no relationship between baseline rACC theta activity and clinical response at week 8. This is inconsistent with our findings, as high baseline sgACC $theta_1$ activity was associated with greater clinical rating decreases within a week of treatment, which extended to 12 weeks, at least with BUP treatment. The association between early clinical response, baseline theta activity and treatment outcome should be further explored in future research.

rACC $theta_2$ and sgACC $theta_{Total}$ activity decreased by week 1, indicating that antidepressants can alter theta activity relatively quickly. Furthermore, greater early decreases in $theta_{2/Total}$ activity (all ROIs) existed in BUP responders versus non-responders. This may reflect rapid antidepressant-induced stabilization of compensatory activity in neural networks involved in mood and cognitive control. However, our findings are inconsistent with work indicating that chronic antidepressant treatment increased frontal theta power/amplitude (Knott et al., 1996; Landolt & Gillin, 2002), though methodological differences (scalp versus source-localized theta; long- versus short-term theta changes) may account for these discrepancies. Clinically, it may be more useful to establish guidelines regarding the extent of early theta activity changes for predicting positive treatment outcome (e.g. >10% decrease within a week of treatment) rather than using absolute cut-off values for high/low baseline theta activity.

Curiously, greater early decreases in $theta_2$ activity existed in ESC+BUP non-responders versus responders. Greater early decreases in $theta_{2/Total}$ activity for ESC+BUP versus BUP and ESC non-responders were also noted. Given the small and unbalanced ESC+BUP responder/non-responder sample (5/10), these results may be spurious. However, it is feasible that while in BUP responders early theta decreases may reflect rapid stabilization of neural networks involved in emotive processing and cognitive control, in ESC+BUP non-responders this could index compensatory response deterioration in the same networks to a pronounced pharmacological challenge. However, this explanation warrants further scrutiny. Finally, though greater early changes in BA 25/32 $theta_2$ activity existed in BUP versus ESC responders, both were associated with

similar patterns of early changes in theta activity in responders versus non-responders. These results indicate that antidepressants may alter early ACC theta activity in a specific manner, which appears to be associated with eventual response outcome.

Regarding alpha power, more treatment non-responders had low baseline frontal and posterior $alpha_2$ power, while more responders had high baseline power. Higher frontal (mastoid reference) and posterior (average reference) baseline $alpha_2$ power was also associated with greater late MADRS decreases. The relationship between baseline posterior alpha power and response prediction replicates previous work (Wiśniewski et al., 2006; Bruder et al., 2008; Tenke et al., 2011). However, our results indicate that this relationship extends beyond posterior alpha. As these findings were restricted to the $alpha_2$ band, this increases the likelihood that observed results were alpha-specific and not confounded with theta.

Greater early alpha power decreases (evident with several reference montages, in various bands and frontal and posterior regions) were associated with favorable outcome. Though chronic antidepressant administration may not alter alpha power (Bruder et al., 2008), decreased alpha in eventual responders at shorter periods (2-4 weeks) after antidepressant initiation has been found (Wiśniewski et al., 2006; Ulrich et al., 1984). In responders, early alpha power decreases may reflect increased cortical arousal, which may stabilize with continued treatment. Clinically, it may be useful to assess if early alpha power decreases emerge during initial treatment stages. If not, altering antidepressant regimens may be warranted.

To our knowledge, no studies have assessed the predictive utility of pretreatment frontal alpha asymmetry on antidepressant response. Negative baseline $alpha_1$ frontal asymmetry (greater left $alpha_1$ power; average reference) existed in non-responders and a positive one (lower left $alpha_1$ power) existed in responders, consistent with predictions that greater left frontal activity would be associated with a positive outcome. Increased left frontal activity has been linked with positive emotion processing and approach-motivation tendencies possibly conferring a therapeutic advantage. Responders also had early shifts towards greater left anterior cortical activity (lower $alpha_2$ power), while the opposite existed in non-responders (Cz reference). Thus, relatively rapid frontal asymmetry changes occur (though in a specific alpha band and reference montage) with

antidepressants, similar to what was noted with cognitive restructuring in MDD (Deldin & Chiu, 2005).

More ESC non-responders exhibited low frontal and parietal $alpha_2$ power (all references); the opposite was noted in ESC responders. These results are consistent with previous work indicating that SSRI responders had greater baseline, especially posterior, alpha power (Wiśniewski et al., 2002; Bruder et al., 2008), though research with non-SSRIs has noted similar findings (Ulrich et al., 1984; 1988; Knott et al., 1996; Tenke et al., 2011). Patients with an under-aroused cortex may be most responsive to antidepressants, which may exert arousing/stabilizing effects. It is curious that no differences emerged with BUP, which consisted of similar responders/non-responders numbers as the ESC group.

Assessment of early changes in alpha power indicated that ESC responders exhibited early decreases in frontal $alpha_2$ power while non-responders had increases (mastoid reference). ESC non-responders also exhibited greater early increases in frontal $alpha_2$ power (mastoid reference) than ESC+BUP and BUP non-responders. It is feasible that different early effects on 5-HT activity, which is implicated in cortical arousal (Lin et al., 2011), associated with ESC versus BUP and combination treatment (Section1.5) may induce somewhat different early modulations in alpha. However, given the relatively small sample sizes, it is difficult to draw strong conclusions about these findings.

Weak frontal $alpha_{Total}$ asymmetry stability existed over the long term, though reference choice influenced stability. Consistent with previous reports (Vuga et al., 2008), posterior versus frontal alpha asymmetry stability was greater. Factors such as sex, MDD history/severity and symptom changes were previously found to be unrelated to alpha asymmetry stability (Allen et al., 2004; Vuga et al., 2006). Our findings thus suggest that asymmetry stability is, at least to a certain extent, influenced by antidepressant use.

3.4.1 Limitations and Future Directions

Despite this study's novel findings and their potential clinical utility, several limitations must be acknowledged, the most notable being sample size. When treatment

groups were divided into responders/non-responders, samples were reduced and statistical analyses became problematic. Thus, interpretations of results relating to specific treatments should be treated with caution. Due to limited samples, the contribution of sex on measures of interest could not be assessed. Additionally, although alpha power/asymmetry analyses were conducted with three reference montages, we did not carry out CSD analyses, though it may be a superior approach to measuring EEG (Tenke & Kayser, 2005). We also did not assess alpha or theta power across the scalp, which may have further differentiated treatment responders/non-responders.

Future research should aim to replicate our results with larger samples. Additionally, a placebo arm should ideally be included in comparable research. Finally, although theories exist regarding the biological bases underlying theta activity and alpha power/asymmetry, further research in this domain is warranted. This is especially true given the aforementioned spatial resolution limitations associated with sLORETA.

4. CHAPTER 4: SCALP- AND sLORETA-DERIVED LOUDNESS DEPENDENCE OF AUDITORY EVOKED POTENTIALS (LDAEPS) IN DEPRESSED AND HEALTHY INDIVIDUALS (STUDY 3)

4.1 Introduction

As outlined in Section 1.8.4, ERPs are, to a certain degree, indirect manifestations of neurotransmitter activity. High 5-HT concentrations exist in primary sensory cortices, such as in layer IV of the primary auditory cortex (Berger et al., 1988), while less 5-HT innervation and activity has been found in the secondary auditory cortex (Campbell et al., 1987; Hegerl et al., 2001). As such, 5-HT neurotransmission is likely implicated in modulating sensory-level processing of auditory input within the primary auditory cortex.

The N1 and P2 AEPs appear to be generated in the primary auditory and association cortices. The LDAEP, also referred to as the intensity dependence of AEPs (IDAP), derived from N1/P2 amplitude has been proposed to index 5-HT activity (Section 1.8.4). Cortical DRN 5-HT efferents are characterized by a pacemaker discharge (Wilson & Molliver, 1991; Jacobs & Azmitia, 1992) and are thus well suited for tonic modulation of cortical activity in the primary auditory cortex (Hegerl et al., 2001). As cortical hyper-activation (with increased auditory intensity) could be damaging, enhanced 5-HT activity may inhibit excessive neuronal activity (Juckel et al., 1999). Hegerl and Juckel (1993) proposed that 5-HT DRN neurons provide tonic pre-activation to the primary auditory cortex. Low 5-HT pre-activation, indexing 5-HT system hypoactivity, would be associated with steeper LDAEPs than when 5-HT pre-activation is higher, and reflected by shallow LDAEPs (Mulert et al., 2005).

Animal work has indicated an inverse relationship between sensory cortex activity and ascending DRN 5-HT discharge (Waterhouse et al., 1990). Juckel et al., (1997; 1999) provided evidence of an inverse relationship between the LDAEP and 5-HT activity in the cat primary auditory cortex, with DRN 5-HT activity inhibition increasing the LDAEP slope, while activation decreased it. Similarly, Wutzler et al., (2008) recorded AEPs in the rat primary auditory cortex while simultaneously measuring extracellular 5-

HT levels following SSRI administration. Consistent with predictions, increased 5-HT levels decreased the intensity-dependence N1 slope (N1 LDAEP).

While pre-clinical research suggests that the LDAEP is sensitive to central 5-HT activity, evidence in humans is less consistent. With acute tryptophan depletion (ATD), several studies found no effects on the LDAEP (Debener et al., 2002; Massey et al., 2004), while one found only weak evidence for its increase (Norra et al., 2008). Yet others have noted that ATD decreased intensity-dependent N1/P2 amplitudes (Dierks et al., 1999; Kähkönen et al., 2002). Studies probing the effects of SSRIs on LDAEPs (and component AEPs) in healthy individuals have also yielded mixed results. Some groups have documented no LDAEP effects with acute SSRI administration (Uhl et al., 2006), while others have shown the predicted LDAEP slope decreases (Nathan et al., 2006; Segrave et al., 2006). Recent work has found that chronic SSRI administration in healthy individuals induced shallower LDAEPs (Simmons et al., 2011). Further evidence for a link between the 5-HT system and AEP intensity modulations comes from associations between altered LDAEP slopes and polymorphisms in terminal 5-HT_{1B} autoreceptors (Juckel et al., 2008) and 5-HT transporters (Lee et al., 2011). Nevertheless, clinical evidence for a direct link between the LDAEP (and associated AEPs) and CNS 5-HT activity is tenuous.

A handful of studies have directly compared intensity-dependent AEPs and the LDAEP in depressed individuals, who are thought to display dysfunctional 5-HT activity (Section 1.4.1). Two studies (Linka et al., 2007; Park et al., 2010) found no LDAEP alterations in MDD. Others noted that depressed individuals with a history of suicide exhibited steeper slopes than those without such a history (Chen et al., 2005). Another group found that melancholic MDD patients had a shallower LDAEP than non-melancholic patients (Fitzgerald et al., 2009). Finally, a positive correlation between the N1 LDAEP slope and specific somatic symptoms in MDD has been noted (Linka et al., 2009). Given the scarcity of research probing the LDAEP in MDD, and whether specific depression features are associated with altered LDAEP slopes, few conclusions can currently be drawn regarding the LDAEP in MDD.

As described in Section 1.8.4, individuals with a steep pretreatment LDAEP are more likely to respond favorably to drugs that directly augment 5-HT (e.g. SSRIs;

Gallinat et al., 2000; Mulert et al., 2002; Lee et al., 2005), while those with shallow LDAEP slopes tend to benefit from treatments not directly targeting 5-HT (Linka et al., 2005; Juckel et al., 2007; Mulert et al., 2007). However, other monoamine systems appear to influence the LDAEP. For instance, the LDAEP has been shown to be modulated by DA transporter (DAT) availability (Lee et al., 2011), DA levels (Beucke et al., 2010) and DA receptor stimulation in cats (Juckel et al., 1997). Additionally, depressed individuals who responded favorably to chronic BUP treatment, which also alters NA and DA system activity (Section 1.5), exhibited a steeper pretreatment P2 intensity-dependence slope (P2 LDAEP; Paige et al., 1995). However, others examining the effects of altered DA levels or activation/antagonism of DA or NA receptors have found no associated LDAEP slope changes (O'Neill et al., 2006, 2008; Oliva et al., 2010). Nevertheless, some evidence indicates that neurotransmitters other than 5-HT modulate the LDAEP, challenging its proposed exclusive 5-HT system influence.

Some of the mixed clinical findings regarding the LDAEP and 5-HT modulations may be sex-dependent. Though several groups have indicated no sex effects on the LDAEP (Linka et al., 2009; Park et al., 2010; Simmons et al., 2011), others have noted steeper slopes in females than males (Oliva et al., 2011). This is consistent with evidence that females have lower baseline 5-HT neurotransmission levels than males (Nishizawa et al., 1997; Sakai et al., 2006). Also in support of an influence of sex on the LDAEP, estrogen pretreatment in females was shown to enhance the LDAEP (Guille et al., 2011).

Single-electrode estimation (typically at Cz) and dipole source analysis (DSA) are most frequently used in generating the LDAEP. Few studies have assessed the LDAEP derived from current source density values of the constituent AEPs using sLORETA or the earlier version LORETA (Pascual-Marqui, 2002). The handful of studies that have assessed s/LORETA-derived LDAEP (s/LORETA-LDAEP) yield comparable results to scalp-derived indices (Mulert et al., 2002; Park et al., 2011).

This study examined whether differences between males and females with MDD and controls exist on the LDAEP. As two previous studies found no group differences, comparable results were expected. Given that 5-HT disturbances are associated with MDD, it was predicted that clinical ratings may be positively related with LDAEP slope. N1 and P2 LDAEP slopes were also examined, in addition to the N1/P2 LDAEP slope, as

previous work has sometimes documented only modulations of N1 or P2 LDAEP slopes and/or intensity-dependent AEP amplitudes when probing monoamine system alterations. A third aim was to correlate scalp-derived (Cz) LDAEP indices with LDAEP slopes constructed from intensity-dependent activation in the primarily cortex using sLORETA (LDAEP-sLORETA). Given some evidence for a correlation between the two, we expected comparable results. Finally, the influence of sex on AEPs and LDAEPs was investigated; we predicted steeper LDAEP slopes in females.

4. 2 Methods

4.2.1 Participants

Please refer to Section 2.2.1, as the same patients and controls were assessed in the current study.

Individuals with significant hearing loss (i.e., using hearing aids and/or unable to hear 60 dB SPL, 1000 Hz) were excluded from participating in the current study.

4.2.2 Testing Session Procedures

Testing procedures were identical to those in Section 2.2.2.

4.2.3 Loudness Dependence of Auditory Evoked Potential (LDAEP) Paradigm

Participants were seated in a sound- and light-attenuated testing chamber with their eyes open and fixed on a point ~1 m in front of them. Auditory stimuli (1000 Hz, 30 ms duration, 10 ms rise/fall) were presented binaurally through headphones (TDH-49, Northeastern Technologies, Glen Cove, NY, USA). Stimuli at five intensities (60, 70, 80, 90, 100 dB SPL) were presented 80 times each in a pseudo-randomized order (no identical tones presented back-to-back) with ISIs randomized at 1200-1800 ms.

4.2.4 Electrophysiological Recordings and Data Reduction

EEG was recorded in the same manner as outlined in Section 2.2.3.

EEG data was re-referenced to the average of the left and right mastoids ($TP_{9/10}$). Signals were filtered (0.1-30 Hz) and ocular-corrected (Gratton et al., 1983). Data was segmented into 600 ms epochs/intensity (-100-500 ms post-stimulus). Segmentation was followed by artifact rejection, which excluded epochs of +/-75 μV. Epochs were baseline corrected (using mean activity 100 ms prior to stimulus onset) and averaged for each participant/intensity. A minimum of 40 epochs/intensity was included in the ERP analyses; three patients were excluded from analyses (N=27 MDD females, N=23 MDD males; N=23 control females, N=20 control males).

4.2.5 ERP Extraction and LDAEP Construction

N1 and P2 peak time windows were established from grand-averages (groups collapsed) at Cz. N1 was the most negative peak 70-140 ms post-stimulus and P2 was the most positive peak 110-260 ms post-stimulus. N1 and P2 amplitudes and latencies were picked from the mean of all epochs at each intensity/participant. The peak-to-peak amplitude difference between the N1 and P2 (N1/P2) was calculated at each intensity/participant. For each participant, a mean slope (least squares linear regression) was constructed for N1, P2 and N1/P2 (according to Linka et al., 2009), with intensity being the independent and amplitude the dependent variables (i.e., three scalp LDAEP slopes were calculated: N1 LDAEP, P2 LDAEP, N1/P2 LDAEP). Median slopes (Hegerl & Juckel, 1994) were significantly correlated with mean slopes (data not shown), thus, only mean slopes are presented and discussed.

4.2.6 Source Localization

The description of sLORETA is outlined in Section 2.2.4.

sLORETA was used to estimate current density values in primary auditory cortices (BA 41) for the scalp-derived N1, P2, N1/P2 components at each

intensity/participant (artifact- and ocular-corrected averaged epochs from 28 electrodes from each participant was used for sLORETA computations).

For each participant, the average current densities 70-140 ms post-stimulus (N1 activation), 110-260 ms post-stimulus (P2 activation) and 70-260 ms post-stimulus (N1/P2 activation) were determined in the primary auditory cortex (i.e., ROI). The ROI was based on a probabilistic map of the primary auditory cortex (Penhune et al., 1996) and precedent work (Mulert et al., 2002; Park et al., 2011; Table 4.1). Average current source density values for each of the N1, P2 and N1/P2 time frames were used to generate LDAEP slopes (N1, P2, N1/P2 LDAEP-sLORETA). Several participants were excluded from the sLORETA analysis due to faulty channels, with 48 MDD (N=25 females) and 40 controls (N=22 females) included.

Left Hemisphere x, y, z	Right Hemisphere x, y, z
-55 -20 5	55 -20 5
-55 -25 5	55 -25 5
-55 -30 10	55 -30 10
-50 -25 5	50 -25 5
-50 -30 10	50 -30 10
-50 -30 15	45 -25 5
-45 -25 5	45 -30 5
-45 -30 5	45 -35 10
-45 -30 15	45 -30 15
-45 -35 10	40 -30 5
-40 -30 5	40 -35 5
-40 -40 10	

Table 4.1 Montreal Neurological Institute coordinates of the sLORETA ROI (BA41: superior temporal gyrus) comprising a volume of 1500 mm^3 on the left (12 voxels) and 1375 mm^3 on the right (11 voxels)

4.2.7 Statistical Analyses

ANOVAs were carried out (SPSS Inc. software; Chicago, IL, USA) on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. N1 and P2 amplitudes and latencies were separately assessed with rmANOVAs with group and sex as between- and intensity (50, 60, 70, 80, 90, 100 dB) as within-subject factors. Similar analyses were carried out for N1/P2 amplitude and N1, P2 and N1/P2-sLORETA activity values. For analysis of N1, P2, N1/P2 LDAEP slopes,

two-way ANOVAs were applied, with group and sex as between-subject factors. N1, P2, N1/P2 LDAEP-sLORETA slopes were analyzed in a similar manner. Main effects and interactions were Greenhouse-Geisser corrected (p<.05) and Tukey adjustments (built into SPSS) were applied to account for multiple comparisons. Pearson's correlations were carried out between the N1, P2, N1/P2 LDAEP-sLORETA and equivalent LDAEP slopes (group and sex collapsed), to assess if sLORETA slopes correlated with the scalp ones. Correlations were carried out between N1, P2 N1/P2 LDAEP and LDAEP-sLORETA slopes and clinical ratings (MADRS, $HAMD_{17/29}$) for the MDD group. Separate correlations were subsequently run for each sex. Significance was set at p<.01 for the correlations to adjust for multiple comparisons.

4.3 Results

4.3.1 Profile of Mood States (POMS)

The POMS results are presented in Section 2.2.2.

4.3.2 N1 Amplitude and Latency

A main effect of intensity existed [F(4,356)=85.91, p<.001], with an N1 amplitude difference between all intensities (min p<.001). The most pronounced N1 was to 100 dB (-12.9 μV ± .7) and was least pronounced to 60 dB (-6.5 μV ± .3). A main effect of sex was noted [F(1,89)=15.37, p<.001], with greater amplitudes for females (-10.6 μV ± .5) than males (-7.7 μV ± .6). A group×sex interaction existed [F(1,89)=4.75, p=.032], with smaller amplitudes for MDD (-6.3 μV ± .8) versus control males (-9.1 μV ± .8; p=.013). MDD females (-10.9 μV ± .7) had larger N1 amplitudes than MDD males (-6.3 μV ± .8, p<.001; Figure 4.1).

Regarding N1 latency, a main effect of intensity existed [F(4,356)=14.43, p<.001], with latency differences between most intensities (min p<.001; no difference between 70 and both 80 and 90 dB; no difference between 80 and 90 dB; trend for a

difference between 60 and 100 dB, p=.092). Latency was longest for 100 dB (104.0 ms ± 1.8) and shortest for 80 dB (95.2 ms ± 1.10; Figure 4.2).

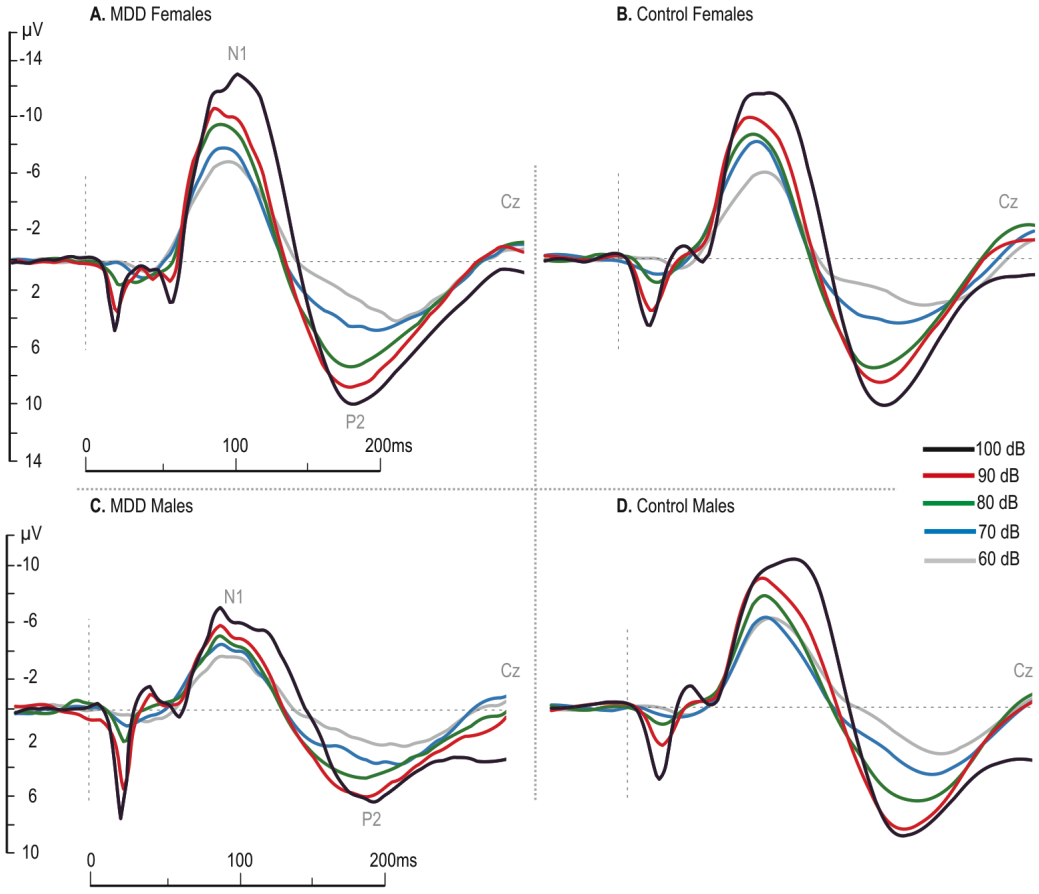


Figure 4.1. Mean N1 and P2 auditory evoked potentials (at Cz) in males and females with MDD and controls to increasing sound intensities

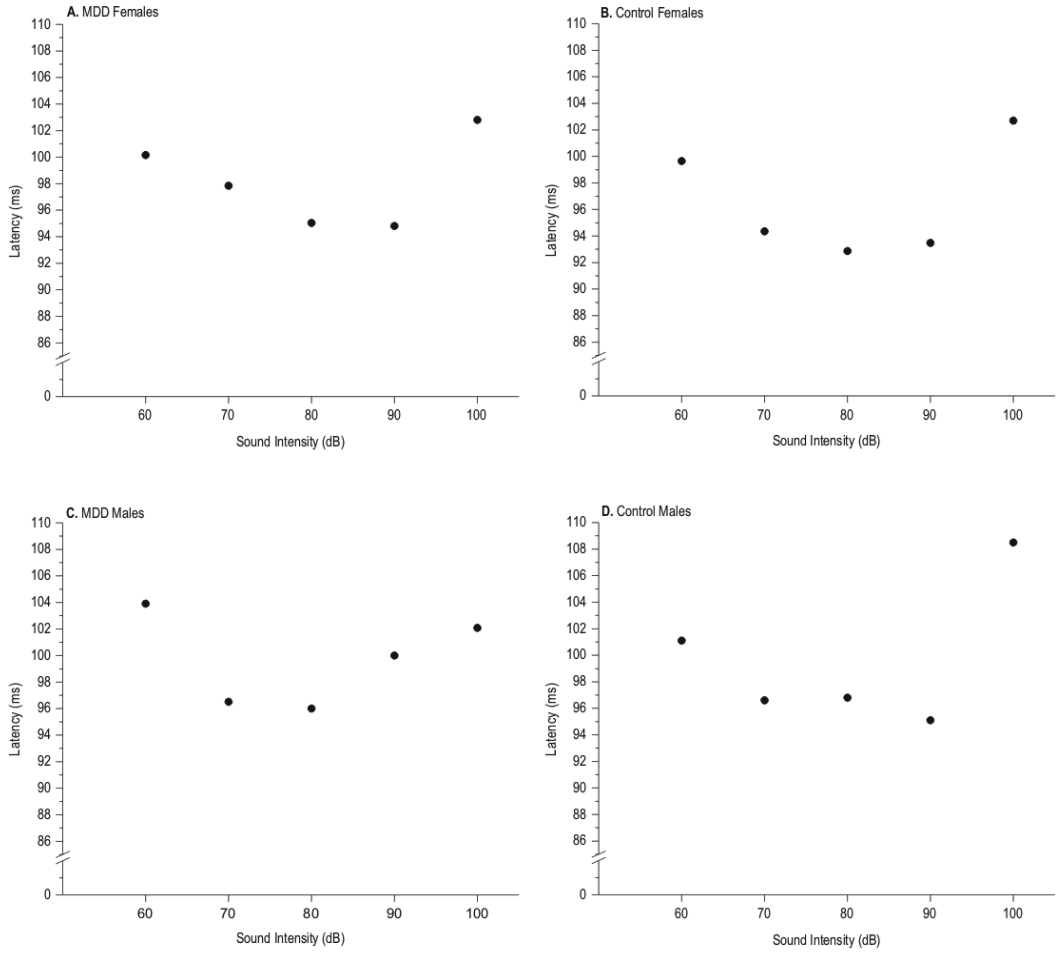


Figure 4.2. Mean N1 latencies (at Cz) in males and females with MDD and controls to increasing sound intensities

4.3.3 P2 Amplitude and Latency

A main effect of intensity existed [$F(4,356)=119.18$, $p<.001$], with P2 amplitude differences between all intensities (min $p<.005$). The largest P2 emerged for 100 dB (10.4 μV ± .6) and the smallest for 60 dB (4.1 μV ± .3). A main effect of sex was found [$F(1,89)=5.41$, $p=.02$], with a greater P2 for females (8.2 μV ± .5) than males (6.6 μV ± .50; Figure 4.1).

For P2 latency, a main effect of intensity existed [$F(4,356)=9.35$, $p<.001$], with differences between most intensities (min $p<.05$; no difference between 80 versus 70, 90 and 100 dB; no difference between 70 and 100 dB). Latency was longest for 60 dB

(200.5 ms ± 2.9) and shortest for 90 dB (184.3 ms ± 2.2). An intensity×sex interaction existed [F(4,356)=3.02, *p*=.026], with females having shorter P2 latencies than males at 80 dB (*p*=.005), with a similar trend for 60 dB and 70 dB (*p*=.07, *p*=.074, respectively). A trend for a main effect of sex existed [F(1,89)=3.37, *p*=.07], with shorter latencies for females (187.4 ms ± 2.4) than males (193.7 ms ± 2.5). A group×sex interaction was found [F(1,89)=4.46, *p*=.037], with MDD females (192.9 ms ± 3.2) having longer latencies than control females (181.8 ms ± 3.5, *p*=.02; Figure 4.3).

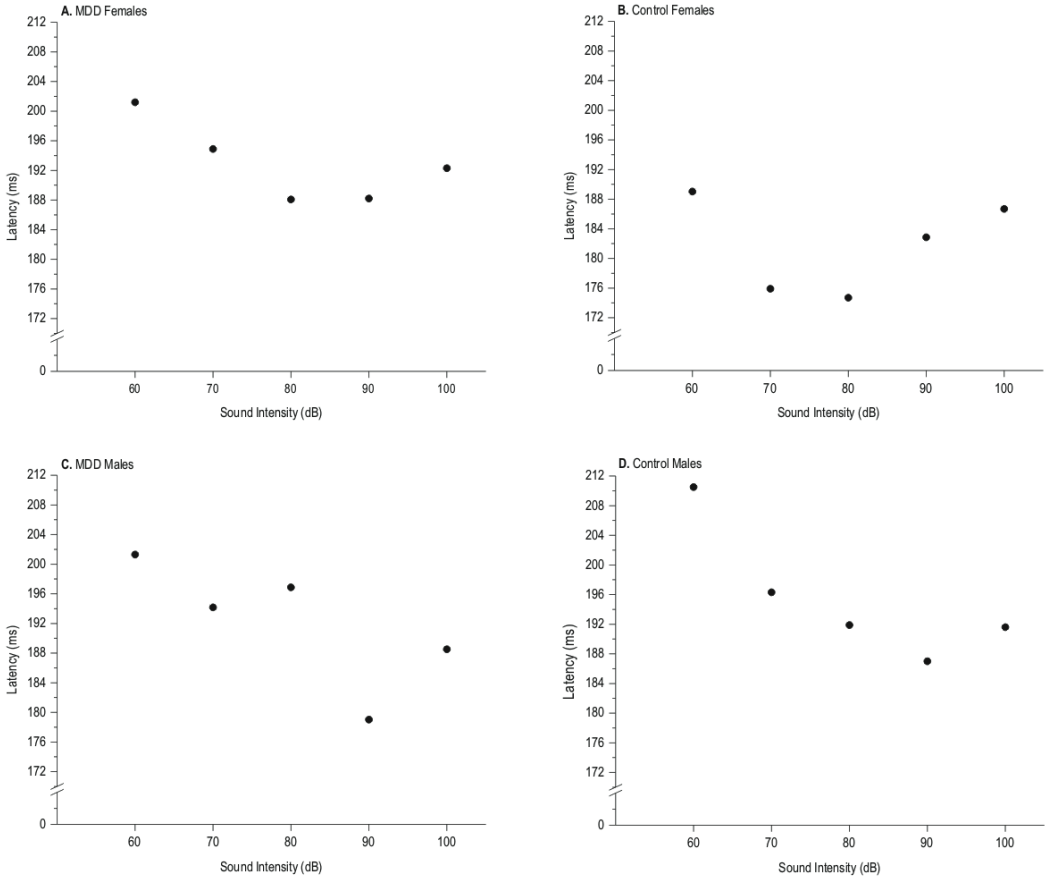


Figure 4.3. Mean P2 latencies (at Cz) in males and females with MDD and controls to increasing sound intensities

4.3.4 N1/P2 Amplitude

A main effect of intensity existed [F(4,356)=177.80, *p*<.001], with an N1/P2 amplitude difference between all intensities (min *p*<.001). The largest amplitude was to 100 dB (23.3 μV ± 1.0) and smallest to 60 dB (10.6 μV ± .4). A main effect of sex was

found [F(1,89)=5.41, p=.022], with a greater amplitude for females (18.8 μV ± .8) versus males (14.3 μV ± .8). A group×sex interaction was noted [F(1,89)=4.56, p=.035], with larger amplitudes for control (16.3 μV ± 1.2) versus MDD males (12.2 μV ± 1.1, p=.013).

4.3.5 N1, P2, N1/P2 LDAEP Slopes

A main effect of sex was noted for N1 LDAEP [F(1,87)=3.96, p=.05], with steeper slopes for females (-.17 ± .02) than males (-.12 ± .02). For N1/P2 LDAEP, a main effect of sex existed [F(1,87)=5.61, p=.020], with steeper slopes for females (.35 ± .03) than males (.26 ± .03; Figure 4.4).

4.3.6 N1, P2, N1/P2 Current Source Density

An intensity effect existed for N1-sLORETA activity [F(4,336)=101.71, p<.001], with differences among all intensities (p<.001); activity was greatest for 100 dB (2.3 ± .2) and smallest for 60 dB (.75 ± .05; Figure 4.5). A sex effect existed [F(1,84)=5.10, p=.027], with greater N1-sLORETA activity in females (1.5 ± .1) than males (1.1 ± .1).

A main effect of intensity was also found for P2-sLORETA [F(4,336)=102.29, p<.001], with differences between all intensities (min p<.001). Greatest P2-sLORETA activity existed for 100 dB (1.3 ± .07) and was smallest for 60 dB (.49 ± .03).

Finally, a main intensity effect existed for N1/P2-sLORETA activity [F(4,336)=132.51, p<.001], with differences between all intensities (min p<.001); greatest activity existed for 100 dB (1.5 ± .08) and least activity for 60 dB (.55 ± .03).

4.3.7 N1, P2, N1/P2 LDAEP-sLORETA Slopes

No significant findings were noted for any of the LDAEP-sLORETA slopes.

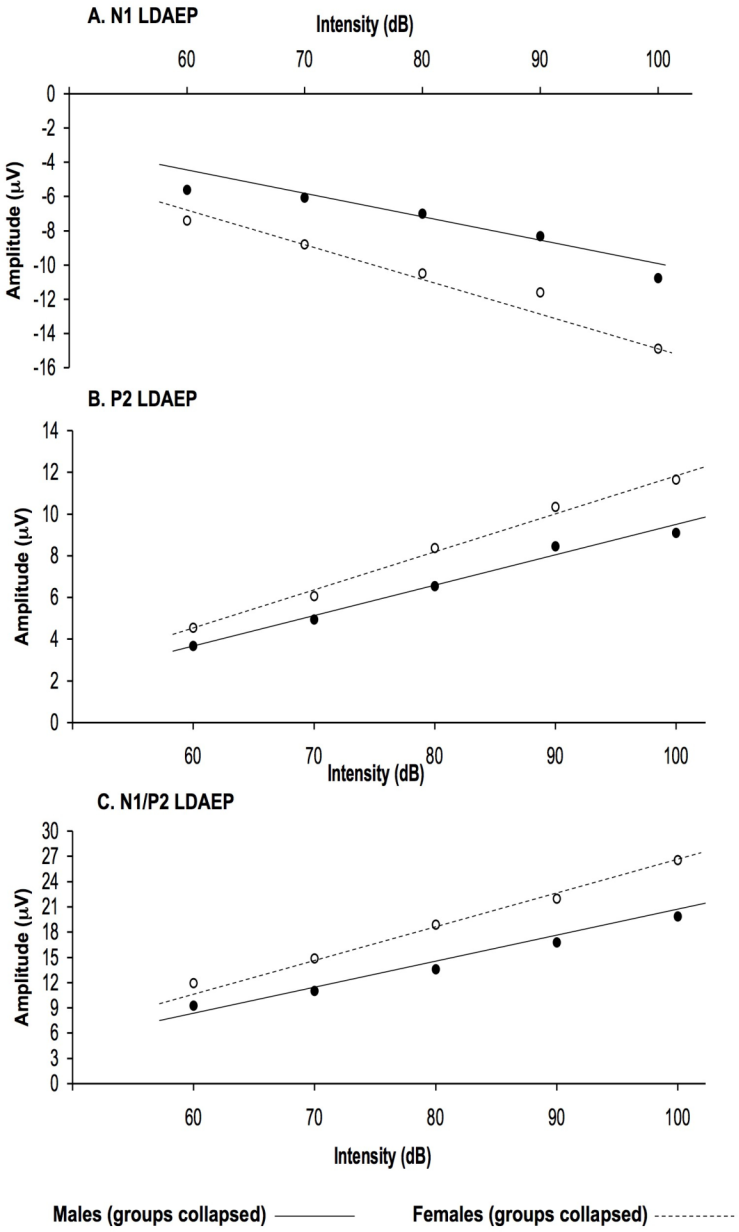


Figure 4.4. Mean N1, P2 and N1/P2 amplitudes plotted against increasing sound intensity (dB), constituting the LDAEP slopes (at Cz), in males and females (MDD and control groups collapsed)

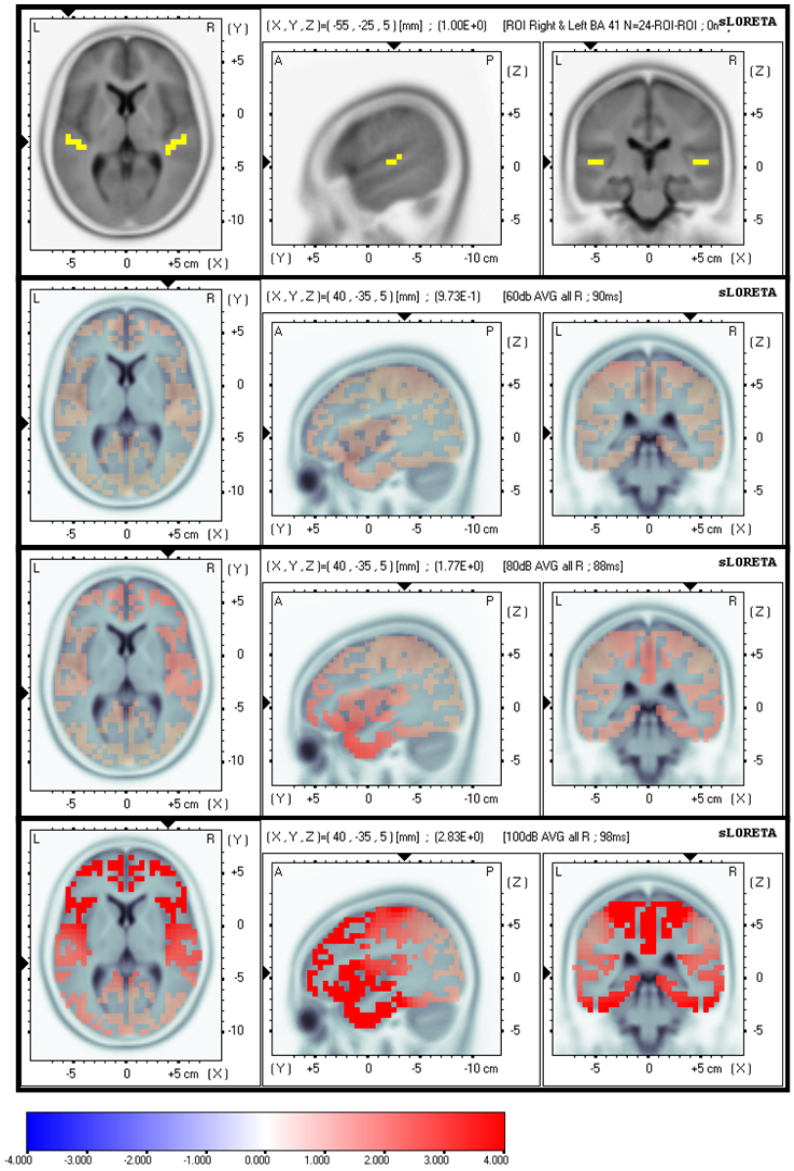


Figure 4.5. Averaged (groups & sex collapsed) sLORETA current source density activation to 60 dB (second panel), 80 dB (third panel) and 100 dB (fourth panel) during the time frame corresponding to the N1. The first panel corresponds to the ROI in the superior temporal gyrus (BA 41) used in the sLORETA analyses

4.3.8 Correlations

All scalp derived LDAEPs correlated with their LDAEP-sLORETA counterparts [group and sex collapsed; N1: $r(87)=-.47$, $p<.001$; P2: $r(87)=.34$, $p=.001$; N1/P2:

$r(87)=.48$, $p<.001$].

P2 LDAEP tended to correlate negatively with MADRS scores [$r(48)=-.32$, $p=.026$; sex collapsed]. Similarly, P2 LDAEP-sLORETA correlated negatively with MADRS scores [$r(48)=-.41$, $p=.004$]; the same trend was noted for N1/P2 LDAEP-LORETA slope [$r(48)=-.35$, $p=.016$]. When correlations were broken down by sex, P2 LDAEP-sLORETA correlated negatively with both $HAMD_{17}$ [$r(25)=-.55$, $p=.004$] and MADRS scores [$r(25)=-.71$, $p<.001$] in females. Similarly, N1/P2 LDAEP-sLORETA correlated negatively with $HAMD_{17}$ [$r(25)=-.50$, $p=.010$] and MADRS [$r(25)=-.55$, $p=.004$] scores in females. In males, P2 LDAEP tended to correlate negatively with MADRS scores [$r(23)=-.46$, $p=.027$].

4.4 Discussion

This study examined if intensity-dependent AEPs and LDAEP slope differences exist in MDD versus controls, and between the sexes. We also assessed if LDAEP slopes from sLORETA-indexed activity in the primary auditory cortex parallel scalp-derived ones. Consistent with diagnosis and hypotheses, the MDD group exhibited POMS-indexed mood disturbances. Subtle group differences in specific scalp AEPs were noted. Steeper scalp LDAEP slopes, increased scalp- and sLORETA-derived AEP amplitudes and activation, respectively, and decreased AEP latencies existed in females versus males. Scalp- and sLORETA-derived LDAEP slopes were comparable, though far from identical. These results and their implications are further discussed below.

Consistent with precedent research (Neukirch et al., 2002; Linka et al., 2007), a main effect of intensity, with the expected maximal AEP amplitudes to 100 dB, was found for the N1 and P2 components. The N1/P2, thought to reflect synchronous neuronal activation in the auditory cortex, was similarly altered by intensities. In line with hypotheses, greater N1, P2 and N1/P2 amplitudes were noted in females. Of the handful of studies specifically assessing intensity-dependent AEPs between the sexes, Hegerl and Juckel (1994) noted no sex differences in intensity-dependent N1 or P2

amplitudes. However, other work examining sex effects on AEPs, albeit with varying experimental tasks, does suggest that sex influences AEPs. For instance, using a sensory gating paradigm (i.e., auditory click pairs, S1 and S2) one group noted that females had higher N1 amplitudes to S2, indicating decreased gating in females (Hetrick et al., 1996). Another study, using a standard auditory oddball paradigm, found that the P2 to deviant tones was greater in females than males (Nagy et al., 2003). However, another group using a similar paradigm noted the opposite with N1/P2 amplitudes (Gölgeli et al., 1999). Combined with the findings of the current study, more evidence than not suggests that females exhibit greater cortical resource allocation to auditory sensory processing than males, consistent with findings that cyclical variations in female sex hormones affect AEPs (Yadav et al., 2002). Given evidence that female sex hormones alter 5-HT activity in forebrain regions (Fink et al., 1998), they may also underlie 5-HT changes in primary sensory areas, which may account for the increased AEPs in females. However, this interpretation is speculative and further work is required to probe the relationship between hormones, 5-HT function and AEPs.

For both the N1and P2, latency progressively decreased with increasing intensity until the highest intensities, at which point it increased. Though this U-shaped relationship is inconsistent with some literature (Neukirch et al., 2002), others have noted similar latency distributions (Adler & Adler, 1989). Increased AEPs latencies are thought to index slowing of neuronal processing, likely related to altered balance in excitatory and inhibitory transmission, which can result in decreased auditory cortex neuronal synchrony. It is feasible that highly intense stimuli elicit greater activation of inhibitory (neuroprotective) mechanisms, which may be reflected by longer latencies. Finally, an intensity×sex interaction existed for P2 latency, with females having speeded processing of auditory stimuli than males at all but the highest intensities. These findings indicate that females exhibit greater automatic cortical processing of auditory stimuli and faster processing of moderately intense auditory stimuli as indexed by the P2.

Smaller N1 and N1/P2 amplitudes were noted in MDD versus control males. This suggests either impaired sensory processing or potentiated inhibitory mechanisms to

auditory processing in MDD males. If the latter is endorsed, it may point to enhanced inhibitory 5-HT neurotransmission in the primary auditory cortex in MDD males. However, this interpretation is tenuous. Decreased N1 amplitudes have also been noted in other clinical disorders, such as schizophrenia (Rosburg et al., 2008) and bipolar disorder (Umbricht et al., 2003); attenuated N1s may thus reflect psychosis vulnerability. However, as individuals with a history of psychosis or a diagnosis of psychotic depression were excluded from this study, it is unlikely that psychotic-like features accounted for the reduced N1 findings in MDD males. MDD females exhibited larger N1 amplitudes than males, consistent with the aforementioned sex effect on AEPs.

Previous work assessing AEPs in MDD have yielded mixed findings, and most studies have noted no AEP amplitudes differences in MDD. However, one study using an auditory oddball paradigm found that depressed individuals exhibited greater P2 amplitudes than controls. Furthermore, eventual treatment non-responders were characterized by higher pretreatment P2 amplitudes than eventual responders and controls (Vandoolaeghe et al., 1998). Though this may suggest impaired inhibitory mechanisms, including attenuated 5-HT neurotransmission in MDD, limited interpretation of the results was provided. With respect to AEP latencies, one study noted an insignificant trend for increased AEP (N1, N2, P1, P2) latencies in MDD in an auditory oddball task (Himani et al., 1999). Similarly, another group, found increased N1 and P2 latencies in depressed melancholic patients relative to controls with the auditory oddball (Urretavizcaya et al., 2003), suggesting slower processing speed of auditory stimuli in MDD, consistent with our findings of longer P2 latencies in MDD versus control females, though the opposite has also been noted (Kähkönen et al., 2007). Based on a handful of studies, including ours, there is some evidence that the latency of preconscious AEPs may be increased in MDD, suggesting delayed processing of auditory sensory information (and perhaps impaired inhibitory mechanisms) in MDD, though we found this to be specific to females.

With respect to scalp-derived N1, P2 and N1/P2 LDAEP slopes, steeper N1 and N1/P2 LDAEP slopes were found in females. Though previous work has reported no sex

difference in the N1/P2 LDAEP (Linka et al., 2009; Park et al., 2010; Simmons et al., 2011), a recent large-scale study noted steeper N1/P2 LDAEP slopes in females versus males (Oliva et al., 2011), consistent with our findings. This may reflect baseline differences in 5-HT neurotransmission between the sexes, in line with some research (Nishizawa et al., 1997; Okazawa et al., 2000; Sakai et al., 2006). However, given the paucity of clinical evidence directly linking 5-HT activity with LDAEPs, as well as the various neurochemical differences evident between the male and the female brain (Cosgrove et al., 2007), we cannot attribute sex slope differences to baseline 5-HT differences.

Much like Linka et al., (2007) we noted no group differences on scalp N1, P2 and N1/P2 LDAEP slopes. Though our null group findings do not necessarily contradict the assumed role of the LDAEP as an indicator of CNS 5-HT activity, MDD individuals do not categorically display altered slopes, and, by extension, impaired modulatory 5-HT activity. Given that certain MDD features, such as suicide history, melancholy and specific somatic symptoms have been associated with LDAEP modulations, it is feasible that specific aspects of MDD, versus the disorder in general, may underlie the relationship. However, it is difficult to speculate which depression features may be associated with altered LDAEPs as there is scant theoretical rationale linking specific MDD aspects and/or sub-types with such modulations.

Consistent with expectations, we observed significant correlations between scalp-LDAEPs and LDAEP-sLORETA counterparts, though these correlations were moderate. Mulert et al., (2002) found no correlations between dipole source analysis (DSA)-derived LDAEPs and LDAEP slopes derived from LORETA-indexed primary auditory cortex activity. Similarly to what was noted with the scalp amplitudes, a main effect of intensity was found for N1, P2 and N1/P2-sLORETA current source density. Further paralleling the scalp ERP results, females exhibited greater N1-sLORETA activity than males. The smaller N1 and N1/P2 scalp-derived AEP amplitudes noted in MDD versus control males did not extend to the sLORETA indices further indicating that the two methods are not equitable. This may be related to the fact that scalp N1 generators extend beyond the

primary auditory cortex (Rosburg et al., 2008), while current source density (CSD) measures were confined to it. No main or interaction effects with group or sex were noted for any of the LDAEP-sLORETA slopes. This contrasts with the observed sex differences for scalp N1 and N1/P2 LDAEP slopes (females>males).

Several correlations were noted between LDAEP slopes and clinical MDD ratings. With sex collapsed, the scalp P2 LDAEP tended to correlate negatively with MADRS scores. Similarly, P2 LDAEP-sLORETA correlated negatively with MADRS scores; the same trend was noted for the N1/P2 LDAEP-LORETA slope. The MADRS indexes depression symptom severity, specifically psychological MDD symptoms, as well as global ratings of disturbance and social functioning. If an inverse relationship between the P2 LDAEP-sLORETA slope and 5-HT neurotransmission is assumed, this outcome suggests that patients with more effective 5-HT systems (i.e., shallower slopes) exhibit greater depression symptoms pretreatment. One study has previously reported a positive associated between the N1 LDAEP (at Fz) and somatic MDD symptoms, including appetite/weight loss, insomnia and sexual dysfunction (Linka et al., 2009). Others noted no associations between LDAEP and MDD-related baseline clinical ratings (Chen et al., 2005; Beucke et al., 2010). Consistent with our results, Fitzgerald et al., (2009) noted a trend towards an inverse relationship between MADRS scores and LDAEP slopes.

This relationship between decreased 5-HT system activity and increased depression ratings, if we endorse the inverse relationship between 5-HT activity and LDAEP slopes, is counterintuitive. It is feasible that individuals with higher clinical scores were those with a longer MDD history (and/or more treatment-resistant MDD) who may have been treated for longer periods or had a more aggressive treatment history. This, in turn, may have induced neuronal alterations that might account for shallower LDAEP slopes. However, this explanation is unsubstantiated and further research probing this interaction is warranted. The negative correlations were noted regardless of sex, though they tended to be stronger in females, who also exhibited negative correlations between P2 and N1/P2 LDAEP-sLORETA slopes and $HAMD_{17}$ scores, which are highly

correlated with MADRS scores (Müller et al., 2000).

Precedent work indicates that LDAEP slopes may be associated with specific personality aspects. Hensch et al., (2007) noted a negative correlation between the LDAEP and hyperthymic temperament and hypomanic personality. Others noted that a steep LDAEP was associated with an action-oriented and extroverted personality style (Juckel et al., 1995) and impulsiveness (Norra et al., 2003). Exploratory correlational analysis between LDAEP slopes (both scalp- and sLORETA-derived) and Eysenck Personality Questionnaire (Eysenck et al., 1985) dimensions in the current study did not reveal significant relationships (data not shown). However, it is feasible that other personality factors common to the MDD group, may mediate the relationship between the MADRS and LDAEP slope.

4.4.1 Study Limitations and Conclusions

Several limitations of this study must be acknowledged. Firstly, we used scalp- and sLORETA-derived measures to construct LDAEP slopes, rather than the perhaps more sensitive DSA method. Secondly, we did not control for menstruation cycle, thus, it is difficult to comment on whether certain menstrual phases may have a specific effect on the observed AEPs and associated LDAEP slopes. Thirdly, we did not assess whether specific MDD subtypes, such as melancholic or atypical depression, or whether the contribution of a secondary anxiety disorder, may be specifically related to the LDAEP. Future work should attempt to control for and examine these parameters.

In conclusion, females exhibited greater scalp intensity-dependent AEPs and sLORETA activation during the N1. They demonstrated steeper N1 and N1/P2 scalp LDAEP slopes, indicating greater auditory sensory processing (or attenuated inhibition) than males. Smaller scalp N1 and N1/P2 amplitudes existed for MDD versus control males suggesting impaired sensory processing or potentiated inhibitory mechanisms to auditory processing in MDD males. Conversely, MDD versus control females exhibited longer scalp P2 latencies suggesting longer processing speed of auditory information in

MDD females. Scalp-derived LDAEPs correlated with their sLORETA counterparts, though a majority of the variance was unaccounted for. Several LDAEP slope measures correlated negatively with depression ratings, suggesting attenuated auditory processing in increasing depression severity.

5. CHAPTER 5: RESPONSE PREDICTION TO SINGLE OR DUAL ANTIDEPRESSANT THERAPIES USING LOUDNESS DEPENDENCE OF AUDITORY EVOKED POTENTIAL (LDAEP) SLOPES (STUDY 4)

5.1 Introduction

Though many pharmacotherapies exist for treating MDD, only about a third of patients remit upon a first trial (Thase, 2003), and those who benefit from antidepressants typically experience delays of several weeks before symptom alleviation. Although SSRIs continue to be the most commonly used antidepressants (Marcus & Olfson, 2010), their therapeutic response variability is high. Some evidence suggests that SSRI efficacy may be enhanced by co-administering other drugs, such as bupropion (BUP) (Spier, 1998; Lam et al., 2004). It has also been proposed that remission rates may be increased and clinical improvement expedited if combination therapies are given at treatment initiation, rather than in response to incomplete/absent remission (Blier et al., 2010), as is currently recommended (APA, 2000). Furthermore, no established markers exist for predicting whether one will benefit from a given SSRI, from a drug with a different mechanism of action (e.g. BUP) or from specific drug combinations. Establishing such markers would aid in optimizing treatments. One such candidate may be an EEG-derived index to an auditory challenge, namely the loudness dependence of the auditory evoked potential (LDAEP).

Despite concerns about the exact nature of the relationship between the LDAEP and central 5-HT transmission (Section 4.1), a growing body of evidence suggests that the LDAEP is a strong predictor of antidepressant response, especially of drugs directly targeting the 5-HT system. As previously discussed (Sections 1.8.4 and 4.1), individuals with steep pretreatment LDAEP slopes, and perhaps attenuated 5-HT neurotransmission, tend to respond more favorably to SSRIs than those with shallow slopes (P2 LDAEP-indexed: Paige et al., 1994; Gallinat et al., 2000; Mulert et al., 2002; 2007; intensity-dependent N1-indexed: Linka et al., 2004; Lee et al., 2005; Park et al., 2011), who tend to

benefit from drugs not targeting the 5-HT system directly, such as the NRI reboxetine (N1 LDAEP-indexed: Linka et al., 2005; Juckel et al., 2007; Mulert et al., 2007). Depressed individuals unresponsive to pharmacotherapies directly targeting the 5-HT system may have more prevalent disturbances in multiple neurotransmitter systems of which the net effect may not necessarily be 5-HT hypoactivity (Fitzgerald et al., 2009). However, a handful of studies have also indicated that steep pretreatment LDAEP slopes predict favorable response to non-SSRIs such as BUP (Paige et al., 1995) and lithium (Juckel et al., 2004). As such, questions remain regarding the specificity of the LDAEP and associated auditory evoked potentials (AEPs) as predictive measures to particular antidepressant regimens. Finally, only a handful of studies have probed whether the LDAEP changes with chronic antidepressant treatment. No LDAEP changes were noted with 4 weeks of SSRI and 6-12 weeks of BUP treatment in depressed adults (Paige et al., 1995; Gallinat et al., 2000), though another group found decreased LDAEP slopes after an average of 24 days of SSRI administration in healthy adults (Simmons et al., 2011). Thus, it is unclear whether chronic antidepressant administration alters LDAEP slopes or whether the LDAEP is a trait-like index unlikely to be substantially altered with drugs.

This study probed the utility of the LDAEP (N1, P2, N1/P2 LDAEP slopes) in characterizing and predicting response to chronic treatment (12 weeks) with ESC, BUP or ESC+BUP in males and females with MDD. LDAEP slopes, subjective mood as well as clinical depression ratings assessments were examined at baseline (pretreatment) and after 1 and 12 weeks of treatment. We aimed to clarify whether baseline LDAEP slopes differentiate response outcome to a specific antidepressant regimen. Early LDAEP changes (at 1 week) were probed to assess if they facilitate with response prediction. Scalp- (at Cz, consistent with Linka et al., 2005; Juckel et al., 2007; Simmons et al., 2011) and sLORETA-derived (from primary auditory cortex activity) LDAEP slopes were examined as recent evidence suggests that source localization and scalp topography measures may not yield entirely comparable results and exhibit different sensitivity (Hagenmuller et al., 2011). We probed LDAEP differences between the sexes as precedent work suggests steeper LDAEP slopes in females (Oliva et al., 2011; Chapter

4). It was hypothesized that eventual responders (i.e., ≥50% reduction in MADRS scores from baseline) would be characterized by steeper baseline LDAEPs for the three treatment regimens relative to non-responders. Given the putative synergistic effects of combination therapy, we predicted normalization (i.e., slope decreases) to emerge 1 week after ESC+BUP treatment; we did not expect LDAEP slope changes for the monotherapies so early after treatment initiation.

5.2 Methods

5.2.1 Patients

Please refer to Section 2.2.1, as the same patient group was assessed in the current study. Non-depressed controls were not assessed.

5.2.2 Antidepressant Treatment Regimen

The antidepressant treatment regimens were identical to those in Section 3.2.2.

5.2.3 Testing Session Procedures

The testing procedures were identical as those outlined in Section 3.2.3.

5.2.4 LDAEP Paradigm

The paradigm was identical as that described in Section 4.2.3.

5.2.5 Electrophysiological Recordings and Data Reduction

EEG recordings and data reduction were identical to what is described in Section

4.2.4.

5.2.6 ERP Extraction and LDAEP Construction

Extraction of ERPs and LDAEP construction were identical to the methods presented in Section 4.2.5.

Due to faulty channels, insufficient epoch numbers and/or patient dropout, EEG data was available for N=51 at baseline, N=48 at week 1 and N=46 at week 12.

5.2.7 Source Localization

The sLORETA description is outlined in Section 2.2.4. Source localization followed the procedures in Section 4.2.6.

Several participants were excluded from sLORETA analyses, resulting in a sample of N=48 at baseline and week 1, and N=44 at week 12.

5.2.8 Statistical Analysis of Clinical Response and Subjective Mood

Statistical analyses of clinical assessments and mood were similar to those outlined in Section 3.2.5. Additionally, Mann-Whitney non-parametric tests were carried out to compare clinical rating changes (i.e., $HAMD_{17/29}$, MADRS scores) between ESC+BUP versus ESC and BUP collapsed (single treatment).

5.2.9 Statistical Analysis of N1, P2, N1/P2 LDAEPs

For analyses of scalp N1, P2, N1/P2 LDAEP slopes, rmANOVAs were applied with time as the within- and treatment, response status and sex as between-subject factors. N1, P2, N1/P2 LDAEP-sLORETA slopes were also analyzed using rmANOVAs with time and hemisphere as within- and response, treatment and sex as between-subject

factors. rmANOVAs were also carried out without hemisphere (activity averaged across hemispheres), with time as the within- and response, treatment and sex as between-subject factors. Only significant two-way interactions were followed up.

Univariate ANOVAs were carried out on scalp and sLORETA (activity averaged across hemispheres) N1, P2 and N1/P2 LDAEP slopes at baseline, with eventual response status, treatment and sex as fixed factors. Univariate ANOVAs were also carried out on slope changes from baseline to week 1 [(week 1-baseline)*100/baseline] to probe if early changes differed according to response, as well as on slope changes from baseline to week 12 [(week 12-baseline)*100/baseline] to examine if slope changes during the course of treatment differed with response outcome (fixed factors: response, treatment and sex). Only significant two-way interactions were followed up. Mann-Whitney tests were carried out to probe if differences in scalp and sLORETA N1, P2 or N1/P2 LDAEP percent slope changes between baseline and week 1 existed between responders/non-responders for BUP, ESC or ESC+BUP treatment.

Chi-square tests were used to examine if the proportion (collapsed/not collapsed across treatments) of responders/non-responders differed according to baseline N1, P2 and N1/P2 scalp and sLORETA-LDAEP slope type [shallow (weak)/steep (strong); established by a median split according to Linka et al., 2004; Juckel et al., 2007; Park et al., 2011]. Additionally, univariate ANOVAs were carried out with baseline N1, P2 and N1/P2 scalp and sLORETA-LDAEP slopes (shallow/steep), sex and treatment as fixed factors and $HAMD_{17/29}$ and MADRS response rates from baseline to weeks 1 [(week 1-baseline)*100/baseline] and 12 [(week 12-baseline)*100/baseline] as dependent variables. Only significant two-way interactions were followed up.

Finally, Pearson's correlations (collapsed across sex and treatment) were carried out between baseline scalp and sLORETA N1, P2 and N1/P2 LDAEP slopes as well as standardized slope changes from baseline to both weeks 1 and 12 [(week 1-baseline)*100/week 1; (week 12-baseline)*100/week 12] and $HAMD_{17/29}$ and MADRS rating changes from baseline to week 12 [(week 12- baseline)*100/week 12]. Significance was set at $p<.01$ to minimize Type I errors for the correlational analysis.

Exploratory Pearson's correlations were also carried out between each of the scalp-derived and sLORETA LDAEP slopes at baseline and at weeks 1 and 12, to assess LDAEP stability; stability was further assessed with single-measure ICCs using a one-way random effects model (Allen et al., 2004). For all the above analyses, main effects and interactions were Greenhouse-Geisser corrected ($p<.05$) and Tukey adjustments (built into SPSS) were applied when appropriate to account for multiple comparisons. Unless stated otherwise, mean values ± S.D. are presented. Scalp-derived LDAEP slopes are expressed as μV/10 dB; LDAEP-sLORETA slopes are expressed as $\mu A/mm^2$/10 dB.

5.3 Results

5.3.1 Patients

Patient information is identical to that outlined in Section 3.3.1, also refer to Tables 2.1 and 3.2.

5.3.2 Treatment Response and Clinical Ratings

Treatment response and clinical ratings are presented in Section 3.3.2.

Additionally, ESC+BUP versus monotherapy comparisons revealed $HAMD_{29}$ response rate differences between baseline and week 1 [$U(51)=190$, $Z=2.2$ $p=.028$], with greater decreases (%) for dual (-31.2 ± 27.9) versus single treatments (-11.7± 19.4).

5.3.3 Subjective Mood Measures

Subjective mood measure results are identical to those presented in Section 3.3.3.

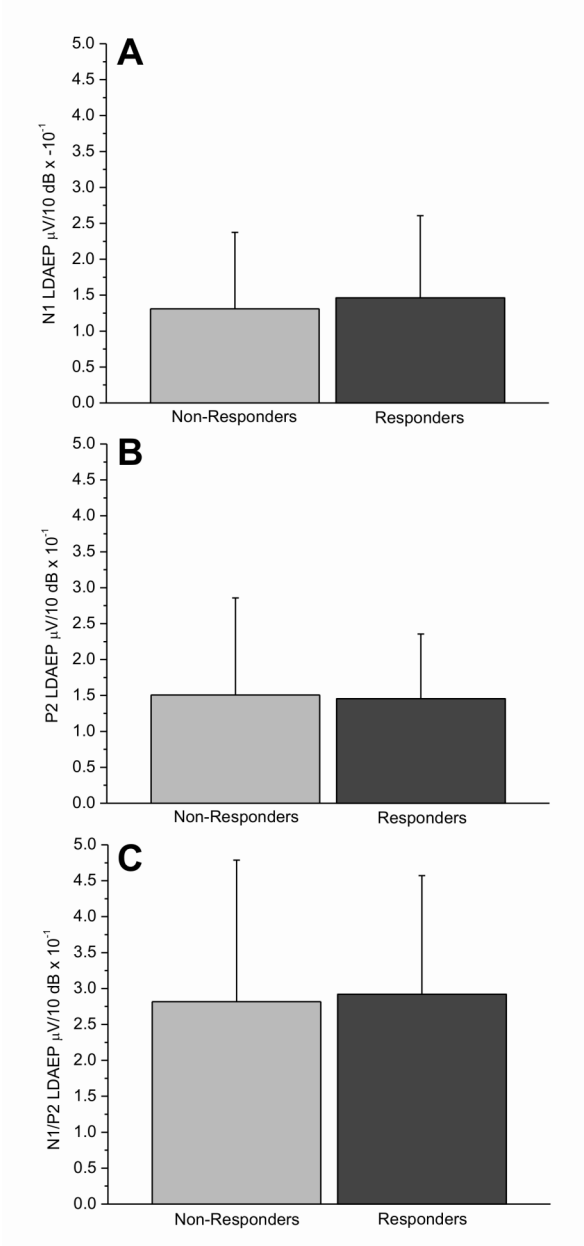


Figure 5.1. Mean baseline N1 (**A**), P2 (**B**) and N1/P2 (**C**) scalp-derived LDAEP slope values in eventual treatment responders and non-responders (treatment groups and sex collapsed)

5.3.4 Scalp N1, P2 and N1/P2 LDAEP

rmANOVAs indicated no main effects of time, treatment, response status or interactions for scalp N1, P2 or N1/P2 LDAEP slopes. A main effect of sex existed for

N1 LDAEPs [F(1,31)=16.87, p<.001], with steeper slopes in females (-.18 ± .018; males: -.072 ± .019). The same was found for N1/P2 LDAEP slopes [F(1,31)=9.75, p=.004; females: .35 ± .030; males: .21 ± .032). When univariate ANOVAs were carried out on N1, P2, N1/P2 baseline slopes and percent slope changes from baseline to weeks 1 and 12 (response, treatment and sex as between-subject factors) only a main effect of sex was noted on baseline N1 slopes [F(1,37)=9.03, p=.005], with steeper slopes in females (-.19 ± .023) than males (-.090 ± .023; Figure 5.1).

Chi-square tests revealed no differences in the proportion of responders/non-responders when baseline scalp N1, P2 and N1/P2 slopes were divided into shallow/steep slopes (treatment collapsed/not collapsed).

Mann-Whitney tests revealed no differences in scalp N1 or P2 LDAEP changes between baseline and week 1 in responders versus non-responders for any treatment; the same was true for scalp N1/P2 slope changes for BUP and ESC. A difference existed for early N1/P2 LDAEP slope changes for ESC+BUP [U(14)=53, Z=-2.22 p=.026], with early slope increases in eventual responders (56.9% ± 108.3) and a decrease in non-responders (-69.3% ± 130.3).

Univariate ANOVAs revealed no differences in $HAMD_{17/29}$ or MADRS ratings at week 12 and response rates (from baseline to weeks 1 and 12) when baseline slope (shallow/steep for N1, P2 and N1/P2 LDAEP), treatment and sex were fixed factors.

No correlations were noted between week 12 $HAMD_{17/29}$ and MADRS ratings as well as response rates (from baseline to week 12) and baseline scalp N1, P2, N1/P2 LDAEP slopes or slope changes between baseline and weeks 1 and 12.

5.3.5 N1 LDAEP-sLORETA Results

rmANOVAs (time, hemisphere as within; response, treatment, sex as between factors) were applied to N1 LDAEP-sLORETA slopes. A main effect of treatment [F(2,27)=5.32, p=.01] existed, with steeper overall N1 LDAEP-sLORETA slopes for ESC+BUP (.044 ± .004) versus both BUP (.023 ± .005; p=.004) and ESC (.029 ± .006;

p=.04). A main effect of treatment [F(2,27)=4.03, *p*=.029] also emerged when analyses were carried out without hemisphere, with steeper slopes for ESC+BUP (.048 ± .005) versus both BUP (.028 ± .006; *p*=.017) and ESC (.030 ± .007; *p*=.038).

Univariate ANOVAs with response outcome (responder/non-responder), sex and treatment as fixed factors were carried on baseline N1 LDAEP-sLORETA slopes (averaged across hemispheres) as well as percent slope changes from baseline to weeks 1 and 12. A main effect of sex exited [F(1,34)=6.34, *p*=.017], with steeper slopes in females (.045 ± .005) versus males (.027 ± .005). A main effect of response was noted [F(1,34)=9.54, *p*=.004], with steeper baseline N1 LDAEP-sLORETA slopes in responders (.047 ± .005) than non-responders (.025 ± .005).

When baseline N1 LDAEP-sLORETA slope was divided into shallow/steep slopes (treatments collapsed), Chi-square tests reveled a difference in the proportion of responders versus non-responders depending on slope [χ^2(1,46)=12.55, *p*=.001], with more non-responders (i.e., specificity: 77.3% ; N=19) versus responders (22.7%; N=5) with shallow baseline N1 LDAEP-sLORETA slopes. Conversely, more responders (i.e., sensitivity: 75%; N=18) than non-responders (25%; N=6) had steep N1 LDAEP-sLORETA baseline slopes (Figure 5.2A).

When Chi-square tests were conducted per treatment, no significant effects were noted for BUP+ESC. For BUP, more non-responders had shallow baseline slopes (80%, N=4) than responders [20%, N=1; χ^2(1,12)=5.18, *p*=.02]. Conversely, a smaller proportion of BUP non-responders had steep baseline slopes (14.3%, N=1) compared with responders (85.7%, N=6). Similar results existed for ESC [χ^2(1,17)=5.13, *p*=.02], with a greater proportion of non-responders having shallow baseline slopes (87.5%, N=7) than responders (12.5%, N=1); a smaller proportion of non-responders had steep baseline slopes (33.3%, N=3) versus responders (66.7%, N=6).

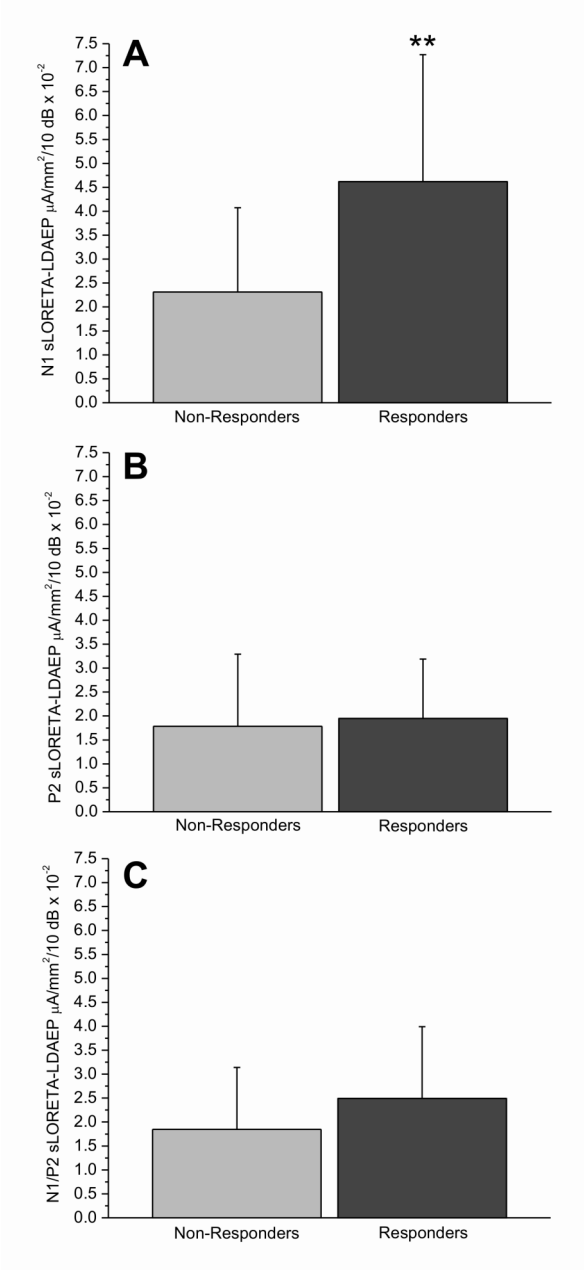


Figure 5.2. Mean baseline N1 (**A**), P2 (**B**) and N1/P2 (**C**) sLORETA-LDAEP slope values in eventual treatment responders and non-responders (treatment groups and sex collapsed; ***p*<.01)

Mann-Whitney tests revealed no differences between responders/non-responders in N1 LDAEP-sLORETA slope change between baseline and week 1 for ESC or ESC+BUP. Analyses for BUP were not carried out because of the limited samples.

Univariate ANOVAs, with baseline slope (shallow/steep), treatment and sex as

fixed factors, revealed a main effect of slope on $HAMD_{17}$ [F(1,34)=7.75, p=.009], $HAMD_{29}$ [F(1,34)=8.86, p=.005] and MADRS [F(1,34)=9.44, p=0.04] response rates between baseline and week 12. In all cases, greater response rates existed in those with steep ($HAMD_{17}$: -60.0% ± 35.5; $HAMD_{29}$: -60.7% ± 31.8; MADRS: -63.2% ± 35.3) versus shallow baseline N1 LDAEP-sLORETA slopes ($HAMD_{17}$: -33.3% ± 35.9; $HAMD_{29}$: -35.2% ± 32.8; MADRS: -34.2% ± 36.8).

Only a trend for a negative correlation was noted between N1 LDAEP-sLORETA slopes and MADRS response rates from baseline to week 12 (r=-.34, p=.023, N=45).

5.3.6 P2 LDAEP-sLORETA Results

rmANOVAs (same factors as for the N1 LDAEP-sLORETA analysis) revealed a main effect of hemisphere [F(1,27)=7.65, p=.01], with a steeper P2 LDAEP-sLORETA slope in the left (.019 ± .002) versus right hemisphere (.013 ± .002).

Univariate ANOVAs (response, sex, treatment as fixed factors) were carried out on baseline P2 LDAEP-sLORETA slopes as well as percent slope changes from baseline to weeks 1 and 12 (averaged across hemispheres). This revealed a main effect of response on slope changes from baseline to week 1 [F(1,31)=4.70, p=.038], with an early slope decrease in non-responders (-30.1% ± 16.8) and an increase in responders (19.5% ± 15.5).

Chi-square tests revealed no differences in the proportion of responders/non-responders based on slope (steep/shallow) when treatment groups were collapsed and not collapsed (Figure 5.2B).

Mann-Whitney tests indicated no differences between eventual responders/non-responders on P2 LDAEP-sLORETA slope change between baseline and week 1 for ESC or ESC+BUP treatments; analyses were not carried out for BUP treatment because of limited sample size.

Univariate ANOVAs were carried out with baseline P2 LDEAP-sLORETA slopes (shallow/steep), treatment and sex as fixed factors on clinical response rates from

baseline to weeks 1 and 12 (MADRS, $HAMD_{17/29}$); no significant effects existed.

No correlations existed between baseline P2 LDAEP-sLORETA slopes (averaged across hemispheres) or P2 LDAEP-sLORETA slope changes from baseline to weeks 1 and 12 and MADRS and $HAMD_{17/29}$ at response rates from baseline to week 12.

5.3.7 N1/P2 LDAEP-sLORETA Results

rmANOVAs (same factors as for the N1 LDAEP-sLORETA analysis) indicated a main effect of hemisphere [$F(1,27)=4.59$, $p=.041$], with a steeper N1/P2 LDAEP-sLORETA slope in the left (.022 ± .003) versus right hemisphere (.017 ± .002).

When baseline N1/P2 LDAEP-sLORETA slopes was divided into shallow/steep slopes, Chi-square tests indicated no differences in the proportion of responders/non-responders based on slope when treatment groups were collapsed (Figure 5.2C). However, Chi-square tests indicated that for ESC, a greater proportion of non-responders exhibited shallow baseline N1/P2 LDAEP-sLORETA slopes (87.5%, N=7) compared with responders [12.5%, N=1; $\chi^2(1,17)=5.13$, $p=.02$]. More responders had steep slopes (66.7%, N=6) than responders (33.3%, N=3).

Univariate ANOVAs with response, sex and treatment as fixed factors were carried out on baseline N1/P2 LDAEP-sLORETA slopes (averaged across hemispheres) and slope changes from baseline to weeks 1 and 12 as dependent variables; no significant effects emerged.

Univariate ANOVAs were carried out with baseline N1/P2 LDEAP-sLORETA slopes (shallow/steep), treatment and sex as fixed factors on clinical response rates from baseline to weeks 1 and 12. No significant effects emerged.

Mann-Whitney tests revealed no differences between responders/non-responders on N1/P2 LDAEP-sLORETA slope changes between baseline and week 1 for ESC+BUP and ESC treatment; analyses were not carried out for BUP treatment because of the small sample.

No correlations existed between baseline N1/P2 LDAEP-sLORETA slopes

(averaged across hemispheres) or slope changes from baseline to weeks 1 and 12 and $HAMD_{17/29}$ and MADRS response rates from baseline to week 12.

5.3.8 LDAEP Stability Analyses

Pearson's correlations indicted that baseline scalp N1 LDAEP slopes correlated positively with N1 slopes at weeks 1 (r=.80, p<.001, N=47) and 12 (r=.61, p<.001, N=45); the single-measures ICC was .63. Baseline scalp P2 LDAEP slopes correlated positively with P2 slopes at weeks 1 (r=.72, p<.001, N=47) and 12 (r=.58, p<.001, N=45); ICC=.67. Finally, baseline scalp N1/P2 LDAEP slopes correlated positively with scalp N1/P2 slopes at weeks 1 (r=.80, p<.001, N=47) and 12 (r=.65, p<.001, N=45); ICC=.69.

Similar analyses were carried out on LDAEP-sLORETA slopes. Baseline N1 LDAEP-sLORETA slopes correlated positively with N1 LDAEP-sLORETA slopes at weeks 1 (r=.71, p<.001, N=44) and 12 (r=.46, p=.003, N=40); the single-measures ICC was .46. Baseline P2 LDAEP-sLORETA slopes correlated positively with P2 slopes at week 1 (r=.65, p<.001, N=44) but not week 12 (r=.22, p=.17, N=40); ICC=.35. Finally, baseline N1/P2 LDAEP-sLORETA slopes correlated positively with N1/P2 slope at week 1 (r=.73, p<.001, N=44) but not week 12 (r=.29, p=.071, N=40); ICC=.43.

5.4 Discussion

This study assessed the utility of scalp and source-localized N1, P2 and N1/P2 LDAEPs in predicting response to ESC, BUP or ESC+BUP treatment in depressed males and females. LDAEP slopes, clinical and subjective mood ratings were measured before and at 1 and 12 weeks post-treatment. No clinical response differences existed between treatments at week 12 in this subsample of patients enrolled in the clinical trial (in total, 241 patients were enrolled). Clinical ratings decreased during the course of treatment, and eventual treatment responders exhibited lower depression ratings at week 1, which

persisted through week 12. Subjective mood scores also stabilized with treatment, with more pronounced stabilization evident in responders. Steeper N1 (scalp/sLORETA) and scalp N1/P2 LDAEP slopes were noted in females. Consistent with expectations, steeper baseline N1 LDAEP-sLORETA slopes existed in responders. Non-responders exhibited shallow N1 LDAEP-sLORETA baseline slopes, which was associated with smaller clinical response rates from baseline to week 12 compared with responders. P2 LDAEP-sLORETA slope decreases from baseline to week 1 were noted in non-responders, while increases existed in responders. When treatment-specific LDAEP effects were probed, results were less robust and likely related to limited power. For ESC+BUP, an increase in N1/P2 LDAEP slopes between baseline and week 1 was noted in responders and decreased in non-responders. Steeper overall N1 LDAEP-sLORETA slopes existed for ESC+BUP versus BUP and ESC. For BUP and ESC, but not ESC+BUP, a greater proportion of responders exhibited steep baseline N1 LDAEP-sLORETA slopes while more non-responders had shallow slopes. Similar results were noted with N1/P2 LDAEP-sLORETA slopes for ESC treatment. LDAEPs were stable over a week, but stability decreased over 12 weeks. The interpretation and implications of these results are discussed below.

A discussion regarding antidepressant treatment response and subjective mood ratings throughout the course of treatment can be found in Section 3.4.

With respect to scalp LDAEP slopes, steeper N1 and N1/P2 slopes existed in females than males (the same was true for N1 sLORETA-LDAEP slopes), consistent with previous observations (Oliva et al., 2011), though not others (Hegerl et al., 1994; 1998; Park et al., 2010). LDAEP sex differences corroborate research indicating that female sex hormone variations influence AEPs (Yadav et al., 2002). When treatments were collapsed, no response effects were found on scalp LDAEP slopes, inconsistent with our hypotheses and research indicating that SSRI (Linka et al., 2004; Lee et al., 2005; Juckel et al., 2007; Mulert et al., 2007) and BUP (Paige et al., 1995) responders versus non-responders exhibit steeper baseline LDAEPs. While methodological differences may have contributed to these results, our protocols were comparable with previous studies.

Additionally, we did not limit our assessments to the N1/P2 LDAEP, but also examined N1 and P2 slopes, which may be more sensitive response predictors (Paige et al., 1994; Linka et al., 2004, 2005).

When treatment-specific effects were probed, only an increase in scalp N1/P2 slope from baseline to week 1 was noted in ESC+BUP responders while a decrease existed in non-responders. This finding is notable as it is among the first to indicate that early changes in scalp N1/P2 LDAEP slopes differentiate eventual responders from non-responders and that LDAEPs may be modulated with short-term antidepressant treatment. Previous studies examining LDAEP changes over the course of antidepressant administration reported no changes with 4 weeks of SSRI (Gallinat et al., 2000) and 6-12 weeks of BUP treatment in MDD (Paige et al., 1995), though one group found decreased slopes with chronic SSRI administration in healthy adults (Simmons et al., 2011). It is curious that short-term N1/P2 LDAEP slope increases indexed a positive response to ESC+BUP. After all, if we endorse the idea that LDAEP slopes are (at least partially) inversely related to 5-HT neurotransmission, then steeper slopes may suggest decreased 5-HT activity with weeklong treatment. However, short-term SSRI administration decreases 5-HT firing rates due to somatodendritic and terminal autoreceptor activation (Artigas, 2001). Thus, initially increased slopes may reflect neurochemical alterations typically observed with 5-HT system modulations that eventually yield a positive treatment response. However, pre-clinical work indicates that ESC+BUP treatment increase 5-HT firing rates relatively rapidly (within days; Ghanbari et al., 2010), though direct inferences from pre-clinical to clinical work should be made cautiously. Given evidence that LDAEPs may be influenced by multiple factors (Lang et al., 2005; O'Neill et al., 2007; Juckel et al., 2008), increased slopes may reflect an initially altered balance between excitatory and inhibitory neurotransmission. As a final point, though the predictive utility of scalp N1/P2 LDAEP findings was limited to ESC+BUP, we cannot discount that this effect would have also emerged to single therapies with larger samples. However, given the multifaceted mechanisms of action ESC+BUP treatment, it may have been more likely than monotherapies to induce rapid and pronounced neurochemical

alterations that modulate the LDAEP with a week.

Steeper baseline N1 LDAEP-sLORETA slopes characterized responders, consistent with predictions and research indicating that steep LDAEP slopes predict positive treatment outcome, especially to 5-HT-trageting drugs. Conversely, higher depression ratings (and decreased response rates) were noted in those with shallow baseline N1 sLORETA-LDAEP slopes. Similarly to the work of Mulert et al., (2002) and Park et al., (2011), the present findings indicate that sLORETA-derived LDAEPs yield comparable results as other source localization methods [e.g. brain electrical source analysis (BESA): Gallinat et al., 2000; Juckel et al., 2007; Mulert et al., 2007] in predicting treatment response. In the current study, only the N1 (versus P2 or N1/P2) sLORETA LDAEP baseline slope was sensitive to eventual treatment outcome, consistent with some previous work (Linka et al., 2004; 2005; 2009). Limited rationale exists as to which of the N1, P2 or N1/P2 LDAEPs is most sensitive to predicting eventual antidepressant response, as predictive utility using all three has been found. Source analysis has localized the N1 to the primary auditory cortex and planum temporale, while P2 sources are less clear and may be more diffuse (Godey et al., 2001). Thus, although LDAEP slopes were constructed from primary auditory cortex activation, the putatively more diffuse P2 generators, and its more likely influence by cognitive factors, may have increased P2 and N1/P2 LDAEP slope variability and influenced its predictive utility.

When results were broken down by treatment, N1 LDAEP-sLORETA slopes were steeper overall for ESC+BUP versus monotherapies. As mentioned, due to the more pronounced neural effects of the combination treatment (Ghanbari et al., 2010), this may translate to more marked LDAEP effects compared to monotherapies. Steeper overall N1 sLORETA-LDAEP slopes with ESC+BUP treatment likely reflect modulated neurochemical activity (e.g. altered excitatory/inhibitory neurotransmitter balance) more so than simply 5-HT hypofunction.

For BUP and ESC, more responders exhibited steep baseline N1 sLORETA-LDAEPs while non-responders were characterized by shallow slopes. To date, only one

study has assessed the predictive LDAEP utility on BUP treatment outcome and noted findings similar to ours (Paige et al., 1995). BUP increases basal DRN 5-HT neuron firing (El Mansari et al., 2008). Thus, if we espouse an inverse relationship between the LDAEP and 5-HT activity it seems reasonable that steep baseline LDAEPs would predict a positive BUP response. However, steep baseline slopes may index a neurochemical environment responsive to several classes of antidepressants that directly or indirectly modulate 5-HT neurotransmission, rather than serve as an index of 5-HT hypofunction. Previous work using an electrophysiological index based on frontal EEG activity (antidepressant treatment response index, ATR), was able to discriminate ESC from BUP responders, though it too was not useful in predicting ESC+BUP response (Leutcher et al., 2008). Although N1 sLORETA-LDAEP baseline slopes did not differentiate ESC+BUP responders/non-responders, it is premature to rule out that these baseline slopes do not predict outcome to combination treatment; power issues (and associated variability) may have contributed to these null results.

Few results emerged for P2 sLORETA-LDAEP slopes, though steeper slopes were noted in the left hemisphere; a similar result existed for N1/P2 sLORETA LDAEP slopes. Previous work has indicated that LDAEPs in the two hemispheres do not yield identical results and may reveal different information (Uhl et al., 2006; Hagenmuller et al., 2011). Therefore, including hemisphere as a factor in comparable studies should be considered. A main effect of response status existed on P2 sLORETA-LDAEP slope changes from baseline to week 1, with slope increases in responders and decreases in non-responders. These results indicate that relatively rapid P2 slope changes may be associated with eventual response outcome, similarly to what was noted for scalp N1/P2 slope changes to ESC+BUP, though P2 sLORETA-LDAEP slope changes were not predictive of response to a particular treatment.

Consistent with previous research assessing the predictive utility of baseline N1/P2 LDAEPs to SSRI response (Gallinat et al., 2000; Mulert et al., 2002; 2007; Lee et al., 2005; Park et al., 2011), a greater proportion of eventual ESC responders exhibited steep baseline N1/P2 LDAEP-sLORETA slopes, while more non-responders exhibited

shallow slopes. Baseline N1/P2 sLORETA-LDAEP slopes did not distinguish responders from non-responders overall, nor did they exhibit predictive utility for BUP or ESC+BUP, which may again be related to inadequate power.

Only a handful of studies have examined if LDAEPs changes with chronic antidepressant administration and none have assessed its stability directly. Scalp baseline LDAEP slopes correlated positively with their respective slopes at weeks 1 and 12; moderately strong scalp slope stability existed. Baseline N1 LDAEP-sLORETA slopes correlated positively with slopes at weeks 1 and 12, but baseline P2 and N1/P2 LDAEP-sLORETA slopes only correlated positively with their slopes at week 1; relatively weak sLORETA-LDAEP slope stability existed. It is difficult to speculate if chronic antidepressant treatment destabilized LDAEP slopes or whether LDAEPs are somewhat temporally unstable electrophysiological measures. LDAEP stability assessments in healthy controls not taking psychotherapeutic drugs are required to resolve this.

5.4.1 Limitations and Conclusions

Despite the novelty and potential clinical relevance of this study, certain limitations exist. Firstly, once treatment groups were divided into responders/non-responders, sample sizes were greatly reduced and statistical analyses became problematic. As such, the results and interpretations of specific treatment effects discussed in the current study are preliminary and should be treated with caution. Similarly, because of limited samples, we could not probe the contribution of sex in treatment by responder status interactions. Given evidence that LDAEP slopes are greater in females than males, sex should be probed in the context of LDAEPs. Thirdly, we used scalp- and sLORETA-derived measures to construct LDAEP slopes, rather than the more validated dipole source analysis (DSA) method, which limits the generalizability of this study.

The logical next step to the presented research would be to replicate it with a larger sample and to explore the utility of a composite electrophysiological index

(consisting of z-transformed LDAEP slope values, alpha power/asymmetry etc.) in predicating treatment response, which may prove to be more sensitive. However, before the utility of the LDAEP and any other such indices in tailoring treatment strategies is possible, normative values must first be established (e.g. what value distinguishes a steep from a shallow slope?), which can only be derived from large-scale, methods-focused studies.

6. Chapter 6: The Temporal Electrocortical Profile of Emotive Facial Processing in Depressed Males and Females and Healthy Controls (Study 5)

6.1 Introduction

As discussed in Section 1.9, effective processing of facial expressions is critical for emotional communication/social interactions. As such, preferential attention and enhanced preconscious processing of facial expressions, especially negative ones, likely occurs. In accordance with cognitive theories proposing that MDD is associated with a mood-congruent processing bias (Kovacs & Beck, 1978), depressed individuals have shown enhanced memory and attention for sad expressions, with this bias extending to negative expressions such as fear and anger (Bouhuys et al., 1999; Leyman et al., 2007). Individuals with depression have also been shown to interpret neutral faces more negatively than controls (Leppänen et al., 2004; Gollan et al., 2008). However, some research also indicates that there may be blunted processing of all emotive information in MDD (Gur et al., 1992; Leppänen et al., 2004). Thus, the disorder may be associated with reduced perceptual sensitivity to positive expressions and more complex/sustained processing of negative ones (Gollan et al., 2008).

The face-sensitive N170 ERP is thought to reflect early visual processes implicated in identifying a stimulus as a face (Eimer & Holmes, 2007). Though some groups have found it to be unaltered by expressions (Ashley et al., 2004; Santesso et al., 2008), others have. For instance, increased emotive intensities (Sprengelmeyer & Jentzsch, 2006) and expressions of anger and fear enhanced the N170 (Batty & Taylor, 2003; Stekelenburg & de Gelder, 2004; Krombholz et al., 2007), though previous work from our group found it to be increased to joyful versus neutral and sad faces (Jaworska et al., 2010). Similarly, the anterior face-sensitive vertex positive potential (VPP) has been shown to be more pronounced to negative versus neutral expressions (Sewell et al., 2008; Foti et al., 2010; Luo et al., 2010), though we found it to be enhanced to emotive

(happy and sad) faces (Jaworska et al., 2012). Both N170 and VPP latencies were decreased to positive expressions (Batty & Taylor, 2003; Jaworska et al., 2012). Thus, face-sensitive ERPs are enhanced to emotive expressions, while their latencies may be shortest to positive ones.

Evidence of rapid brain responses to and modulation by expressions (<170 ms) indicates that affect detection precedes face recognition (Eimer & Holmes, 2007). The posterior positive P1 component (~100 ms), thought to index preconscious attention allocation, appears to be modulated by emotive intensity (Turetsky et al., 2008; Utama et al., 2009). The P1 was found to be decreased to sad expressions (Turetsky et al., 2008), and its latency shortened to fearful ones (Lee et al., 2010). However, others found it to be unaltered by either emotive expressions or intensity (Degabriele et al., 2011). Although less frequently studied, the mid-anterior negative N1 was greater to fearful expressions (Luo et al., 2010), though another group reported no emotion-related N1 modulations (Rossignol et al., 2005).

Mid-latency ERPs (post-N170) appear to also be influenced by facial expressions. The posterior positive P2 component (~200 ms), thought to reflect orientation to salient stimuli (Carretié et al., 2001), was attenuated by fearful and angry expressions (Schutter et al., 2004; Stekelenburg & de Gelder, 2004), though we previously found it to be increased to sad ones (Jaworska et al., 2010). The anterior negative N2, indexing attention orienting, was enhanced by expressions (Balconi & Pozzoli, 2008), and has been shown to emerge earlier and be maximal for threatening faces (Liddell et al., 2004; Kiss & Eimer, 2008). The effects of facial expressions on the posterior P3 (~350 ms), reflecting conscious attention allocation, are mixed. While some have found its enhancement to fearful or happy faces (Liddell et al., 2004; Luo et al., 2010), others reported no P3 changes to expressions (Balconi & Lucchiari, 2005).

Finally, a handful of studies have investigated the effects of emotive facial processing on later ERPs (post-P3), such as the late positive potential (LPP), though to index conscious, elaborate and evaluative processing (Schupp et al., 2004). The LPP is preferentially elicited by negative expressions, such as fear and sadness (Orozco &

Ehlers, 1998; Schupp et al., 2004; Van Strien et al., 2010) and intense versus mild and neutral faces (Jaworska et al., 2012) have been shown to preferentially evoke it.

Few studies have investigated the temporal ERP profiles associated with facial expression processing in MDD. No published work exists on the influence of facial expressions on the N170 or ERPs that precede it in the disorder. One study examined the VPP to specific expressions in MDD versus control groups, but noted no differences (Foti et al., 2010). The few studies that have assessed mid-latency ERPs to facial processing in the depression have yielded inconsistent results (Deldin et al., 2000; Kayser et al., 2000; Cavanagh & Geisler, 2006). Studies examining slow wave ERPs (1-5 s) suggest that depressives exhibit more sustained processing of negative, and diminished processing of positive, expressions (Deveney & Deldin, 2004; Shestyuk et al., 2005). However, one group examining the LPP noted that it was increased to threatening faces in controls but not in MDD, suggesting blunted processing (or avoidance) of negative information.

Finally, there is scant research probing sex effects on ERPs to facial expressions in MDD. This is despite evidence of a close relationship between emotional sensitivity and mood disturbance liability/disorders (Hofer et al., 2006), which are more prevalent in females (Parker & Brotchie, 2010). Furthermore, the dynamics of and neural activity to facial processing appears to differ between the sexes (Fusar-Poli et al., 2009), with females exhibiting enhanced/speeded facial encoding mechanisms than males (Lewin & Herlitz, 2002; Felmingham et al., 2010). The few studies that have assessed sex differences to expression-elicited ERPs have document increased ERPs in females (P1: Proverbio et al., 2006; Lee et al., 2010; P3: Yamamoto et al., 2000), suggesting greater cortical resource allocation to face processing (at various stages) in females. One study indicated that females exhibited greater N2 and P3 amplitudes to moderately negative images (not specifically faces) that were absent in males (Yuan et al., 2009).

Early- (anterior N1, posterior P1), mid- (anterior N2, posterior P2, P3) and late-latency (LPP) ERPs, as well as face-specific ERPs (N170, VPP) were examined to neutral and emotive expressions (non-target) as well as to target surprised faces in MDD males and females and healthy controls. ERPs were expected to be smaller to neutral

versus emotive faces; greater intensities (100% expression) were predicted to be associated with larger ERPs. Early-mid latency ERPs were expected to be enhanced in females. In line with the mood-congruent processing bias, group differences to specific ERPs were expected to manifest as larger amplitudes (and perhaps shorter latencies) to sad expressions in MDD. However, it was also possible that smaller ERPs to emotive expressions (i.e., blunted processing) would emerge in MDD.

6.2 Methods

6.2.1 Participants

Please refer to Section 2.2.1, as the same patients and controls were assessed in the current study.

6.2.2 Testing Session Procedures

Testing procedures were identical to those presented in Section 2.2.2.

6.2.3 Emotional Faces Recognition Task

The faces recognition task was adapted from Krolak-Salmon et al. (2001). Thirty-six photographic faces displaying one of four expressions (sadness [sad], joy, surprise [sur], neutral) were presented individually on a screen in front of the seated participant (~1 m) in a dim, electrically-shielded and sound-attenuated room. Each emotion was expressed at three intensities (20%, 50%, 100%) by one actor. Two males and two females displayed one emotion at all intensities (i.e., 12 actors). Expressions at 20% intensity were considered "neutral" as they are not reliably distinguished (Orgeta & Phillips, 2008) and 0% expressions are more likely to be confused with negative than with other facial expressions (Palermo & Coltheart, 2004). Photographs were digitized

and converted to grey-scale images, matched for luminance and contrast, with the neck and hair cropped out (Figure 6.1).

Each expression (neutral, sad50, sad100, joy50, joy100, sur50, sur100) was pseudo-randomly presented 80 times (no identical faces presented back-to-back) for 400 ms (ISI: 1500 ms; Presentation Software, Neurobehavioral Systems, Albany, CA, USA). Participants pressed a button to surprised faces (sur50, sur100) to ensure that they paid attention to expressions. Hits (% correct responses to sur50 & sur100), false alarms (FA; % responses to non-surprised faces) and reaction times (RT) were recorded.

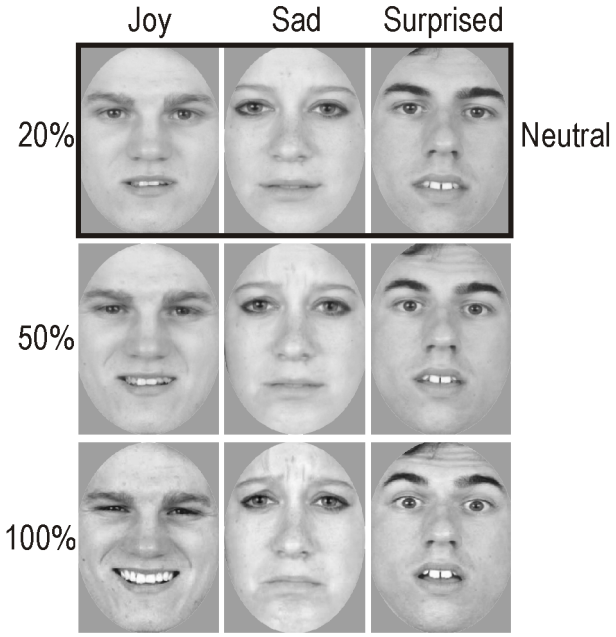


Figure 6.1. Examples of facial stimuli

6.2.4 Facial Expression Rating Questionnaire

After the task, participants rated 10 faces (one male and one female expressing each of joy50, joy100, sad50, sad100 and neutral) presented during the task. Faces were rated using a Likert scale from 0 (not at all) to 10 (very much) on two valence questions regarding how 1) “sad” and 2) “happy” faces looked. Participants rated faces based on their gut reaction, taking ~3 min to rate all faces. Two questionnaire versions, containing

different faces but bearing the same expressions, were administered. No differences existed between the versions, thus, ratings were averaged across the two questionnaires.

6.2.5 Electrophysiological Recordings & Data Reduction

EEG was recorded in the same manner as outlined in Section 2.2.3.

EEG data was re-referenced to the average of the left and right mastoids ($TP_{9/10}$). Signals were filtered (0.1-30 Hz) and ocular corrected (Gratton et al., 1983). Data was segmented into epochs (1200 ms) for each stimulus (-100-1100 ms post-stimulus). Segmentation was followed by artifact rejection, which excluded epochs exceeding +/-75 μV and containing faulty channels. Epochs were baseline corrected (mean activity -100 ms pre-stimulus). Codes synchronized with stimuli delivery were used to average epochs for specific stimuli (sad50, sad100, joy50, joy100, sur50, sur100; neutral: average of sad20, joy20, sur20) per participant. At least 40 epochs were included in any further ERP analysis (N=51 MDD; N=43 control).

6.2.6 ERP Analyses

ERPs were identified based on grand-averaged waveforms and precedent literature. The following components were identified for non-target emotive faces: P1 (at $O_{1/2}$; max +ve voltage at 70-140 ms), N1 (at Fz; max –ve voltage at 70-110 ms), N170 (at $P_{7/8}$; max –ve voltage at 140-180 ms), VPP (at Cz; max +ve voltage at 120-180 ms), P2 (at $O_{1/2}$; max +ve voltage at 200-250 ms), N2 (at Fz; max –ve voltage at 180-260 ms) and P3 (at Pz; max +ve voltage at 280-500 ms). Peak latencies of each component were evaluated from stimulus onset time. The mean positive amplitude was assessed for the LPP (at Pz; 500-650 ms post-stimulus). The amplitude and latency of the P3 (at Pz; 350-600 ms post-target) were assessed for target sur50 and sur100 faces. Trials with false alarm and missed responses were excluded from ERP analyses.

6.2.7 Statistical Analyses

Separate, rmANOVAs (SPSS Inc., Chicago, IL, USA) were carried out on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. Similarly, behavioural performance indices (hits, FA, RTs) to targets (sur50, sur100) were assessed with separate ANOVAs, with group and sex as between-subject factors. Face ratings on the "sad" and "happy" questions were carried out using rmANOVAs with non-target faces (joy50, joy100, sad50, sad100, neutral) as the within- and sex and group as between-subject factors. Amplitudes and latencies (except for the LPP) were assessed for each ERP with rmANOVAs with non-target faces and hemisphere for select ERPs (N170, P1, P2) as the within- and sex and group as between-subject factors. Univariate ANOVAs were also applied to P3 amplitudes and latencies to sur50 and sur100 faces separately, with group and sex as between-subject factors. All main effects and interactions ($p<.05$) were Greenhouse-Geisser corrected. Bonferroni corrections (built into SPSS) were applied to adjust for multiple comparisons. Exploratory correlations were carried out between the N170 (averaged at $P_{7/8}$), P3 and LPP amplitudes, to sad100 and joy100 expressions and MADRS, $HAMD_{17}$ and $HAMD_{29}$ scores. Separate correlations were run for each sex; significance level was $p<.01$ for the correlations to correct for multiple comparisons.

6.3 Results

6.3.1 Profile of Mood States (POMS)

The POMS results are identical to those presented in Section 2.2.2.

6.3.2 Emotional Faces Recognition Task

There were no group or sex effects on hits, RT or FA (Table 6.1; sexes collapsed).

Table 6.1 Behavioral performance measures on the emotive faces recognition task in MDD and control groups (Mean ± S.E.M.)

Performance Measures	MDD (N=52)	Control (N=43)
Hits (%)	81 ± 14	79 ± 14
Reaction Time (ms)	522 ± 108	525 ± 78
False Alarms (%)	.8 ± .9	.9 ± .9

6.3.3 Facial Expression Rating Questionnaire

As no sex specific effects were noted, ratings in Table 6.2 are collapsed across sexes. For the "happy" rating, a main effect of face was noted [$F(4,364)=653.66$, $p<.001$], with a difference in ratings between all faces (min $p<.001$). In validation of the presented stimuli, joy100 faces were rated as most happy, while sad100 were least happy.

For the "sad" rating, a main effect of face existed [$F(4,364)=406.41$, $p<0.001$], with a difference in sad ratings between all faces (min $p<.001$). As expected, sad100 faces were rated as most sad while joy100 were rated as least sad. A main effect of group was noted [$F(1,91)=3.90$, $p=0.05$] with the MDD group rating the faces as sadder overall (3.74 ± .11) than controls (3.42 ± .12; Table 6.2).

Table 6.2 Facial stimuli ratings on the "happy" and "sad" dimensions in MDD and control groups (mean ± S.E.M.)

		MDD (N=52)	Control (N=43)
"Happy" Rating	Joy50	7.2 ± 1.6	7.5 ± 1.5
	Joy100	8.9 ± 1.0	9.3 ± .8
	Neutral	3.3 ± 1.6	3.4 ± 1.4
	Sad50	2.0± 1.9	2.0± 1.5
	Sad100	1.0 ± 1.5	.6 ± 1.0
"Sad" Rating*	Joy50	.9 ± 1.2	.7 ± .9
	Joy100	.4 ± .7	.4 ± 1.0
	Neutral	3.6 ± 1.8	2.7 ± 1.9
	Sad50	5.8 ± 1.9	5.7 ± 1.9
	Sad100	7.9 ± 1.7	7.7 ± 2.1

For both happy and sad ratings, all faces were rated differently (min. $p<.001$)
*$p<.05$: Overall, the MDD vs. control group rated the faces as more sad

6.3.4 P1 Amplitude and Latency

A main effect of face was noted for P1 amplitude [$F(4,360)=11.72$, $p<.001$], with follow-up comparisons indicating a smaller P1 for joy100 versus all other faces (min $p<.005$). The P1 for joy50 was also smaller than for all other faces (min $p<.05$; Figure 6.2).

A main effect of face was noted for P1 latency [$F(4,360)=13.05$, $p<.001$], with a shorter latency for joy100 versus all other faces (min $p<.05$). Additionally, a shorter latency was noted for joy50 than for neutral and sad50 (min $p<.05$; Figure 6.2).

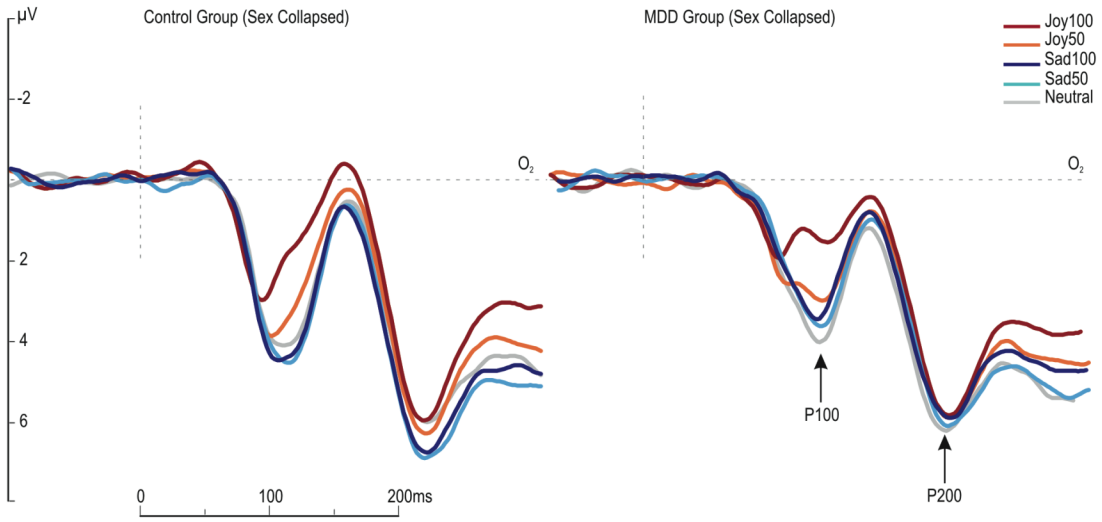


Figure 6.2. P1 and P2 (at O_2) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in MDD and control groups

6.3.5 N1 Amplitude and Latency

No main effects or interactions were noted for N1 amplitude.

A main effect of sex was found for N1 latency [$F(1,90)=25.86$, $p<.001$], with longer latencies for males (99.09 ± .95 ms) versus females (92.48 ± .89 ms). A face×sex interaction also existed [$F(4,360)=3.46$, $p=.012$], with longer latencies for neutral versus both joy100 ($p=.006$) and sad100 ($p=.021$) faces for females. For males, N1 latency for

joy100 was longer than for joy50 (p=.038). For all faces, N1 latency was shorter for females than males (min p<.05; Figure 6.3).

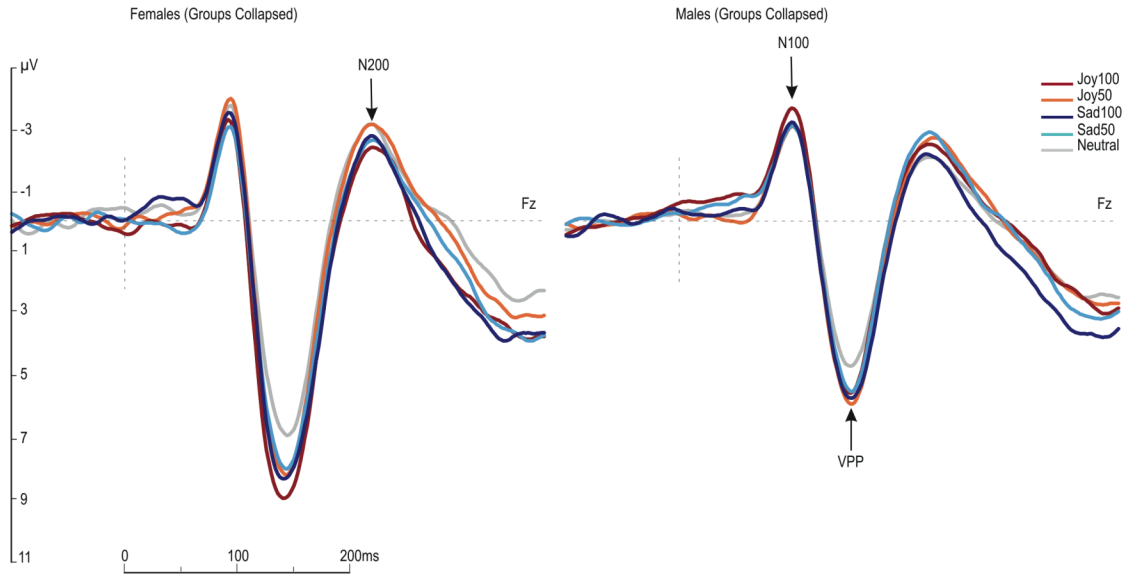


Figure 6.3. N1, N2 and VPP (at Fz) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral faces in males and females (collapsed across groups)

6.3.6 N170 Amplitude and Latency

A main effect of face was found for N170 amplitude [F(4,360) = 4.85, p=.001], with a smaller amplitude for sad100 versus both joy50 (p=.011) and joy100 (p<.001). The N170 for neutral was smaller than for both joy50 (p=.024) and joy100 (p=.003); the amplitude for sad50 was smaller than for joy100 (p=.022; Figure 6.4).

No main or interaction effects were found for N170 latency.

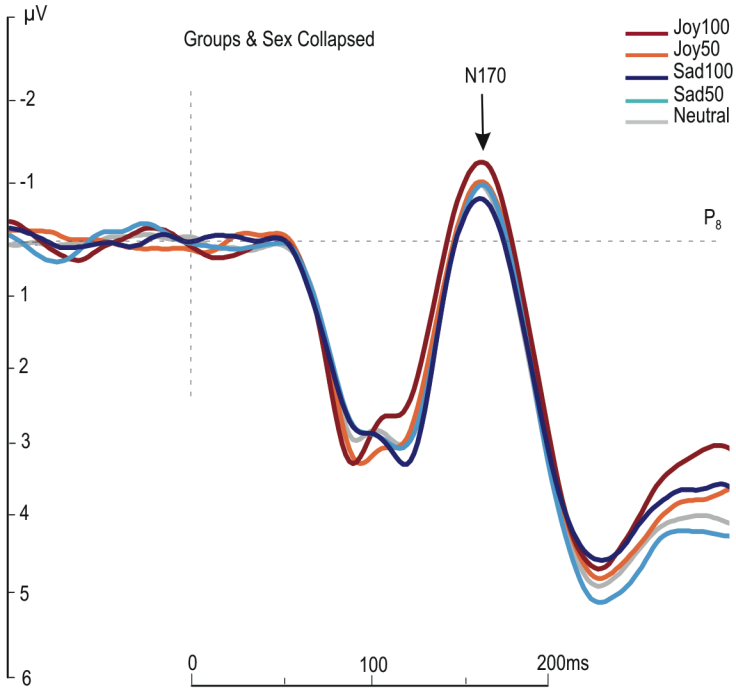


Figure 6.4. N170 amplitude (at O_8) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral faces in MDD and control groups collapsed

6.3.7 VPP Amplitude and Latency

A main effect of face was noted for VPP amplitude [$F(4,360) = 17.34$, $p<.001$], with follow-up comparisons indicating a smaller VPP for neutral versus all other faces (min $p<.001$). Additionally, the VPP for sad50 was smaller than for joy100 and sad100 (min $p<.05$). A main effect of sex was found [$F(1,90)=14.14$, $p<.001$], with females (10.39 ± 0.66 μV) having larger VPP amplitudes than males (6.74 ± 0.71 μV; Figure 6.3).

A main effect of sex existed for VPP latency [$F(1,90)=10.81$, $p=.001$], with shorter latencies in females (141.1 ± 1.53 ms) than males (148.47 ± 1.64 ms; Figure 6.3).

6.3.8 N2 Amplitude and Latency

A main effect of face was found for N2 amplitude [$F(4,360)=3.530$, $p=.01$], with

a more negative amplitude for joy50 versus both neutral (p=.038) and sad100 (p=.001). The N2 amplitude to sad50 was also more negative than to sad100 (p=.006; Figure 6.3).

Assessment of N2 latency indicated a face×sex×group interaction [F(4,360)=2.87, p=.027] but no direct group differences were noted. For the MDD group, sex differences were found in N2 latency for joy50 (p=.017) and joy100 (p=.015), with shorter latencies for females versus males. For control males, N2 latency for sad100 was longer than for neutral faces (p=.038). For MDD females, N2 latency for sad100 was longer than for neutral, joy100, and sad50 (min p<.05). For MDD males, N2 latency was longer for joy50 versus neutral, sad50 and sad100 (min p<.05).

6.3.9 P2 Amplitude and Latency

A main effect of face was found for P2 amplitude [F(4,360)=3.7, p=.006], with a greater amplitude for sad50 versus neutral, joy50 and joy100 (min p<.05). P2 amplitude was also larger for joy100 than sad100 (p=.027; Figure 6.2). A face×group interaction existed [F(4,360)=3.35, p=.013], though follow-up comparisons revealed no direct group differences. For controls, P2 amplitude was greater for sad50 versus all other faces (min p<.005) but sad100; it was also greater for sad100 versus neutral (p=.012) and joy100 (p=.006), with a similar trend compared with joy50 (p=.058). For the MDD group, the P2 to neutral was greater than joy50 (p=.016; Figure 6.2).

A face×hemisphere×group interaction trend was noted for P2 latency [F(4,360)=2.22, p=.07]. Pairwise comparisons indicated that P2 latency for the MDD group (224.38 ± 1.78 ms) was longer than for controls (218.52 ± 1.94 ms) for sad100 in the left hemisphere (p<.05).

6.3.10 P3 Amplitude and Latency

A main effect of face was noted for P3 amplitude [F(4,360)=6.34, p<.001], with a greater P3 for sad50 versus neutral, joy50 and joy100 (min p<.05). Similarly, a greater P3

existed for sad100 versus neutral, joy50 and joy100 (min $p<.001$). A main effect of sex was found [$F(1,90)=7.26$, $p=.008$], with larger P3 amplitudes in females (8.99 ± 0.48 μV) than males (7.09 ± 0.52 μV; Figure 6.5).

A main effect of face existed for P3 latency [$F(4,360)=2.53$, $p=.049$], with a longer latency for sad100 than for neutral, joy50 and sad50 (min. $p<.05$).

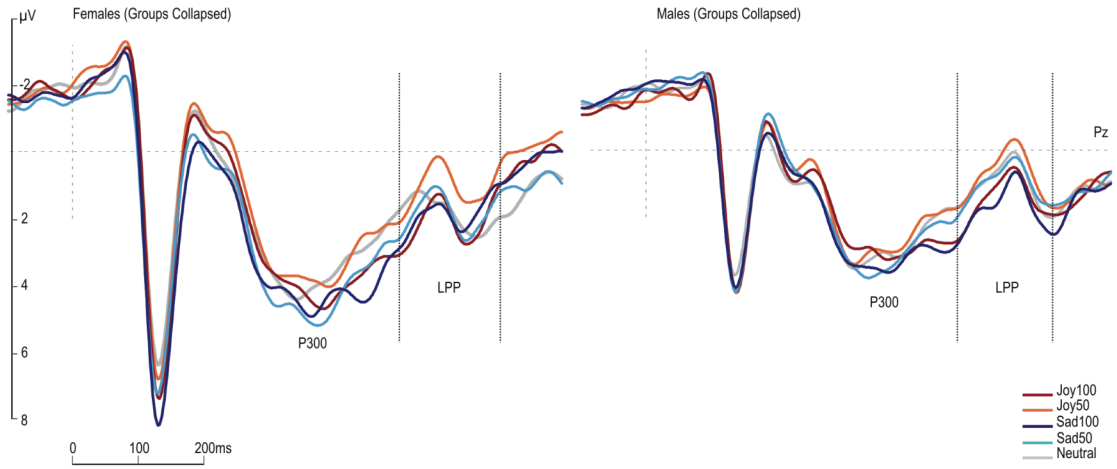


Figure 6.5. P3 and mean LPP (500-650 ms; Pz) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in males and females, collapsed across groups

6.3.11 LPP Mean Amplitude

A main effect of face was found for mean LPP amplitude [$F(4,360)=6.34$, $p<.001$], with larger LPPs for sad100 than neutral ($p=.003$), joy50 ($p<.001$) and sad50 ($p=.001$). The LPP to joy50 was smaller than for neutral ($p=.021$) and joy100 ($p=.004$). A main effect of sex existed [$F(1,90)=3.95$, $p=.05$], with a greater LPP for females (4.14 ± .40 μV) versus males (2.96 ± .42 μV; Figure 6.5).

6.3.12 Correlations

For females, only a trend for a negative correlation between MADRS scores and

P3 amplitude to sad100 faces was found (r=-0.39, p=.043, N=27).

6.3.13 P3 Amplitude & Latency to Target Faces

A main effect of sex was noted for P3 amplitude to sur50 [F(1,75)=7.40, p=.008] and sur100 faces [F(1,91)=16.82, p<.001], with females exhibiting a greater P3 (sur50: 14.59 ± .69 μV; sur100: 18.28 ± .74 μV) than males (sur50: 11.76 ± .78 μV; sur100: 13.84 ± .79 μV). No main effects or interactions existed for sur50/100 latency.

6.4 Discussion

This study examined performance and ERPs evoked by a simple facial expression recognition task in depressed males and females and controls. Consistent with expectations and diagnosis, the MDD group was characterized by mood disturbances (refer to Section 2.3.1). In line with the mood-congruent processing bias, depressed individuals rated faces as sadder overall than controls, suggesting that emotive and socially meaningful information is evaluated more negatively in the disorder. Expressions influenced all ERPs, though valence and intensity selectively modulated specific ERPs. Females typically had larger ERPs with shorter latencies than males, indicating enhanced pre- and conscious as well as speeded facial processing, respectively, in females. Depressed individuals did not exhibit robust ERP differences to specific expressions than controls. Subtle group differences were noted in mid-latency ERPs, with controls exhibiting increased P2 amplitudes to sad expressions that was absent in the MDD group, though P2 latency to intensely sad faces was longer in MDD; a similar finding existed for N2 latency in MDD versus control females. No correlations between select ERPs to intense expressions and depression ratings existed. Further interpretation and implications of these results are discussed below.

We noted an attenuated P1 to joyful expressions and decreased latency to intensely joyful ones, confirming previous results indicating that early perceptual ERPs

are emotion-sensitive (Pourtois & Vuilleumier, 2006; Santesso et al., 2008). However, research assessing the influence of less arousing positive (happy) and negative (sad) expressions on the P1 has yielded inconclusive findings (Lee et al., 2010). Somewhat in-line with our results, others noted an attenuated P1 to liked (versus disliked) and attractive (versus unattractive) faces (Halit et al., 2000; Pizzagalli et al., 2002). We previously found a blunted P1 to joyful versus intensely sad faces in the right occipital region, though an increased P1 to intensely joyful versus mildly emotive and neutral expressions was found in the left parietal region (Jaworska et al., 2010). Our current results suggest "automaticity" in very early perceptual processing of positive expressions.

With respect to the N1, shorter latencies were noted for intensely sad and joyful expressions compared with neutral ones in females, suggesting longer perceptual processing of ambiguous faces. In males, N1 latency was enhanced to intensely versus mildly joyful faces, indicating somewhat different early, perceptual processing of emotive information between the sexes. This was further supported by decreased overall N1 latencies in females versus males, indicating speeded perceptual processing of faces in females (Lewin & Herliz, 2002; Felmingham et al., 2010). We found no evidence for altered early, preconscious processing of emotive information in MDD.

Though notable exceptions exist, the N170 has been found to be expression-sensitive, with most studies documenting its enhancement to highly arousing negative expressions (Batty & Taylor, 2003; Stekelenburg & de Gelder, 2004; Krombholz et al., 2007). We found it to be most pronounced to joyful faces, consistent with our previous findings (Jaworska et al., 2010). Given that an opposite pattern was observed for the P1, it is feasible that early sensory processing is most automatic for positive expressions while face identification may be maximal for them. Consistent with the idea that highly arousing stimuli elicit a maximal N170, pilot work in our laboratory indicated that intensely joyful faces were rated as most aroused while mildly sad ones were least aroused (data not shown). Thus, it is feasible that increased arousal versus positive valence *per se* elicits a prominent N170.

The VPP has also been shown to be enhanced to fearful and angry expressions

(Sewell et al., 2008; Foti et al., 2010; Luo et al., 2010). However, we previously found it to be enhanced to emotive (happy and sad) faces (Jaworska et al., 2012), consistent with the current study. Previous work has also found the VPP to be shortest to positive expressions (Batty & Taylor, 2003; Jaworska et al., 2012). Thus, highly arousing and positive faces appear to elicit maximal VPPs with shortest latencies. Though it has been argued that the VPP and N170 are equivalent (Joyce & Rossion, 2005), we noted distinct features between the two. The VPP was smallest to neutral faces indexing preferential processing of emotional (versus simply arousing) faces. A main effect of sex emerged for the VPP but not N170, suggesting increased cortical resource allocation and faster processing of faces in females. We found no evidence that face-sensitive ERPs were uniquely altered by specific expressions in MDD.

The P2 has been shown to be modulated by emotive information, with reported P2 reductions to fearful and angry faces (Schutter et al., 2004; Stekelenburg & de Gelder, 2004). Previous work in our laboratory found it to be maximal to sad versus neutral and mildly positive expressions in the right occipital region (Jaworska et al., 2010). Similarly, in the current study, a greater P2 was noted to mildly sad versus neutral and joyful expressions, though it was also greater for intensely joyful versus intensely sad ones. These results suggest a maximal P2 to less arousing negative expressions. The P2 may reflect perceptual grouping processes as it tends to be small for stimuli that facilitate grouping and maximal for those that hinder it (Rousselet et al., 2008). Highly arousing and positive expressions may facilitate grouping and be accompanied by a decreased P2. In a similar vein, following initially enhanced preconscious processing of positive and arousing stimuli, reflecting rapid stimulus identification/categorization, increased perceptual processing may subsequently be devoted to ambiguous expressions. A similar interpretation could apply for the N2 as it was maximal to mildly joyful versus neutral and intensely sad faces.

Subtle group differences emerged for the P2 and N2. For controls, the P2 was greater for sad versus all other expressions. This was not observed for the MDD group; instead, only a larger P2 to neutral versus mildly positive expressions existed. This may

reflect increased automaticity in late preconscious processing of negative faces in MDD. Alternatively, it suggests attenuated perceptual processing of emotive information (Leppänen et al., 2004). P2 latency for the MDD versus control group was longer to intensely sad expressions in the left hemisphere, indicating longer late preconscious processing of these faces. Though no direct group differences were noted for the N2, subtle sex-dependent N2 latency differences emerged. Specifically, though no N2 latency differences existed between faces in control females, for MDD females latencies were enhanced to intensely sad expressions, consistent with the P2 latency results. For control males, N2 latency to intensely sad faces was longer than to neutral ones, indexing longer processing of intense negative stimuli. In MDD males, N2 latency was longer for mildly joyful versus neutral and sad expressions suggesting increased processing of mild, mood-incongruent faces.

We noted maximal P3s to sad expressions and longer latencies to intensely sad versus all but intensely joyful faces, consistent with the idea that the most informative social cues preferentially capture conscious attention resources. Additionally, we found that P3-indexed conscious processing of faces was greater in females. Given that performance was comparable between the sexes, this did not confer a performance advantage, though task ease may have prevented the emergence of sex differences. Previous work has found no P3 differences to faces between sexes (Campanella et al., 2004; Lee et al., 2010), another group noted opposite results to ours (Oliver-Rodríguez et al., 1999), while yet another indicated that P3 sex differences to facial expressions may be hemisphere-dependent (Gasbarri et al., 2006). The current study indicates enhanced pre- and conscious facial processing in females. We found no evidence of altered conscious attention capture by specific facial expressions in MDD. The handful of studies that have assessed the P3 in emotive tasks in MDD suggest blunted conscious attention allocation to emotive information (Kayser et al., 2000; Cavanagh & Geisler, 2006; Bruder et al., 2012). Our findings did not support this, though study design variability may partially account for this.

In line with our previous work (Jaworska et al., 2012), we noted greater LPPs to

intensely sad versus all but intensely joyful expressions. The LPP to mildly joyful faces was also smaller than to neutral and intensely joyful faces, indicating that neutral, perhaps due to their ambiguity yet potential relevance, and intense expressions elicit greater sustained motivated processing than mildly emotive ones. LPP-indexed enhanced sustained processing of faces was evident in females versus males. Previous work indicates that MDD individuals exhibited blunted LPPs to threatening faces (Foti et al., 2010), while others noted no effect of positive or negative pictures (not faces) on an LPP-like component in MDD (Kayser et al., 2000).

6.4.1 Conclusions and Limitations

We assessed ERP profiles associated with facial expression processing in MDD. Consistent with the purported mood-congruent processing bias in MDD, MDD individuals rated expressions as sadder overall than controls. However, we found little evidence for substantially altered ERPs to specific expressions in MDD. Subtle modulations in mid-latency ERPs suggested attenuated late preconscious perceptual processing of emotive stimuli in MDD, though this was accompanied by longer processing of intensely sad faces, especially in females. Females exhibited increased and speeded pre- and conscious facial processing.

Precedent work indicates that robust ERPs tend to emerge to threatening faces, especially at early-mid latencies, perhaps reflecting a pre-attentive scan of threat. Our rationale for excluding these was because we wanted to examine the influence of valence on ERPs in MDD while minimizing the influence of arousal. However, inclusion of threatening faces may have revealed more pronounced group ERP differences. Task design is another important consideration when comparing study outcomes. In the current study, participants responded to surprised faces; a more involved task (e.g. memory task) may have, more robustly, differentiated the groups. Although given that we wanted to assess temporal profiles of expression processing, our task was well-suited for this aim. Another methodological consideration that may complicate direct comparisons between

studies (in addition to reference choice) is the site at which an ERP is assessed.

Despite our subtle between-group differences, the potential utility of ERPs during emotive processing in MDD should not be discounted. Previous work indicates that cognitive changes may emerge with short-term treatment (Harmer et al., 2003). Assessing attention allocation to emotive stimuli and associated ERPs before and during initial treatment periods may be useful in predicting clinical response. If clinical outcome can be predicted based on short-term ERP changes to emotive stimuli, earlier switching to more effective antidepressants may be feasible, and should be probed in future studies.

7. CHAPTER 7: GENERAL DISCUSSION

7.1 Summary

The work comprising this thesis assessed if specific electrophysiological indices distinguish individuals with MDD from non-depressed controls. It also probed the role of sex on these indices, as sex tends to be neglected in research exploring depression biomarkers, likely because its inclusion may complicate analyses and interpretation of results. However, given that MDD tends to be approximately twice as prevalent in females, this omission is notable. The second broad aim of this thesis was to examine whether these electrophysiological indices assist with predicting antidepressant response in general, and to specific drug regimens. With respect to the first goal, certain electrophysiological markers distinguished individuals with MDD from those without the disorder; pronounced sex differences also emerged in some of these markers. Specific electrophysiological indices also differentiated eventual antidepressant treatment responders from non-responders, though their specificity in predicting response to a particular treatment regimen was limited, which may have been related to small sample sizes.

7.2 Resting brain activity indices in MDD and their utility in predicting antidepressant response: A critical summary

Greater left anterior alpha power, reflecting cortical hypoactivity, existed in MDD, especially in depressed males, and was inversely related to depression scores. This is consistent with the large body of literature implicating the left anterior cortex in processing positive emotions/information and in regulating approach-related motivation tendencies. Hypoarousal in this region has been associated with decreased mood, greater withdrawal and a negative-processing bias, features consistent with a typical MDD profile. Though reference montage influenced both alpha power and frontolateral alpha

asymmetry, midfrontal alpha asymmetry was least susceptible to reference choice. This finding is noteworthy, as it suggests a degree of consistency across studies reporting decreased relative left fronto-cortical activity in MDD via asymmetry assessments in midfrontal regions, despite the use of varying reference montages. Nevertheless, with the digitization of EEG and analyses automation, it should be feasible to examine alpha power and asymmetry using several reference schemes, at least within an experimental setting. The use of current source density (CSD) is a relatively uncommon reference choice in EEG processing, though it may be superior to other montages given that it is "reference-free" and has been associated with revealing unique EEG features in MDD (Stewart et al., 2010). However, the utility of CSD may be limited as it has yet to be incorporated within most of the common EEG/ERP analyses platforms. Additionally, given that most research on alpha power/asymmetry in MDD has relied on more conventional reference montages, direct comparisons with CSD-referenced EEG findings may be somewhat problematic.

We also noted increased alpha activity in MDD in anterior regions, where it was assessed, though others have noted its increase posteriorly (Pollock & Schneider, 1990; Roemer et al., 1992; Ricardo-Garcell et al., 2009; Kemp et al., 2010). These findings indicate that cortical hypoarousal is associated with the disorder. Sex differences also emerged, with depressed versus control males exhibiting greater alpha power; observations in females were in the same direction, but were less pronounced. As such, a more robust resting EEG profile existed in MDD males despite the absence of baseline clinical differences between the sexes. Additionally, only $alpha_2$ power proved to be specifically decreased in the left fronto-cortical region in MDD versus control males (a group difference also existed). Given that the functional significance of alpha sub-bands is unclear, this should be further investigated in comparable studies. It is also unknown whether high/low alpha are related (inversely) to cortical arousal/activation to the same extent.

Inconsistent with some precedent work (Bruder et al., 2005; 2011; Kentgen et al., 2000), group differences reflecting right parietotemporal hypoarousal in MDD were not

found. However, when broken down by sex, males exhibited the expected profile. Right parietotemporal hypoactivity has been suggested to reflect emotional under-arousal, which may be linked with the clinical feature of anhedonia in MDD, though this association is somewhat speculative. Anxiety, which is highly co-morbid in MDD and reflects a hyper-aroused emotive state, has been linked with right parietotemporal hyperarousal and may have contributed to the EEG profile evident in depressed females, and should thus be directly for controlled in future work.

Midfrontal $theta_{Total}$ power did not differentiate MDD and control groups, though the fact that it was only assessed at one site may have accounted for this. The rationale for such a simple assessment was based on precedent work indicating that baseline theta power at Fz differentiated antidepressant treatment responders from non-responders (Spronk et al., 2011). As such, it was feasible that Fz theta power differences may have also emerged between depressed and control individuals. Furthermore, midfrontal theta power is thought to be strongly correlated with ACC-localized theta, which is known to be altered in MDD. Finally, there is inherent appeal in assessing power at one site as a means of identifying a psychiatric population since such an approach would be easy to apply within a clinical setting. However, given the relatively mixed body of work regarding directional differences in frontal theta power in MDD (Ohashi et al., 1994; Wienbruch et al., 2003; Roemer et al., 1992; Köhler et al., 2011; Knott et al., 2000; Pollock & Schneider 1990), fronto-cortical theta power, even if assessed at more sites, may simply lack the sensitivity to discriminate depression.

Despite the lack of group differences in scalp-assessed midfrontal theta power, increased sgACC/BA 25-localized theta activity existed in MDD. This group difference appeared to be primarily driven by $theta_2$ activity, though a trend for a difference also existed for $theta_1$. It is feasible that high versus low theta may better reflect fronto-cortical oscillations, indexing activity in networks that include the ACC. However, similarly to the alpha sub-bands, the functional significance of high versus low theta and whether one sub-band better reflects fronto-cortical network activity should be further investigated. Additionally, though increased theta activity was statistically limited to the

sgACC/BA 25 region, the spatial specificity of this finding cannot be guaranteed given the resolution limitations of sLORETA. Furthermore, as relatively few electrodes were used in this thesis work, a spatial localization bias may have emerged. Nevertheless, the sgACC theta activity increases observed in MDD are consistent with precedent literature indicating that activity modulations in this region are implicated in MDD etiology and in antidepressant treatment response (Johansen-Berg et al., 2008; Mayberg, 2009). The significance of elevated ACC theta activity in MDD is somewhat ambiguous though it may reflect compensatory activity increases in frontal midline structures (Pizzagalli, 2011). Increased activity in and connectivity between these structures may be associated with increased rumination associated with MDD (Zhu et al., 2011).

Following the assessment of baseline EEG profiles in depressed males and females, the predicative utility of specific resting electrocortical indices to antidepressant treatment response was probed. Regarding alpha power, more responders exhibited high baseline $alpha_2$ power, while more non-responders were characterized by low power. Given that power in the $alpha_2$ sub-band was most consistently altered in resting baseline brain activity profiles in MDD, it is perhaps not surprising that it was most useful in characterizing treatment response. This finding suggests that cortical hypoarousal predicts a positive response outcome, regardless of specific antidepressant treatment or site of assessment, since increased alpha power was noted in both frontal and posterior regions. Thus, cortical hypoarousal in MDD may benefit from the stimulating/stabilizing effects of antidepressant pharmacotherpaies, though direct comparisons between antidepressants from various drug classes on cortical activity are lacking. This diffuse cortical hypoactivity in eventual treatment responders appears to accompany the more specific patterns of cortical hypoactivity in MDD previously discussed (i.e., right parietotemporal and left frontal hypoactivity).

Greater early (within a week) alpha power decreases were also associated with a favorable antidepressant response. This finding is notable as it suggests that relatively early changes in electrocortical activity may predict treatment outcome, though behavioral changes/symptom alleviation may not always emerge at such short periods

(though we noted greater clinical changes in responders versus non-responders after a week of treatment). Clinically, it may be prudent to assess if alpha power decreases (versus increases) occur within a week of antidepressant treatment initiation. Presumably, if alpha decreases rapidly and is accompanied by decreases in clinical scores (or at least no increases in depressive symptoms), this bodes well for a positive antidepressant outcome. If alpha power increases are noted shortly after treatment commencement this may indicate that a positive antidepressant response is unlikely and that accelerated dosing, a switch in antidepressant regimens and/or adjunct medication administration may be warranted. Future work should probe if the directionality of clinical and electrophysiological changes is opposite (i.e., mood worsens but alpha power decreases, or vice versa), which out of the two measures is more likely to predict eventual antidepressant response.

Responders also exhibited frontal $alpha_1$ asymmetry profiles reflecting increased left frontal activity and shifts towards this profile following a week of antidepressant treatment; non-responders exhibited opposite early alpha asymmetry profile shifts (i.e., towards decreased left fronto-cortical activity). This finding was also notable, as no known previous research has examined the predictive utility of frontal asymmetry or changes in asymmetry in antidepressant treatment outcome. Furthermore, these findings indicate that frontal alpha asymmetry may be less trait-like than is sometimes proposed. Though relatively stable resting frontal asymmetry profiles have been reported, some work indicates that it can be influenced by state affect (e.g. Papousek et al., 2011). Our results regarding pharmacotherapy-induced alterations in frontal asymmetry are consistent with the findings of Segrave et al., (2011), who noted that increased left cortical activity was associated with antidepressant use. Finally, we also found that with chronic antidepressant treatment, weak frontal and moderate posterior alpha asymmetry stability existed. Collectively, these results indicate that antidepressant pharmacotherapies and/or resultant mood changes are associated with modulating alpha asymmetry profiles.

When broken down by treatment, only ESC responders versus non-responders

exhibited high baseline frontal and parietal alpha$_2$ power as well as early decreases in frontal alpha$_2$ power. This suggests that these indices may be most consistently associated with a positive outcome to antidepressants that directly target the 5-HT system, which is known to be implicated in modulating cortical arousal/activation, though likely via involvement of other neurotransmitter systems (Monti, 2011). However, given that ESC+BUP administration has been pre-clinically associated with increasing 5-HT firing rates faster than monotherapies, we expected the most pronounced electrocortical differences to emerge with this treatment regimen. Additionally, one recent study has noted that high posterior alpha power was predictive of positive outcome with SSRI+BUP treatment (Tenke et al., 2011). However, given that the ratio of responders to non-responders in the dual treatment group was unbalanced, this may have contributed to the lack of predictive utility in early alpha alterations in the dual treatment group. The lack of BUP-induced early changes in alpha power in responders/non-responders may be associated with its different mechanisms of action relative to SSRIs, though two-week administration of BUP in healthy adults was previously shown to induce alpha power reductions (Siepmann et al., 2005).

Consistent with our findings indicating no distinction between the MDD versus control group in midline frontal theta power, no differences existed between responders/non-responders in Fz baseline theta power, inconsistent with the findings of Spronk et al., (2011). Baseline ACC-localized theta activity also did not differentiate responders/non-responders when treatment groups were collapsed, conflicting with a growing body of literature indicating that greater baseline ACC theta activity exists in antidepressant treatment responders. No obvious explanation for this discrepancy exists, though it is feasible that a handful of outliers may have contributed to these null findings. However, greater early decreases in $HAMD_{17}$ ratings were found in individuals with high versus low baseline sgACC theta$_1$ activity; an observation that may have clinical utility in a similar manner as the association between early alpha decreases and eventual treatment response. However, incorporating the assessment of ACC-localized theta activity into routine psychiatric practice to aid in tracking and predicating treatment effectiveness

would likely be more complicated than assessment of scalp-derived alpha power to accomplish the same aim. Though the availability and utility of EEG source localization methods (e.g. sLORETA and BESA) is increasingly routine, these methodologies nevertheless require a certain level of technical expertise. However, it is possible that, with time, greater automation of source-localization techniques may occur thereby allowing EEG technologists/clinicians to rapidly pre-process EEG data and extract relevant indices with minimal training and time burdens.

When broken down by treatment, more BUP responders had high baseline ACC theta, especially in the rACC, while more non-responders exhibited low baseline theta. Given that the r/sgACC is implicated in emotive processing and cognitive control, elevated theta-indexed ACC activity in MDD may reflect compensatory activity in frontal networks comprising of the ACC, which may be a prerequisite for positive treatment outcome (Pizzagalli et al., 2011), in this case to BUP. As discussed in Chapter 3, it seems unlikely that high baseline ACC theta activity would solely characterize BUP responders, as similar findings have been noted with other drugs (Pizzagalli et al., 2001; Mulert et al., 2007; Korb et al., 2011). BUP responders were also characterized by greater early decreases in ACC theta$_2$ activity, perhaps reflecting rapid stabilization in frontal network activity; ESC+BUP responders, however, exhibited early increases in ACC theta activity. These varying results may be associated with different fronto-cortical activity modulations accompanying the combination versus BUP treatments. However, the early ACC theta$_2$ increase in ESC+BUP responders may be spurious given the aforementioned unbalanced numbers of responders/non-responders and that, overall, theta activity decreased with treatment from baseline to week 1, regardless of response.

Though EEG recordings are routinely conducted in patients taking certain antipsychotic medications and in the context of attention-deficit hyperactivity disorder, for instance, we suggest incorporating them in the assessment of patients with MDD. Specifically, EEG recordings should be carried out before commencing antidepressant pharmacotherapy and shortly thereafter. Evaluating relative left fronto-cortical hypoactivity and increased overall alpha power, which can be obtained from relatively

short resting EEG recordings and which require relatively limited pre- and post-processing of EEG data, may be clinically useful in aiding with MDD assessment (particularly in complex clinical profiles) and/or in steering treatment selection.

7.3 The LDAEP and AEPs in MDD and the utility of the LDAEP in predicting antidepressant response: A critical summary

The most robust finding stemming from the examination of intensity-derived auditory evoke potentials (AEPs) and loudness dependence of AEPs (LDAEP) slopes was increased cortical resource allocation to auditory stimuli and speeded processing of moderately intense sounds in females compared with males. Subtle, sex-specific differences characterized the MDD group, with smaller N1 and N1/P2 amplitudes noted in MDD versus control males. If we espouse the idea that enhanced/efficient 5-HT DRN firing is associated with smaller AEPs, these results may index greater cortical inhibitory 5-HT neurotransmission in MDD males. However, given the mixed clinical evidence for an inverse relationship between 5-HT activity and intensity-dependent AEPs, as well as research indicating the involvement of other neurotransmitter systems in the relationship, this interpretation is likely too simplistic. Furthermore, 5-HT neurotransmission has been inversely related with LDAEP slopes as well as AEPs to the highest intensities, which are most likely to evoke increased (inhibitory) 5-HT neuron firing, and less so with AEPs averaged across intensities. Finally, some, albeit limited, evidence suggests that auditory processing disturbances may exist in MDD (Canbeyli et al., 2010). As such, lower AEPs in depressed males may simply reflect this, though individuals with significant hearing loss were not included in the study. We also noted increased P2 latencies in MDD versus control females, which may reflect delayed/impaired processing of auditory sensory information in depressed females.

Consistent with some reports (Oliva et al., 2011), steeper LDAEP slopes were noted in females, and may reflect baseline differences in 5-HT neurotransmission between the sexes (Nishizawa et al., 1997; Okazawa et al., 2000; Sakai et al., 2006).

However, it is also feasible that varying levels of other neurotransmitters (or a difference in the balance between excitatory/inhibitory neurotransmitters) may contribute to these LDAEP sex differences. In line with other clinical work, no differences in the LDAEP (either scalp- or sLORETA-derived) between the MDD versus control group were found. This indicates that depressed individuals do not categorically display altered neurotransmission, including 5-HT activity, implicated in dampening/modulating cortical hyper-activation to tones of increasing intensity.

Assessment of scalp- versus sLORETA-derived AEPs and LDAEP slopes yielded somewhat different findings. Specifically, the subtle group differences evident with scalp-derived AEPs did not emerge with sLORETA-derived ones. As such, caution should be applied when drawing inferences regarding scalp versus source-localized LDAEPs, as they do not appear to reflect identical brain activity. Curiously, we noted a negative relationship between baseline P2 LDAEP-sLORETA and pretreatment MADRS scores. While this may indicate that more effective 5-HT neurotransmission (indexed by shallow slopes) is associated with increased depression scores, this explanation is contrary to our hypotheses and previous research. While several explanations for these unexpected findings are presented in Chapter 4, another interpretation may be that other clinical features (e.g. anxiety) mediated this relationship. It is also feasible that this may simply reflect attenuated auditory processing in more severe MDD, though these explanations warrant further scrutiny.

With respect to the predictive utility of the LDAEP in treatment response, only the N1 (versus P2 or N1/P2) sLORETA LDAEP baseline slope was sensitive to eventual treatment outcome, consistent with some precedent research (Linka et al., 2004; 2005; 2009). As discussed in Chapter 5, limited rationale exists as to which of the N1, P2 or N1/P2 LDAEP slopes may be most sensitive in predicting treatment outcome. The fact that scalp-localized LDAEP slopes predicted treatment response to a lesser extent than sLORETA-derived ones was somewhat unexpected and inconsistent with the reported utility of scalp-derived LDAEP slopes in response prediction (Paige et al., 1995; Linka et al., 2004; Lee et al., 2005; Mulert et al., 2007). These findings suggest that the LDAEP

derived specifically from primary cortex activity is superior in predicting antidepressant outcome likely because the primary auditory cortex receives dense 5-HT DRN innervation (relative to the secondary auditory cortex). Thus, LDAEP-sLORETA slopes may correlate with 5-HT activity more specifically and be most predicative of treatment outcome compared with scalp-derived ones. Additionally, P2 LDAEP-sLORETA slope decreases from baseline to week 1 existed in non-responders, while increases existed in responders. Similarly to findings of relatively rapid decreases in ACC theta and alpha power, this LDAEP change may reflect modulated neurotransmission and associated alterations in cortical activity shortly after treatment initiation. This rapid neuroadaptive response may be a hallmark in positive antidepressant outcome.

Consistent with the overall results, ESC and BUP responders exhibited steep baseline N1 sLORETA-LDAEP slopes while non-responders were characterized by shallow ones. Both drugs eventually increase 5-HT neural firing, thus, it seems reasonable that steep baseline LDAEPs slopes, reflecting inefficient 5-HT neurotransmission, would predict a positive response to both. However, given pre-clinical evidence indicating synergistic activity of BUP+ESC on 5-HT neural firing, it is surprising that steep baseline LDAEP slopes did not also predict a positive response to this regimen. Again, this null finding may be related to sample size issues. Unexpectedly, early increases in scalp N1/P2 LDAEP slopes in ESC+BUP responders were noted while decreases existed in non-responders. It is feasible that increased slopes may reflect a specific alteration in cortical neurotransmitter activity to a treatment regimen with multiple mechanisms of action, which may be associated with an eventual treatment response. Shallower slopes may reflect a somewhat different neurochemical environment shortly after treatment commencement, one that may be less conducive to positive outcome. However, this interpretation is tenuous and requires further investigation with larger sample sizes.

In conclusion, it appears that no one electrophysiological index is markedly more superior then another in predicting antidepressant treatment outcome. After all, both resting alpha power and specific LDAEP slope measures differentiated eventual

treatment responders/non-responders with comparable sensitivity and specificity. The probed electrophysiological indices were not particularly sensitive in predicting response to a particular antidepressant regimen, though resting baseline ACC theta activity only predicted outcome to BUP treatment while ESC treatment responders/non-responders were most consistently distinguished with resting alpha activity; N1 LDAEP-sLORETA slope distinguished responders/non-responders for both BUP and ESC. Response outcome to ESC+BUP treatment tended to be associated with early changes in electrophysiological indices; the directionality of these changes in ESC+BUP responders tended to be in the opposite direction as for the monotherapy responders, though the validity of this finding is questionable. A composite electrophysiological index, comprised of several z-transformed electrophysiological markers, may prove to be most sensitive in predicating treatment response. From a practical perspective, however, it is likely easier to probe resting alpha power profiles in a clinical setting to assist with antidepressant treatment outcome prediction. After all, unlike LDAEP-sLORETA slopes, resting alpha power does not require source-localization analysis or the administration of auditory stimuli, extraction of AEPs and construction of the LDAEP-sLORETA slope.

7.4 Temporal ERP profile to emotive facial expression processing in MDD: A critical summary

The last study comprising this thesis probed the purported mood-congruent processing bias and/or hyposensitivity to positive (and perhaps emotive) information in MDD. Consistent with the idea that depressed individuals exhibit a negative processing bias, they rated emotive faces as sadder overall than controls. Females were found to typically exhibit larger ERPs with shorter latencies than males, indicating enhanced and speeded pre- and conscious facial expression processing, regardless of group. Enhanced sensitivity in females to socially relevant emotive information may be associated with the increased incidence of MDD in females as well as the varying symptom profiles and depression severity sometimes reported between the sexes (Smith et al., 2008). Though

only subtle differences emerged between the groups in the facial expression processing task, this study provided a comprehensive temporal profile (spanning pre- to conscious processing) of electrocortical activity associated with emotive face processing, which was lacking from the literature. In brief, P1 assessments indicated "automaticity" in early, preconscious perceptual processing of positive expressions, while N1 facial expression modulations interacted with sex. The face-sensitive N170 was maximal to highly arousing (intensely joyful faces), while the related VPP was greatest to intense emotive expressions. Conversely, the P2/N2 were maximal to less intense facial expressions, perhaps reflecting increased processing of more ambiguous emotive information. The attention-sensitive P3 was greatest to sad faces, indicating that informative social cues preferentially capture attention resources; similar findings were noted for the LPP, reflecting more sustained conscious processing.

Despite subtle between-group differences suggesting attenuated cortical resource allocation in later-stage perceptual processing of emotive information in MDD as well as longer preconscious processing of sad expressions, the potential utility of ERPs during emotive processing in characterizing MDD and in predicting antidepressant treatment outcome should not be discounted. Assessing ERPs to specific facial expressions before and during initial treatment periods may prove to be useful in predicting clinical response and future work should assess this.

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APPENDIX A

Hamilton rating scale for depression, version 17 ($HAMD_{17}$)

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name

Date of Assessment

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)
   _____
   0= Absent
   1= These feeling states indicated only on questioning
   2= These feeling states spontaneously reported verbally
   3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
   4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**
   _____
   0= Absent
   1= Self reproach, feels he has let people down
   2= Ideas of guilt or rumination over past errors or sinful deeds
   3= Present illness is a punishment. Delusions of guilt
   4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**
   _____
   0= Absent
   1= Feels life is not worth living
   2= Wishes he were dead or any thoughts of possible death to self
   3= Suicidal ideas or gesture
   4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**
   _____
   0= No difficulty falling asleep
   1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
   2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**
   _____
   0= No difficulty
   1= Patient complains of being restless and disturbed during the night
   2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. **INSOMNIA LATE**
   _____
   0= No difficulty
   1= Waking in early hours of the morning but goes back to sleep
   2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**
   _____
   0= No difficulty
   1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3= Decrease in actual time spent in activities or decrease in productivity
   4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   _____
   0= Normal speech and thought
   1= Slight retardation at interview
   2= Obvious retardation at interview
   3= Interview difficult
   4= Complete stupor

9. **AGITATION**
   _____
   0= None
   1= Fidgetiness
   2= Playing with hands, hair, etc.
   3= Moving about, can't sit still
   4= Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**
    _____
    0= No difficulty
    1= Subjective tension and irritability
    2= Worrying about minor matters
    3= Apprehensive attitude apparent in face or speech
    4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)
    _____
    0= Absent
    1= Mild
    2= Moderate
    3= Severe
    4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0**= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0**= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0**= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____ **0**= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____ **0**= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____ **0**= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____ **0**= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____ **0**= Absent
1= Mild
2= Severe

Total Score _____

APPENDIX B

Montgomery-Åsberg depression rating scale (MADRS) questionnaire

Name:_____ Date:_____

Montgomery-Asberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. ***Apparent Sadness***
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.
0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

2. ***Reported Sadness***
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3. ***Inner Tension***
Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
0 Placid. Only reflecting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

4. ***Reduced Sleep***
Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.
0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

5. ***Reduced Appetite***
Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat.

6. ***Concentration Difficulties***
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great initiative.

7. ***Lassitude***
Representing a difficulty getting started or slowness initiating and performing everyday activities.
0 Hardly no difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. ***Inability to Feel***
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interest.
3
4 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. ***Pessimistic Thoughts***
Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.
0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. ***Suicidal Thoughts***
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.
0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score:_____

APPENDIX C

Modified non-patient version of the structured clinical interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR diagnoses (SCID-IV-I/NP) screen

Date: _____ ID:_____ Session:_____

DUAL TREATMENT STUDY (ADULT DEPRESSION)

Screening Questionnaire:

Date: _____ ID#: _____

Name: _____ Age: _____ DOB (dd/mm/yy): _____

Handedness: *Left* / *Right* Normal hearing: *Y* / *N* Vision: *Normal* / *Corrected*

Smoker:_____ Years smoking: _____ # of cigarettes / day: _____

Telephone: (h) _____ I _____ (w) _____
E-mail:_____

EXCLUSION CRITERIA

- Are you currently on medication on a regular basis for any physical condition (e.g. pain)? _____
- Do you have high blood pressure? _____
- Do you have diabetes? _____
- Do you have allergies? _____
- Have you been diagnosed with a cardiac or respiratory condition? _____
- Have you had a head or brain injury in the past 6 months? _____
  If yes, did you lose consciousness for one or more hours? _____
- Do you have a brain disorder, like epilepsy? _____
- What is your daily (or weekly) alcohol consumption? _____

- Do you use street drugs? _____
  If yes: How often? _____
- Have you ever been treated for drug or alcohol abuse? _____

NOTES

SCID-Adapted Screening Questions

- Have you ever sought treatment or been treated for emotional or psychiatric problems?

NO YES: _____

If YES: What for? Did you obtain any treatment?

_____

- Have you ever sought treatment or been treated for drug or alcohol abuse?

NO YES: _____

What is your daily (or weekly) alcohol consumption? _____

- Do you use street drugs? (e.g. marijuana, cocaine)

NO YES: _____

If YES: What kind(s)? How Often?

_____

MOOD EPISODES

Depressive

- Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?

NO YES: _____

- …what about losing interest or pleasure in things you usually enjoy?

NO YES: _____

(Skip the following if NO)

If YES: How long did this period last? _____

If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?

NO YES: _____

Manic

- Has there been a period of time when you were feeling so good, excited, or hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?

NO YES: _____

(Skip the following if NO)

If YES: How long did this period last? _____

If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs?

NO YES: _____

ANXIETY DISORDERS

Panic

- Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?

NO YES: _____

(Skip the following if NO)

If YES: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable?

NO YES: _____

If YES: Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

Agoraphobia

- Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?

NO YES: _____

(Skip the following if NO)

If YES: What were you afraid would happen?

Does participant mention anxiety about being in place/situation from escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

NO YES: _____

If YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

Social Phobia

- Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

NO YES: _____

(Skip the following if NO)

If YES to "Public Speaking": Do you think that you are more uncomfortable than most people who are in a similar situation?

NO YES: _____

IF YES: What were you afraid would happen?

_____

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

NO YES: _____

IF YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

GAD

- In the last six months, have you been particularly nervous or anxious?

NO YES: _____

(Skip the following if NO)

IF YES: What do you worry about? _____

- During the past six months, would you say that you are worrying more often than not?

NO YES: _____

- When you are worrying, do you find it difficult to stop?

NO YES: _____

- When you're feeling anxious or nervous, do you feel:

___Restless ___Frequently tired ___Trouble concentrating/Mind goes blank ___Irritable
___Tense muscles ___Sleep disturbance
(3 of the above must be present)

PSYCHOTIC SYMPTOMS

Delusions

- Has it ever seemed like people were talking about you or taking special notice of you?

NO YES: _____

(Skip the following if NO)

If YES: Were you convinced they were talking about you or did you think it might have been your imagination?

NO YES: _____

- What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?
  NO YES: _____

- What about anyone going out of their way to give you a hard time, or trying to hurt you?
  NO YES: _____

- Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?
  NO YES: _____

- Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?
  NO YES: _____

Auditory Hallucinations

- Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?)
  NO YES:_____

(Skip the following if NO)
If YES: What did you hear? How often did you hear it?
_____
If VOICES: Did they comment on what you were doing or thinking? _____
How many voices did you hear? Were they talking to each other?_____

Visual Hallucinations

- Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?)

NO YES:_____

Other Symptoms
(The following items are rated based on observations)
Catatonic behaviour, Grossly disorganized behaviour, Grossly inappropriate affect or Disorganized speech
NO YES:_____
Affective flattening
NO YES:_____

APPENDIX D

Beck depression inventory-II (BDI-II) questionnaire

1. Sadness:
0 I do not feel sad.
1 I feel sad much of the time.
2 I feel sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism:
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure:
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure:
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings:
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel guilty most of the time.
3 I feel guilty all the time.

6. Punishment Feelings:
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike:
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness:
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes:
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying:
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation:
0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

13. Indecisiveness:
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficult in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness:
0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy:
0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern:
0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability:
0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite:
0 I have not experienced any changes in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty:
0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue:
0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex:
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Total____(sum)

APPENDIX E

Modified family interview for genetic studies (FIGS) questionnaire

FIGS
11-Feb-1999

FIGS: GENERAL SCREENING QUESTIONS

Interview date: ___ ___ – ___ ___ – ___ ___ ___ ___
Month Day Year

Use One Per Informant

Family last name: _____ Family ID Number: ___ ___ ___ ___

Informant name: _____ ___ _____ ID: ___ ___ ___ ___ ___
First MI Last

INTERVIEWER: Before you begin, you need to generate or obtain a pedigree on which to record all of the responses to the following General Screening Questions. (See FIGS Manual for details.)

Step 1: *Let's go over your family tree*. (Include spouse and his/her parents and siblings, offspring, parents, siblings, aunts, uncles, cousins, grandparents, as well as any other relatives the informant can recall.)

Step 2: *Now I am asking you to keep in mind all those in your family tree as I go through this list of questions*. (Note all positive responses on the pedigree.)

Was anyone adopted?

Was anyone mentally retarded?

Did anyone:

Have problems with their nerves or emotions? Take medicine or see a doctor for it? Take lithium?

Feel very low for a couple of weeks or more, or have a diagnosis of depression?

Attempt or complete suicide?

Seem overexcited (or manic) day and night, or have a diagnosis of mania?

Have visions, hear voices, or have beliefs that seem strange or unreal?

Have unusual or bizarre behavior, or have a diagnosis of schizophrenia?

Have trouble with the police, with completing school, or with keeping a job?

Have alcohol or drug use that caused problems (with health, family, job, or police)? Go to AA or NA, or have treatment for this?

(Was anyone) hospitalized for psychiatric problems, or for drug or alcohol problems?

Have inherited medical diseases such as Huntington's disease or seizure disorder or any other disorders of the brain or nervous system?

(Did anyone) have few friends, or seem to be a loner?

(Did anyone) seem odd or eccentric in behavior or appearance?

(Was anyone) extremely jealous, or suspicious, or believe in magic, or see special meanings in things that no one else saw?

APPENDIX F

Profile of Mood States (POMS) Questionnaire

NAME _____ DATE _____

SEX: Male (M) Female (F)

IDENTIFICATION

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

Col (C) O.P. (O)

	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1. Friendly	0	1	2	3	4
2. Tense	0	1	2	3	4
3. Angry	0	1	2	3	4
4. Worn out	0	1	2	3	4
5. Unhappy	0	1	2	3	4
6. Clear-headed	0	1	2	3	4
7. Lively	0	1	2	3	4
8. Confused	0	1	2	3	4
9. Sorry for things done	0	1	2	3	4
10. Shaky	0	1	2	3	4
11. Listless	0	1	2	3	4
12. Peeved	0	1	2	3	4
13. Considerate	0	1	2	3	4
14. Sad	0	1	2	3	4
15. Active	0	1	2	3	4
16. On edge	0	1	2	3	4
17. Grouchy	0	1	2	3	4
18. Blue	0	1	2	3	4
19. Energetic	0	1	2	3	4
20. Panicky	0	1	2	3	4
21. Hopeless	0	1	2	3	4
22. Relaxed	0	1	2	3	4
23. Unworthy	0	1	2	3	4
24. Spiteful	0	1	2	3	4
25. Sympathetic	0	1	2	3	4
26. Uneasy	0	1	2	3	4
27. Restless	0	1	2	3	4
28. Unable to concentrate	0	1	2	3	4
29. Fatigued	0	1	2	3	4
30. Helpful	0	1	2	3	4
31. Annoyed	0	1	2	3	4
32. Discouraged	0	1	2	3	4
33. Resentful	0	1	2	3	4
34. Nervous	0	1	2	3	4
35. Lonely	0	1	2	3	4
36. Miserable	0	1	2	3	4
37. Muddled	0	1	2	3	4
38. Cheerful	0	1	2	3	4
39. Bitter	0	1	2	3	4
40. Exhausted	0	1	2	3	4
41. Anxious	0	1	2	3	4
42. Ready to fight	0	1	2	3	4
43. Good natured	0	1	2	3	4
44. Gloomy	0	1	2	3	4
45. Desperate	0	1	2	3	4
46. Sluggish	0	1	2	3	4
47. Rebellious	0	1	2	3	4
48. Helpless	0	1	2	3	4
49. Weary	0	1	2	3	4
50. Bewildered	0	1	2	3	4
51. Alert	0	1	2	3	4
52. Deceived	0	1	2	3	4
53. Furious	0	1	2	3	4
54. Efficient	0	1	2	3	4
55. Trusting	0	1	2	3	4
56. Full of pep	0	1	2	3	4
57. Bad-tempered	0	1	2	3	4
58. Worthless	0	1	2	3	4
59. Forgetful	0	1	2	3	4
60. Carefree	0	1	2	3	4
61. Terrified	0	1	2	3	4
62. Guilty	0	1	2	3	4
63. Vigorous	0	1	2	3	4
64. Uncertain about things	0	1	2	3	4
65. Bushed	0	1	2	3	4

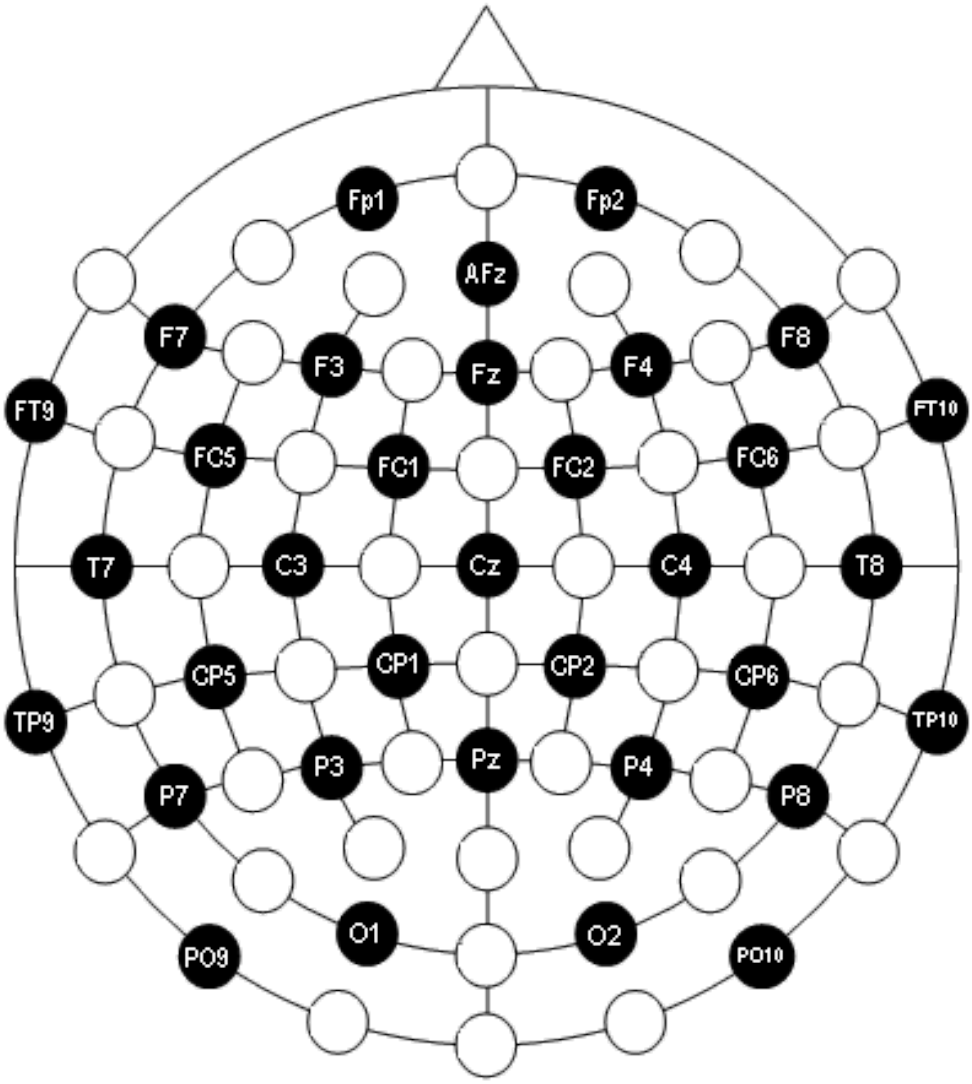
MAKE SURE YOU HAVE ANSWERED EVERY ITEM.

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APPENDIX G

32-channel electrode montage



APPENDIX H

Supplementary Table 1.1 Montreal Neurological Institute coordinates of the standardized low-resolution brain electromagnetic tomography (sLORETA) regions of interests (ROIs: BA 32, BA 25 and BA 24ab; Anterior Cingulate Cortex [ACC] ROI)

Regions of Interest	Left Hemisphere x, y, z	Midline x, y, z	Right Hemisphere x, y, z
TableBA 32	-20 45 10	0 45 0	5 20 -10
	-15 45 -5	0 50 0	5 25 -10
	-15 45 0	0 40 10	5 30 -10
	-15 45 10	0 45 10	5 35 -10
	-10 35 -10		5 40 -10
	-10 35 -5		5 35 -5
	-10 45 -5		5 40 -5
	-10 45 0		5 45 -5
	-10 45 5		5 35 0
	-10 45 10		5 40 0
	-5 20 -10		5 45 0
	-5 25 -10		5 50 0
	-5 30 -10		5 40 5
	-5 35 -10		5 40 10
	-5 40 -10		5 45 10
	-5 35 -5		10 20 -10
	-5 40 -5		10 35 -10
	-5 45 -5		10 35 -5
	-5 35 0		10 45 -5
	-5 40 0		10 45 0
	-5 45 0		10 45 5
	-5 50 0		10 45 10
	-5 40 5		15 45 -5
	-5 45 10		15 45 5
			15 45 10
			20 45 10
BA 25	-5 15 -10	0 5 -10	5 10 -10
	-5 20 -5	0 10 10	5 15 -10
		0 15 -10	5 5 -5
		0 0 -5	5 20 -5
		0 5 -5	
		0 10 -5	
BA 24ab	-5 25 -5	0 35 10	5 25 -5
	-5 30 -5	0 30 15	5 30 -5
	-5 30 0		5 30 0
	-5 35 5		5 35 5
	-5 35 10		5 35 10
	-5 25 15		5 25 15
	-5 30 15		5 30 15
ACC ROI (BA 10, 24, 32)	-10 45 -5	0 45 0	5 40 -5
	-10 45 5	0 50 5	5 45 -5
	-5 45 -5		5 35 5
	-5 40 -5		5 40 5
	-5 35 5		10 35 -5
			10 40 -5
			10 45 -5
			10 50 -5
			10 55 -5
			10 50 0
			10 45 5

Appendix I

The temporal electrocortical profile of emotive facial processing in depressed males and females and healthy controls (published manuscript in *Affective Disorders*)
Constitutes pages 177-186

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Preliminary communication

The temporal electrocortical profile of emotive facial processing in depressed males and females and healthy controls

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ABSTRACT

Background: Previous work indicates that emotive processing, such as of facial expressions, may be altered in major depressive disorder (MDD). Individuals with MDD tend to exhibit a mood-congruent processing bias, though MDD may also be characterized by blunted emotive processing in general. Females tend to exhibit enhanced facial emotive processing than males. Few groups have examined the temporal electrophysiological event-related potential (ERP)-indexed profiles, spanning preconscious to sustained, conscious processing of facial expressions in MDD; systematic comparisons of ERPs to emotive stimuli between depressed males and females are also lacking.
Methods: This study examined the temporal ERP profile to a simple expression recognition task in depressed adult males and females (N = 52; 29 females) and controls (N = 43; 23 females).
Results: The MDD group rated facial expressions as sadder overall than controls. Females exhibited enhanced and speeded pre- and conscious face processing than males. Subtle group differences emerged to specific expressions at mid-latency ERPs (N2, P2) indicating both blunted late pre-conscious perceptual processing of expressions and prolonged processing of intensely sad faces.
Limitations: A more involved emotive processing task, employing threatening faces, may have revealed more robust group ERP differences. Menstrual cycle should also be controlled for in future work.
Conclusions: This is the first study to systematically assess the temporal ERP profile, including of ERPs preceding the face-sensitive N170/VPP, to expressions in MDD. Overall, early perceptual and late conscious expression processing did not differ fundamentally between groups. Altered emotive processing may be a candidate index for monitoring and predicting antidepressant treatment outcome.

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1. Introduction

The identification and effective processing of facial expressions are critical for successful emotional communication and in regulating social interactions. Therefore, preferential recruitment of attentional resources and enhanced pre-conscious processing of faces and associated expressions versus non-face stimuli is likely. Negative expressions are most effective in interfering with on-going tasks and in recruiting attention (Mathews et al., 2004), likely because they convey critical information for effective interpersonal interactions and, more broadly, for survival.

In accordance with cognitive theories proposing that major depressive disorder (MDD) is associated with a

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mood-congruent processing bias (Kovacs and Beck, 1978), depressed individuals have shown enhanced memory and attention for sad expressions, and interpret neutral faces more negatively than controls (Gollan et al., 2008; Leppänen et al., 2004). This bias may extend to all negative expressions, such as fear and anger (Bouhuys et al., 1999; Leyman et al., 2007). However, some research also indicates that there may be blunted processing of all emotive information in MDD (Gur et al., 1992; Leppänen et al., 2004). Thus, MDD may be associated with reduced perceptual sensitivity to positive expressions and more complex/sustained processing of negative ones (Gollan et al., 2008), though few studies demonstrate this clear double-dissociation. Mood-congruent biased emotive processing has also been noted in treated and remitted depressives (Bhagwagar et al., 2004; Savaskan et al., 2008) and has been correlated with symptom severity and less favorable recovery (Bouhuys et al., 1999; Hale, 1998).

The face-sensitive N170 is thought to reflect early visual processes implicated in identifying a stimulus as a face (Eimer and Holmes, 2007). Though some have found the N170 to be unaltered by expressions (Ashley et al., 2004; Santesso et al., 2008), others have. For instance, increased emotive intensities (Sprengelmeyer and Jentzsch, 2006) and expressions of anger and fear enhanced the N170 (Batty and Taylor, 2003; Krombholz et al., 2007; Stekelenburg and de Gelder, 2004), though previous work from our group found it to be increased to joyful versus neutral and sad faces (Jaworska et al., 2010). Similarly, the anterior face-sensitive vertex positive potential (VPP) has been shown to be more pronounced to negative versus neutral expressions (Foti et al., 2010; Luo et al., 2010; Sewell et al., 2008), though we found it to be enhanced to emotive (happy and sad) faces (Jaworska et al., 2012). Both N170 and VPP latencies also were decreased to positive expressions (Batty and Taylor, 2003; Jaworska et al., 2012). Thus, face-sensitive ERPs are enhanced to emotive expressions, while their latencies may be shortest to positive ones.

Evidence of rapid brain responses to and modulation by expressions (<170 ms) indicates that affect detection precedes face recognition (Eimer and Holmes, 2007). The posterior P1, thought to index preconscious attention allocation, appears to be modulated by emotive intensity (Turetsky et al., 2007; Utama et al., 2009). The P1 was found to be decreased to sad expressions (Turetsky et al., 2007), and its latency shortened to fearful ones (Lee et al., 2010). However, others found it to be unaltered by either emotive expressions or intensity (Degabriele et al., 2011). Although less frequently studied, the mid-anterior N1 was greater to fearful expressions (Luo et al., 2010), though another group reported no emotion-related N1 modulations (Rossignol et al., 2005).

Mid-latency ERPs (post-N170) appear to be influenced by facial expressions. The posterior P2, thought to reflect orientation to salient stimuli (Carretié et al., 2001), was attenuated by fearful and angry expressions (Schutter et al., 2004; Stekelenburg and de Gelder, 2004), though we previously found it to be increased to sad ones (Jaworska et al., 2010). The anterior N2, indexing attentional orienting, was enhanced by expressions (Balconi and Pozzoli, 2008), and has been shown to emerge earlier and be maximal for threatening faces (Kiss and Eimer, 2008; Liddell et al., 2004). The effects of facial expressions on the P3, reflecting conscious attention allocation, are mixed. While some have found its enhancement to fearful or happy faces (Liddell et al., 2004; Luo et al., 2010), others reported no P3 changes to expressions (Balconi and Lucchiari, 2005).

Finally, a handful of studies have investigated the effects of emotive facial processing on later ERPs (post-P3), such as the late positive potential (LPP), though to index conscious, elaborate and evaluative processing (Schupp et al., 2004). The LPP is preferentially elicited by negative expressions, such as fear and sadness (Orozco and Ehlers, 1998; Schupp et al., 2004; Van Strien et al., 2010) and intense versus mild and neutral faces (Jaworska et al., 2012) have been shown to preferentially evoke it.

Relatively few studies have investigated the temporal ERP profiles associated with facial expression processing in MDD. To date, there appears to be no published work on the influence of facial expressions on the N170 or ERPs that precede it in the disorder. One study examined the VPP to specific expressions in MDD versus control groups, but noted no differences (Foti et al., 2010). The few studies that have assessed mid-latency ERPs to facial processing in the context of depression have yielded inconsistent results (Cavanagh and Geisler, 2006; Deldin et al., 2000; Kayser et al., 2000). Studies examining slow wave ERPs (1–5 s) suggest that depressives exhibit more sustained processing of negative, and diminished processing of positive, expressions (Deveney and Deldin, 2004; Shestyuk et al., 2005). However, one group examining the LPP noted that it was increased to threatening faces in the control but not MDD group, suggesting blunted processing (or avoidance) of negative information.

As a final point, there is scant research probing sex effects on ERPs to facial expressions in MDD. This is despite evidence of a close relationship between emotional sensitivity and mood disturbance liability/disorders (Hofer et al., 2006), which are more prevalent in females (Parker and Brotchie, 2010). Furthermore, the dynamics of and neural activity to facial processing appears to differ between the sexes (Fusar-Poli et al., 2009), with females exhibiting enhanced/speeded facial encoding mechanisms than males (Felmingham et al., 2010; Lewin and Herlitz, 2002). The few studies that have assessed sex differences to expression-elicited ERPs have document increased ERPs in females (P1: Lee et al., 2010; Proverbio et al., 2006; P3: Yamamoto et al., 2000), suggesting greater cortical resource allocation to face processing (at various stages) in females. One study indicated that females exhibited greater N2 and P3 amplitudes to moderately negative images (not specifically faces) that were absent in males (Yuan et al., 2009).

Early- (anterior N1, posterior P1), mid- (anterior N2, posterior P2, P3) and late-latency (LPP) ERPs, as well as face-specific ERPs (N170, VPP) were examined to neutral and emotive expressions (non-target) as well as to target surprised faces in MDD males and females and healthy controls. ERPs were expected to be smaller to neutral versus emotive faces; greater intensities (100% expression) were predicted to be associated with larger ERPs. Early-mid latency ERPs were expected to be enhanced in females. In line with the mood-congruent processing bias, group differences to specific ERPs were expected to manifest as larger amplitudes (and perhaps shorter latencies) to sad expressions.

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However, it was also possible that smaller ERPs to emotive expressions (i.e., blunted processing) would emerge in MDD.

2. Methods

2.1. Patients

Fifty-three (N = 53) adults with a primary diagnosis of Major Depressive Disorder (MDD) were tested (Table 1). Patients were recruited from the Mood Disorders Research Unit at the University of Ottawa Institute of Mental Health Research Center. Patients were diagnosed by trained psychiatrists with the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR Diagnoses, Axis I, Patient Version (SCID-IV-I/P; First et al., 1997). The Hamilton Rating Scale for Depression, 17 and 29 item versions (HAMD-17/29; Hamilton, 1960) and the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) were also administered to index symptom severity. All patients had MADRS scores ≥22 at the time of study enrollment. Notable exclusion criteria were: Bipolar Disorder (BP-I/II or NOS) diagnosis, life-time history of psychosis, current (<6 months) drug/alcohol abuse/dependence (except nicotine/smoking), seizure history or increased seizure risk (e.g. brain trauma/lesion, pro-convulsant medication use), unstable medical condition (i.e., unstabilized for ≥3 months) and history of anorexia/bulimia. Patients at a significant risk for suicide were also excluded. No patients were taking antidepressants at the time of testing as they were enrolled in a clinical trial and were tested prior to starting study medication. Washout consisted of five times the t½ of medication(s) previously taken.

2.2. Control participants

Forty-three (N = 43) non-depressed, healthy controls were recruited and matched to patients on gender, age and education (Table 1). Controls were interviewed to ensure the absence of a personal psychiatric history and alcohol/drug abuse or dependence (assessed with a modified non-patient version of the SCID [SCID-IV-I/NP]), history of seizures, brain trauma or known brain lesion(s). Controls also completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) to assess for the existence and severity of depression symptoms and were included in the study only if they scored ≤13. Finally, only controls with no psychiatric history in first-degree relatives were included in this study (assessed with the Family Interview for Genetic Studies [FIGS]; Maxwell, 1992).

Table 1
Major depressive disorder (MDD) and control group characteristics and demographics (sexes collapsed).

	MDD (N = 53)	Control (N = 43)
Sex (female/male)	29/24	23/20
Age range	19–63	21–60
Age (M ± S.D.)	40.7 ± 11.8	36.5 ± 9.8
Education years (M ± S.D.)	16.0 ± 2.4	16.4 ± 1.9
HAMD-17 (M ± S.D.)	20.9 ± 5.2	–
HAMD-29 (M ± S.D.)	31.1 ± 6.2	–
MADRS (M ± S.D.)	30.8 ± 5.4	–
BDI-II (M ± S.D.)	–	3.7 ± 4.8
Ethnicity	48 Caucasian; 3 Asian; 1 South Asian; 1 African	39 Caucasian; 1 Asian; 2 South Asian; 1 African

HAMD-17/29: Hamilton Rating Scale for Depression, 29 and 17 item versions; MADRS: Montgomery-Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory-II.

2.3. Testing session procedures

Prior to testing, participants abstained for >3 h from caffeine and/or smoking/nicotine, as well as from alcohol/drugs (other than contraceptives and medication required for a stabilized physical condition) beginning at midnight. Upon arrival to the laboratory, subjective mood evaluations were carried out. Concurrently, electrodes were applied, after which the experiment commenced. This study was approved by the Royal Ottawa Health Care Group and the University of Ottawa Social Sciences and Humanities Research Ethics Boards and informed consent was obtained from all participants. Participants were compensated $30.00 CDN/session (patients participated in multiple sessions as part of a larger study).

2.4. Subjective mood questionnaires

Mood was assessed with the Profile of Mood States (POMS; McNair et al., 1992) on which participants rated their subjective state using a Likert scale on 65 mood adjectives, from which values were aggregated to form seven mood dimensions (tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, confusion–bewilderment and total mood disturbance).

2.5. Emotional faces recognition task

The faces recognition task was adapted from Krolak-Salmon et al. (2001). Thirty-six photographic faces displaying one of four expressions (sadness [sad], joy, surprise [sur], neutral) were presented individually on a screen in front of the seated participant (~1 m) in a dim, electrically-shielded and sound-attenuated room. Each emotion was expressed at three intensities (20%, 50%, 100%) by one actor. Two males and two females displayed one emotion at all intensities (i.e., 16 actors). Expressions at 20% intensity were considered "neutral" as they are not reliably distinguished (Orgeta and Phillips, 2008) and 0% expressions are more likely to be confused with negative than with other facial expressions (Palermo and Coltheart, 2004). Photographs were digitized and converted to gray-scale images, matched for luminance and contrast, with the neck and hair cropped out (Fig. 1).

Each expression (neutral, sad50, sad100, joy50, joy100, sur50, sur100) was pseudo-randomly presented 80 times (no identical faces presented back-to-back) for 400 ms (ISI: 1500 ms; Presentation Software, Neurobehavioral Systems, Albany, CA, USA). Participants pressed a button to surprised faces (sur50, sur100) to ensure that they paid attention to expressions. Hits (% correct responses to sur50 and sur100), false alarms (FA; % responses to non-surprised faces) and reaction times (RT) were recorded.

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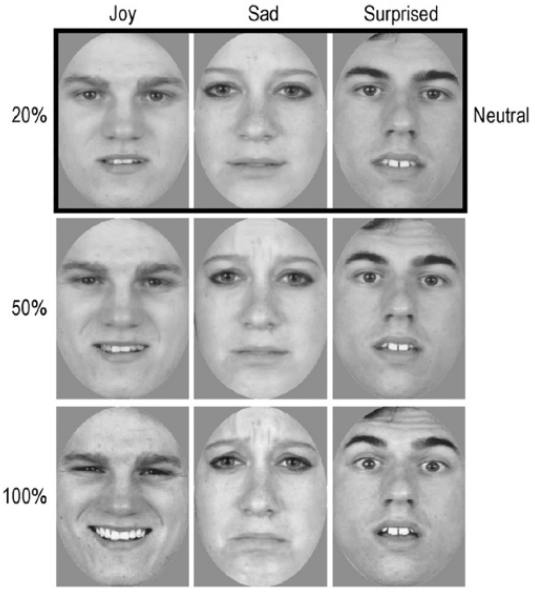


Fig. 1. Examples of facial stimuli.

2.6. Facial expression rating questionnaire

After the task, participants rated 10 faces (one male and one female expressing each of joy50, joy100, sad50, sad100 and neutral) presented during the task. Faces were rated using a Likert scale from 0 (not at all) to 10 (very much) on two valence questions: how 1) "sad" and 2) "happy" does the face look. Participants rated the faces based on their gut reaction, taking 2–3 min to rate all faces. Two questionnaire versions, containing different faces but bearing the same expressions, were administered. No differences existed between the versions, thus, ratings were averaged across the questionnaires.

2.7. Electrophysiological recordings and data reduction

EEG activity was recorded (500 Hz) using a cap embedded with 32 Ag/AgCl electrodes (EasyCap, Herrsching-Breitbrunn, Germany) positioned according to the 10–10 system (Chatrian et al., 1985). Additional electrodes on the supraorbital ridges and external canthi of the eyes monitored electrooculographic (EOG) activity. An AFz electrode served as the ground. Impedance was maintained at ≤5 kΩ and EEG activity was recorded with an amplifier bandpass filter set at 0.1–80 Hz (BrainVision Recorder, Richardson, TX, USA). Acquired signals were stored for subsequent analyses (BrainVision Analyzer, Richardson, TX, USA).

EEG data was re-referenced to the average of the left and right mastoids ($TP_{9/10}$). Signals were filtered (0.1–30 Hz) and ocular corrected (Gratton et al., 1983). Data was segmented into epochs (1200 ms) for each stimulus (−100–1100 ms post-stimulus). Segmentation was followed by artifact rejection, which excluded epochs exceeding +/−75 μV and containing faulty channels. Epochs were baseline corrected (mean activity −100 ms pre-stimulus). Codes synchronized with stimuli delivery were used to average epochs for specific stimuli (sad50, sad100, joy50, joy100, sur50, sur100; neutral: average of sad20, joy20, sur20) per participant. At least 40 epochs were included in any further ERP analysis; one patient was excluded from analyses (N = 51 MDD; N = 43 control).

2.8. ERP analyses

ERPs were identified based on grand-averaged waveforms and precedent literature. The following components were identified for non-target emotive faces: P1 (at $O_{1/2}$; max + ve voltage at 70–140 ms), N1 (at Fz; max −ve voltage at 70–110 ms), N170 (at $P_{7/8}$; max −ve voltage at 140–180 ms), VPP (at Cz; max +ve voltage at 120–180 ms), P2 (at $O_{1/2}$; max +ve voltage at 200–250 ms), N2 (at Fz; max −ve voltage at 180–260 ms) and P3 (at Pz; max +ve voltage at 280–500 ms). Peak latencies of each component were evaluated from stimulus onset time. The mean positive amplitude was assessed for the LPP (at Pz; 500–650 ms post-stimulus). The amplitude and latency of the P3 (at Pz; 350–600 ms post-target) were assessed for target sur50 and sur100 faces. Trials with false alarm and missed responses were excluded from ERP analyses.

2.9. Statistical analyses

Separate, repeated-measures analyses of variances (ANOVAs; SPSS Inc., Chicago, IL, USA) were carried out on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. Similarly, behavioral performance indices (hits, FA, RTs) to targets (sur50, sur100) were assessed with separate ANOVAs, with group and sex as between-subject factors. Face ratings on the "sad" and "happy" questions were carried out using repeated-measures ANOVAs with non-target faces (joy50, joy100, sad50, sad100, neutral) as the within- and sex and group as between-subject factors. Amplitudes and latencies (except for the LPP) were assessed for each ERP with repeated-measures ANOVAs with non-target faces and hemisphere for select ERPs (N170, P1, P2) as the within- and sex and group as between-subject factors. Univariate ANOVAs were also applied to P3 amplitudes and latencies to sur50 and sur100 faces separately, with group and sex as between-subject factors. All main effects and interactions ($p<.05$) were Greenhouse-Geisser corrected. Bonferroni corrections (built into SPSS) were applied to adjust for multiple comparisons. Exploratory correlations were carried out between the N170 (averaged at $P_{7/8}$), P3 and LPP amplitudes, to sad100 and joy100 expressions and MADRS, HAMD-17 and HAMD-29 scores. Separate correlations were run for each sex; significance level was $p<.01$ to correct for multiple comparisons.

3. Results

3.1. Profile of mood states (POMS)

As no sex effects existed, scores in Table 2 are collapsed across sexes. POMS scores were unavailable for one MDD patient (N = 52; controls: N = 43). A main group effect was noted for all POMS dimensions: Tension–Anxiety [F(1,91) =

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110.59, $p<.001$], Depression–Dejection [$F(1,91)=243.47$, $p<.001$], Anger–Hostility [$F(1,91)=71.36$, $p<.001$], Fatigue [$F(1,91)=216.76$, $p<.001$], Confusion–Bewilderment [$F(1,91)=155.18$, $p<.001$], Vigor–Activity [$F(1, 91)=169.29$, $p<.001$] and Total Mood Disturbance [$F(1,91)=300.20$, $p<.001$]. Scores were greater for the MDD versus control group for all dimensions except for lower vigor–activity scores in the MDD group.

3.2. Emotional faces recognition task

There were no group or sex effects on hits, RT, or FA (Table 3; sexes collapsed).

3.3. Facial expression rating questionnaire

As no sex specific effects were noted, ratings in Table 4 are collapsed across sexes. For the "happy" rating, a main effect of face was noted [$F(4,364)=653.66$, $p<.001$], with a difference in ratings between all faces (min $p<.001$). In validation of the presented stimuli, joy100 faces were rated as most happy, while sad100 were least happy.

For the "sad" rating, a main effect of face existed [$F(4,364)=406.41$, $p<0.001$], with a difference in sad ratings between all faces (min $p<.001$). As expected, sad100 faces were rated as most sad while joy100 were rated as least sad. A main effect of group was noted [$F(1,91)=3.90$, $p=.05$] with the MDD group rating the faces as more sad overall ($3.74\pm.11$) than controls ($3.42\pm.12$; Table 4).

3.4. ERP amplitudes and latencies to non-target emotional faces

3.4.1. P1 amplitude and latency

A main effect of face was noted for P1 amplitude [$F(4,360)=11.72$, $p<.001$], with follow-up comparisons indicating a smaller P1 for joy100 versus all other faces (min $p<.005$). The P1 for joy50 was also smaller than for all other faces (min $p<.05$; Fig. 2).

A main effect of face was noted for P1 latency [$F(4,360)=13.05$, $p<.001$], with a shorter latency for joy100 versus all other faces (min $p<.05$). Additionally, a shorter latency was noted for joy50 than for neutral and sad50 (min $p<.05$; Fig. 2).

Table 2
Profile of mood states (POMS) in major depressive disorder (MDD) and control groups (mean ± standard error).

POMS dimensions	MDD*** (N = 52)	Control (N = 43)
Depression–dejection	35.4 ± 1.4	3.4 ± 1.5
Vigor–activity	5.0 ± .7	19.4 ± .8
Confusion–bewilderment	16.5 ± .7	4.1 ± .7
Fatigue–inertia	20.2 ± .7	4.4 ± .8
Anger–hostility	16.9 ± 1.0	3.9 ± 1.1
Tension–anxiety	18.2 ± .8	5.2 ± .9
Total mood disturbance	102.5 ± 3.9	1.6 ± 4.3

*** $p<.001$: All POMS dimensions differed between the MDD vs. control groups.

Table 3
Behavioral performance measures on the emotive faces recognition task in major depressive disorder (MDD) and control groups (mean ± standard error).

Performance measures	MDD (N = 52)	Control (N = 43)
Hits (%)	81. ± 14	79 ± 14
Reaction time (ms)	522 ± 108	525 ± 78
False alarms (%)	.8 ± .9	.9 ± .9

3.4.2. N1 amplitude and latency

No main effects or interactions were noted for N1 amplitude.

A main effect of sex was found for N1 latency [$F(1,90)=25.86$, $p<.001$], with longer latencies for males ($99.09\pm.95$ ms) versus females ($92.48\pm.89$ ms). A face × sex interaction also existed [$F(4,360)=3.46$, $p=.012$], with longer latencies for neutral versus both joy100 ($p=.006$) and sad100 ($p=.021$) faces for females. For males, N1 latency for joy100 was longer than for joy50 ($p=.038$). For all faces, N1 latency was shorter for females than males (min $p<.05$; Fig. 3).

3.4.3. N170 amplitude and latency

A main effect of face was found for N170 amplitude [$F(4,360)=4.85$, $p=.001$], with a smaller amplitude for sad100 versus both joy50 ($p=.011$) and joy100 ($p<.001$). The N170 for neutral was smaller than for both joy50 ($p=.024$) and joy100 ($p=.003$); the amplitude for sad50 was smaller than for joy100 ($p=.022$; Fig. 4).

No main or interaction effects were found for N170 latency.

3.4.4. VPP amplitude and latency

A main effect of face was noted for VPP amplitude [$F(4,360)=17.34$, $p<.001$], with follow-up comparisons indicating a smaller VPP for neutral versus all other faces (min $p<.001$). Additionally, the VPP for sad50 was smaller than for joy100 and sad100 (min $p<.05$). A main effect of sex was found [$F(1,90)=14.14$, $p<.001$], with females (10.39 ± 0.66 μV) having larger VPP amplitudes than males (6.74 ± 0.71 μV; Fig. 3).

Table 4
Facial Stimuli ratings on the "happy" and "sad" dimensions in major depressive disorder (MDD) and control groups (mean ± standard error).

		MDD (N = 52)	Control (N = 43)
"Happy" rating	Joy50	7.2 ± 1.6	7.5 ± 1.5
	Joy100	8.9 ± 1.0	9.3 ± .8
	Neutral	3.3 ± 1.6	3.4 ± 1.4
	Sad50	2.0 ± 1.9	2.0 ± 1.5
	Sad100	1.0 ± 1.5	.6 ± 1.0
"Sad" rating*	Joy50	.9 ± 1.2	.7 ± .9
	Joy100	.4 ± .7	.4 ± 1.0
	Neutral	3.6 ± 1.8	2.7 ± 1.9
	Sad50	5.8 ± 1.9	5.7 ± 1.9
	Sad100	7.9 ± 1.7	7.7 ± 2.1

For both happy and sad ratings, all faces were rated differently (min. $p<0.001$).
* $p=0.05$: Overall, the MDD vs. control group rated the faces as more sad.

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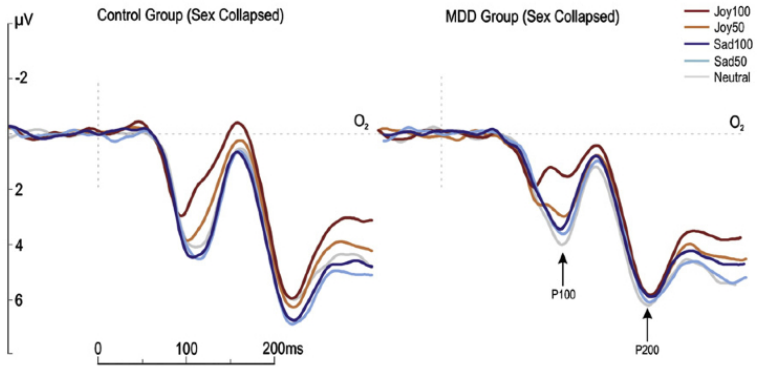


Fig. 2. P1 and P2 (at O_2) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in the MDD and control groups.

A main effect of sex existed for VPP latency [$F(1,90) = 10.81$, $p = .001$], with shorter latencies in females (141.1 ± 1.53 ms) than males (148.47 ± 1.64 ms; Fig. 3).

3.4.5. N2 amplitude and latency

A main effect of face was found for N2 amplitude [$F(4,360) = 3.530$, $p = .01$], with a more negative amplitude for joy50 versus both neutral ($p = .038$) and sad100 ($p = .001$). The N2 amplitude to sad50 was also more negative than to sad100 ($p = .006$; Fig. 3).

Assessment of N2 latency indicated a face × sex × group interaction [$F(4,360) = 2.87$, $p = .027$] but no direct group differences were noted. For the MDD group, sex differences were found in N2 latency for joy50 ($p = .017$) and joy100 ($p = .015$), with shorter latencies for females versus males. For control males, N2 latency for sad100 was longer than for neutral ($p = .038$). For MDD females, N2 latency for sad100 was longer than for neutral, joy100, and sad50 (min $p < .05$). For MDD males, N2 latency was longer for joy50 versus neutral, sad50 and sad100 (min $p < .05$).

3.4.6. P2 amplitude and latency

A main effect of face was found for P2 amplitude [$F(4,360) = 3.7$, $p = .006$], with a greater amplitude for sad50 versus neutral, joy50 and joy100 (min $p < .05$). P2 amplitude was also larger for joy100 than sad100 ($p = .027$; Fig. 2). A face × group interaction existed [$F(4,360) = 3.35$, $p = .013$], though follow-up comparisons revealed no direct group differences. For controls, P2 amplitude was greater for sad50 versus all other faces (min $p < .005$) but sad100; it was also greater for sad100 versus neutral ($p = .012$) and joy100 ($p = .006$), with a similar trend compared with joy50 ($p = .058$). For the MDD group, the P2 to neutral was greater than joy50 ($p = .016$; Fig. 2).

A face × hemisphere × group interaction trend was noted for P2 latency [$F(4,360) = 2.22$, $p = .07$]. Pairwise comparisons indicated that P2 latency for the MDD group (224.38 ± 1.78 ms) was longer than for controls (218.52 ± 1.94 ms) for sad100 in the left hemisphere.

3.4.7. P3 amplitude and latency

A main effect of face was noted for P3 amplitude [$F(4,360) = 6.34$, $p < .001$], with a greater P3 for sad50 versus neutral, joy50 and joy100 (min $p < .05$). Similarly, a greater P3 existed for sad100 versus neutral, joy50 and joy100 (min $p < .001$). A main effect of sex was found [$F(1,90) = 7.26$, $p = .008$], with larger P3 amplitudes in females (8.99 ± 0.48 μV) than males (7.09 ± 0.52 μV; Fig. 5).

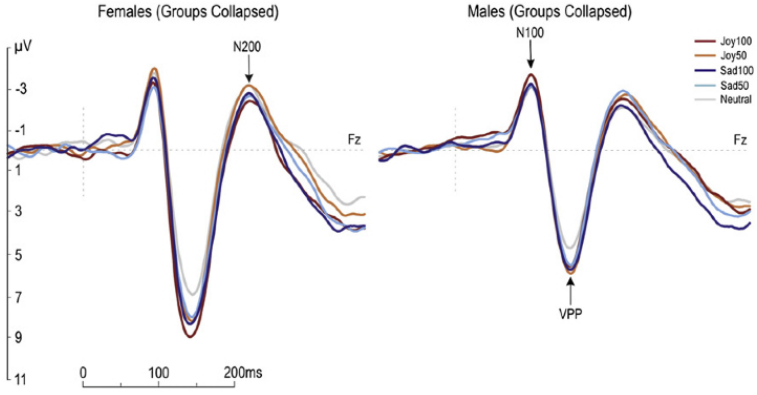


Fig. 3. N1, N2 and VPP (at Fz) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in males and females.

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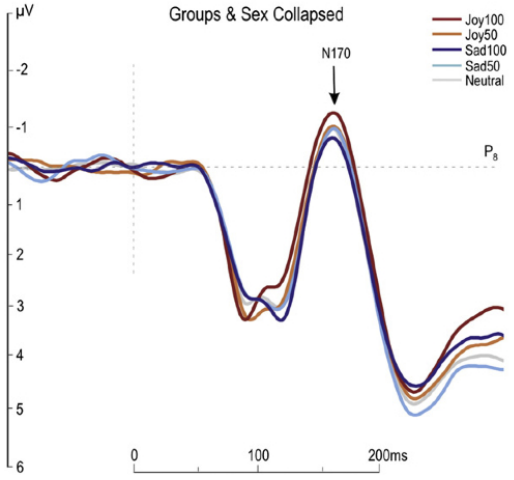


Fig. 4. N170 amplitude (at O_8) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in MDD and control groups.

A main effect of face existed for P3 latency [$F(4,360) = 2.53$, $p = .049$], with a longer latency for sad100 than for neutral, joy50 and sad50 (min. $p < .05$).

3.4.8. LPP mean amplitude

A main effect of face was found for mean LPP amplitude [$F(4,360) = 6.34$, $p < .001$], with larger LPPs for sad100 than neutral ($p = .003$), joy50 ($p < .001$) and sad50 ($p = .001$). The LPP to joy50 was smaller than for neutral ($p = .021$) and joy100 ($p = .004$). A main effect of sex existed [$F(1,90) = 3.95$, $p = .05$], with a greater LPP for females ($4.14 \pm .40$ μV) versus males ($2.96 \pm .42$ μV; Fig. 5).

3.5. Correlations

For females, only a trend for a negative correlation between MADRS scores and P3 amplitude to sad100 faces was found ($r = -0.39$, $p = .043$, $N = 27$).

3.6. P3 amplitude and latency to target faces

A main effect of sex was noted for P3 amplitude to sur50 [$F(1,75) = 7.40$, $p = .008$] and sur100 faces [$F(1,91) = 16.82$, $p < .001$] faces, with females exhibiting a greater P3 (sur50: $14.59 \pm .69$ μV; sur100: $18.28 \pm .74$ μV) than males (sur50: $11.76 \pm .78$ μV; sur100: $13.84 \pm .79$ μV). No main effects or interactions existed for sur50/100 latency.

4. Discussion

This study examined performance and ERPs on a simple facial expression recognition task in depressed males and females and controls. Consistent with expectations and diagnosis, the MDD group was characterized by mood disturbances. In line with the mood-congruent processing bias, depressed individuals rated faces as sadder overall than controls, suggesting that emotive and socially meaningful information is evaluated more negatively in the disorder. Expressions influenced all ERPs, though valence and intensity selectively modulated specific ERPs. Females typically had larger ERPs with shorter latencies than males, indicating enhanced pre- and conscious as well as speeded facial processing, respectively, in females. Depressed individuals did not exhibit robust ERP differences to specific expressions than controls. Subtle group differences were noted in mid-latency ERPs, with controls exhibiting increased P2 amplitudes to sad expressions that was absent in the MDD group, though P2 latency to intensely sad faces was longer in MDD; a similar finding existed for N2 latency in MDD females. No correlations between select ERPs to intense expressions and depression ratings existed. Further interpretation and implications of these results are discussed below.

We noted an attenuated P1 to joyful expressions and decreased latency to intensely joyful ones, confirming previous results indicating that early perceptual ERPs are emotion-sensitive (Pourtois and Vuilleumier, 2006; Santesso et al., 2008). However, research assessing the influence of less arousing positive (happy) and negative (sad) expressions on the P1 has yielded inconclusive findings (Lee et al., 2010). Somewhat in-line with our results, others noted an attenuated P1 to liked (versus disliked) and attractive (versus unattractive) faces (Halit et al., 2000; Pizzagalli et al., 2002). We previously found a blunted P1 to joyful versus

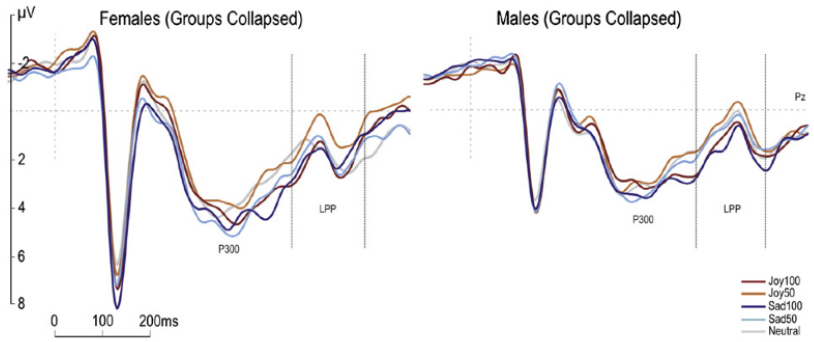


Fig. 5. P3 and mean LPP (50–650 ms; at Pz) to sadness at 50% and 100% intensity (sad50, sad100), joy at 50% and 100% intensity (joy50, joy100) and neutral in males and females.

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intensely sad faces in the right occipital region, though an increased P1 to intensely joyful versus mildly emotive and neutral expressions was found in the left parietal region (Jaworska et al., 2010). Our current results suggest "automaticity" in very early perceptual processing of positive expressions.

With respect to the N1, shorter latencies were noted for intensely sad and joyful expressions compared with neutral ones in females, suggesting longer perceptual processing of ambiguous faces. In males, N1 latency was enhanced to intensely versus mildly joyful faces, indicating somewhat different early, perceptual processing of emotive information between the sexes. This was further supported by decreased overall N1 latencies in females versus males, indicating speeded perceptual processing of faces in females (Felmingham et al., 2010; Lewin and Herlitz, 2002). We found no evidence for altered early, pre-conscious processing of emotive information in MDD.

Though exceptions exist, the N170 has been found to be expression-sensitive, with most studies documenting its enhancement to highly arousing negative expressions (Batty and Taylor, 2003; Krombholz et al., 2007; Stekelenburg and de Gelder, 2004). We found it to be most pronounced to joyful faces, consistent with our previous findings (Jaworska et al., 2010). Given that an opposite pattern was observed for the P1, it is feasible that early sensory processing is most automatic for positive expressions while face identification may be maximal for them. Consistent with the idea that highly arousing stimuli elicit a maximal N170, pilot work in our laboratory indicated that intensely joyful faces were rated as most aroused while mildly sad ones were least aroused (data not shown). Thus, it is feasible that increased arousal versus positive valence per se elicits a prominent N170.

The VPP has also been shown to be enhanced to fearful and angry expressions (Foti et al., 2010; Luo et al., 2010; Sewell et al., 2008). However, we previously found it to be enhanced to emotive (happy and sad) faces (Jaworska et al., 2012), consistent with the current study. Previous work has also found the VPP to be shortest to positive expressions (Batty and Taylor, 2003; Jaworska et al., 2012). Thus, highly arousing and positive faces appear to elicit maximal VPPs with shortest latencies. Though it has been argued that the VPP and N170 are equivalent (Joyce and Rossion, 2005), we noted distinct features between the two. The VPP was smallest to neutral faces indexing preferential processing of emotional (versus just arousing) faces. A main effect of sex emerged for the VPP but not N170, suggesting increased cortical resource allocation and faster processing of faces in females. We found no evidence that face-sensitive ERPs were uniquely altered by specific expressions in MDD.

The P2 has been shown to be modulated by emotive information, with reported P2 reductions to fearful and angry faces (Schutter et al., 2004; Stekelenburg and de Gelder, 2004). Previous work in our laboratory found it to be maximal to sad versus neutral and mildly positive expressions in the right occipital region (Jaworska et al., 2010). Similarly, in the current study a greater P2 was noted to mildly sad versus neutral and joyful expressions, though it was also greater for intensely joyful versus intensely sad ones. These results suggest a maximal P2 to less arousing negative expressions. The P2 may reflect perceptual grouping processes as it tends to be small for stimuli that facilitate grouping and maximal for those that hinder it (Rousselet et al., 2008). Highly arousing and positive expressions may facilitate grouping and be accompanied by a decreased P2. In a similar vein, following initially enhanced pre-conscious processing of positive and arousing stimuli, reflecting rapid stimulus identification/categorization, increased perceptual processing may subsequently be devoted to ambiguous expressions. A similar interpretation could apply for the N2 as it was maximal to mildly joyful versus neutral and intensely sad faces.

Subtle group differences emerged for the P2 and N2. For controls, the P2 was greater for sad versus all other expressions. This was not observed for the MDD group; instead, only a larger P2 to neutral versus mildly positive expressions existed. This may reflect increased automaticity in late pre-conscious processing of negative faces in MDD. Alternatively, it suggests attenuated perceptual processing of emotive information, consistent with previous work (Leppänen et al., 2004). P2 latency for the MDD versus control group was longer to intensely sad expressions in the left hemisphere, indicating longer late pre-conscious processing of these faces. Though no direct group differences were noted for the N2, subtle sex-dependent N2 latency differences emerged. Specifically, though no N2 latency differences existed between faces in control females, for MDD females latencies were enhanced to intensely sad expressions, consistent with the P2 latency results. For control males, N2 latency to intensely sad faces was longer than to neutral ones, indexing longer processing of intense negative stimuli. In MDD males, N2 latency was longer for mildly joyful versus neutral and sad expressions suggesting increased processing of mild, mood-incongruent faces.

We noted maximal P3s to sad expressions and longer latencies to intensely sad versus all but intensely joyful faces, consistent with the idea that the most informative social cues preferentially capture conscious attention resources. Additionally, we found that P3-indexed conscious processing of faces was greater in females. Given that performance was comparable between the sexes, this did not confer a performance advantage, though task ease may have prevented the emergence of sex differences. Previous work has found no P3 differences to faces between sexes (Campanella et al., 2004; Lee et al., 2010), another group noted opposite results to ours (Oliver-Rodríguez et al., 1999), while yet another indicated that P3 sex differences to facial expressions may be hemisphere-dependent (Gasbarri et al., 2006). The current study indicates enhanced pre- and conscious facial processing in females. We found no evidence of altered conscious attention capture by specific facial expressions in MDD. The handful of studies that has assessed the P3 in emotive tasks in MDD suggest blunted conscious attention allocation to emotive information (Bruder et al., in press; Cavanagh and Geisler, 2006; Kayser et al., 2000). Our findings did not support this, though study design variability may partially account for this.

In line with our previous work (Jaworska et al., 2012), we noted greater LPPs to intensely sad versus with all but intensely joyful expressions. The LPP to mildly joyful faces was also smaller than to neutral and intensely joyful faces, indicating that neutral, perhaps due to their ambiguity yet potential relevance, and intense expressions elicit greater sustained motivated processing than mildly emotive ones.

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LPP-indexed enhanced sustained processing of faces was evident in females versus males. Previous work indicates that MDD individuals exhibited blunted LPPs to threatening faces (Foti et al., 2010), while others noted no effect of positive or negative pictures (not faces) on an LPP-like component in MDD (Kayser et al., 2000).

4.1. Conclusions and limitations

We assessed ERP profiles associated with facial expression processing in MDD. Consistent with the purported mood-congruent processing bias in MDD, MDD individuals rated expressions as sadder overall than controls. However, we found little evidence for substantially altered ERPs to specific expressions in MDD. Subtle modulations in mid-latency ERPs suggested attenuated late pre-conscious perceptual processing of emotive stimuli in MDD, though this was accompanied by longer processing of intensely sad faces, especially in females. Females exhibited increased and speeded pre- and conscious facial processing.

Precedent work indicates that robust ERPs tend to emerge to threatening faces, especially at early-mid latencies, perhaps reflecting a pre-attentive scan of threat. Our rationale for excluding these was because we wanted to examine the influence valence on ERPs in MDD while minimizing the influence of arousal. However, inclusion of threatening faces may have revealed more pronounced group ERP differences. Task design is another important consideration when comparing study outcomes. In the current study, participants responded to surprised faces; a more involved task (e.g. memory task) may have, more robustly, differentiated the groups. Although given that we wanted to assess temporal profiles of expression processing, our task was well-suited for this aim. Another methodological consideration that may complicate direct comparisons between studies (in addition to reference choice) is the site at which an ERP is assessed.

Despite our subtle between-group differences, the potential utility of ERPs during emotive processing in MDD should not be discounted. Previous work indicates that cognitive changes may emerge with short-term treatment (Harmer et al., 2003). Assessing attention allocation to emotive stimuli and associated ERPs before and during initial treatment periods may be useful in predicting clinical response. If clinical outcome can be predicted based on short-term changes in ERPs to emotive stimuli, earlier switching to more effective antidepressants may be feasible, and should be probed in future studies.

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Conflict of interest

Dr. Pierre Blier has been a speaker for, on the advisory boards of, and has received grants/honoraria from Biovail, Eli Lilly, Lundbeck, Organon, Pfizer, and Wyeth; and has a financial interest in Medical Multimedia Inc. None of these companies had any association with the work submitted in this manuscript. None of the other authors have any conflict of interest to disclose.

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Appendix J

Scalp- and sLORETA-derived loudness dependence of auditory evoked potentials (LDAEPs) in unmedicated depressed males and females and healthy controls (published manuscript) Constitutes pages 187-196

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Scalp- and sLORETA-derived loudness dependence of auditory evoked potentials (LDAEPs) in unmedicated depressed males and females and healthy controls

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HIGHLIGHTS

- The loudness dependence of auditory evoked potentials (LDAEP) was unaltered in depression, though the LDAEP derived from primary auditory cortex activity correlated negatively with depression ratings.
- Smaller auditory evoked potentials (AEPs) existed in depressed versus control males.
- Females had enhanced cortical responses to auditory stimuli.

ABSTRACT

Objective: As major depressive disorder (MDD) is associated with altered 5-HT activity, we probed intensity-dependent auditory evoked potentials (AEPs) and loudness dependence of the AEP (LDAEP) slopes, shown pre-clinically to be inversely related to 5-HT activity, in MDD.
Methods: AEPs and LDAEP slopes were measured in MDD ($N = 50$; 27 females) and controls ($N = 43$; 23 females). Correlations between scalp AEPs/LDAEPs and low-resolution electromagnetic tomography (sLORETA)-derived indices were assessed.
Results: Smaller scalp intensity-dependent N1 and N1/P2 amplitudes in MDD versus control males and longer P2 latencies in MDD versus control females were found; no LDAEP group differences existed. Females had greater scalp AEPs, steeper N1 and N1/P2 scalp LDAEPs as well as greater intensity-dependent primary auditory cortex activation during the N1 than males. Scalp LDAEPs correlated weak-moderately with sLORETA counterparts. P2 LDAEP-sLORETA correlated negatively with MADRS scores. Female P2 and N1/P2 LDAEP-sLORETA correlated negatively with HAMD-17 and MADRS scores.
Conclusions: MDD was not associated with altered LDAEPs. Impaired processing or potentiated inhibition of auditory stimuli was found in MDD males; longer processing existed in MDD females. Inverse relationships between LDAEPs and clinical scores may be related to treatment history, personality and/or MDD features.
Significance: MDD was not associated with an altered LDAEP, though subtle AEPs alterations were noted in MDD.
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1. Introduction

Event-related potentials (ERP) are averaged from electroencephalographic (EEG) activity resulting from summed postsynaptic potentials triggered by neurotransmitter release (Mitzdorf, 1994). Thus, ERPs are, to a certain degree, direct manifestations of neurotransmitter activity. High 5-hydroxytryptamine (5-HT) concentrations have been found in primary sensory cortices, such the primary auditory cortex (Berger et al., 1988); comparatively less 5-HT innervation and activity exists in the secondary cortex (Azmitia and Gannon, 1986; Hegerl et al., 2001). Thus, 5-HT neurotransmission is likely implicated in modulating sensory-level processing of auditory input into the primary auditory cortex.

Two auditory evoked potentials (AEPs), the N1 and P2, are generated in the primary auditory and association cortices. Their peak-to-peak amplitude difference (N1/P2) correlates positively with

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stimulus intensity. By plotting N1/P2 amplitude against intensity, a loudness dependence of the AEP [LDAEP; or intensity dependence of AEP (IDAEP)] slope is constructed, which has been proposed to index 5-HT activity. Cortical 5-HT efferents from the dorsal raphe nucleus (DRN) are characterized by a pacemaker discharge (Jacobs and Azmitia, 1992). As such, 5-HT neurotransmission is well suited for tonic modulation of cortical activity in the primary auditory cortex (Hegerl et al., 2001). As cortical hyper-activation (with increased intensity) could be damaging, enhanced 5-HT activity may inhibit excessive neural activity (Juckel et al., 1999). Hegerl and Juckel (1993) proposed that 5-HT DRN neurons provide tonic pre-activation to the primary auditory cortex. They further suggested that low 5-HT pre-activation, indexing 5-HT system hypoactivity, would be associated with steeper LDAEPs than when 5-HT pre-activation is higher, and reflected by shallow LDAEPs (Mulert et al., 2005).

Preclinical work has indicated an inverse relationship between the LDAEP slope and ascending DRN 5-HT discharge (Waterhouse et al., 1990; Juckel et al., 1997, 1999; Wutzler et al., 2008). However, while pre-clinical research suggests that the LDAEP is sensitive to central 5-HT neurotransmission, evidence in humans is less consistent. With acute tryptophan depletion (ATD), which transiently lowers CNS 5-HT, several studies found no effect on the LDAEP (Debener et al., 2002; Massey et al., 2004), while one found only weak evidence for its increase (Norra et al., 2008). Yet others have noted that ATD decreased intensity-dependent N1/P2 amplitudes (Dierks et al., 1999; Kähkönen et al., 2002). Studies probing the effects of SSRIs in healthy individuals have also yielded mixed results on LDAEP/AEPs sensitivity to acute 5-HT changes. Several groups have documented no LDAEP effects with acute SSRI administration in healthy individuals (Uhl et al., 2006; Guille et al., 2008), while others have shown the predicted LDAEP slope decreases (Nathan et al., 2006; Segrave et al., 2006). Chronic SSRI administration in healthy individuals also induced shallower LDAEPs (Simmons et al., 2011). Further evidence for a link between the 5-HT system and AEP intensity modulations comes from associations between altered LDAEP slopes and polymorphisms in 5-HT_{1B} terminal autoreceptor (Juckel et al., 2008) and 5-HT transporters (5-HTT; Lee et al., 2011; Gallinat et al., 2003; Strobel et al., 2003; Hensch et al., 2006). Combined, these studies indicate a link between auditory processing and genetic variants in the 5-HT system. Nevertheless, clinical evidence for a direct association between the LDAEP (and associated AEPs) and CNS 5-HT activity is tenuous.

It is feasible that individuals with aberrant 5-HT system function, as is thought to occur in major depressive disorder (MDD), may be more likely to exhibit altered LDAEPs. However, relatively few studies have directly compared intensity-dependent AEPs in such groups. Two studies (Linka et al., 2007; Park et al., 2010) found no LDAEP changes in MDD, though others noted greater N1/P2 amplitudes with increasing intensity in the disorder (Gopal et al., 2004). Similarly, a steeper LDAEP existed in diabetic depressed patients (no differences existed in non-diabetic patients versus controls; Manjarrez-Gutierrez et al., 2009). Depressed individuals with a history of suicide were also found to exhibit steeper LDAEP slopes than those without such a history (Chen et al., 2005). However, melancholic MDD patients had a shallower LDAEP than non-melancholic patients (Fitzgerald et al., 2009). Finally, a positive correlation between the N1 LDAEP slope and specific somatic symptoms in MDD has been noted (Linka et al., 2009). Given the scarcity and inconsistency of research probing the LDAEP in MDD few conclusions can currently be drawn regarding its profile in the disorder. Interestingly, the LDAEP appears to predict antidepressant drug response, with steep pre-treatment slopes indicating a positive outcome to 5-HT-targeting drugs (Gallinat et al., 2000; Mulert et al., 2002; Lee et al., 2005), while shallow slopes seem to index positive outcome to other antidepressants (Linka et al., 2005; Juckel et al., 2007; Mulert et al., 2007).

Other monoamine systems are known to influence the LDAEP. For instance, the LDAEP has been shown to be influenced by dopamine (DA) transporter availability (Lee et al., 2011), DA levels (Beucke et al., 2010) and DA receptor stimulation (Juckel et al., 1997). Additionally, MDD individuals who responded favorably to chronic bupropion treatment, which modulates 5-HT, NA and DA systems, exhibited a steeper pre-treatment P2 intensity-dependence slope (P2 LDAEP; Paige et al., 1995). Though others examining the effects of altered DA levels and/or activation/antagonism of DA or noradrenaline (NA) receptors have found no associated LDAEP changes (O'Neill et al., 2006, 2008; Oliva et al., 2010). Such evidence challenges the proposed exclusive 5-HT system influence on the LDAEP.

Some of the mixed clinical findings regarding the LDAEP and 5-HT modulations may be sex-dependent. Though several groups have indicated no sex effects on the LDAEP (Linka et al., 2009; Park et al., 2010; Simmons et al., 2011), others have (Buchsbaum and Pfefferbaum, 1971; Hensch et al., 2008). A recent study specifically probing the influence of sex on the LDAEP also found higher slopes in females than males (Oliva et al., 2011). In support of the putative influence of sex on the LDAEP, estrogen pre-treatment in females enhanced the LDAEP (Guille et al., 2010). This is consistent with PET research indicating that females have lower baseline 5-HT neurotransmission levels than males (Nishizawa et al., 1997; Sakai et al., 2006). As such, steeper LDAEP slopes may exist in MDD females versus males, possibly due to the effects of female sex hormones on 5-HT neurotransmission.

Single-electrode estimation (at Cz) and dipole source analysis (DSA) are typically used in generating the LDAEP. Few studies have assessed LDAEP slopes derived via standardized low-resolution brain electromagnetic tomography (sLORETA or LORETA; Pascual-Marqui, 2002). The handful of studies that have assessed s/LORETA-derived LDAEP (s/LORETA-LDAEP) yield comparable results to scalp-derived indices (Mulert et al., 2002; Park et al., 2011).

This study examined whether differences between males and females with MDD and controls exist on the LDAEP. As two previous studies found no group differences, we expected comparable results. Given that 5-HT disturbances are associated with MDD, we predicted that clinical ratings may be positively related with LDAEP slope, though precedent literature probing this issue has found limited associations between depression symptom/severity and LDAEPs (Chen et al., 2005; Fitzgerald et al., 2009; Beucke et al., 2010). In addition to the N1/P2 LDAEP slope, we also examined N1 and P2 LDAEP slopes, as previous work has sometimes documented only modulations of N1 or P2 LDAEP slopes and/or intensity-dependent AEP amplitudes when probing monoamine system alterations. A third aim was to correlate scalp-derived (Cz) LDAEP indices with intensity-dependent activation in the primarily cortex using sLORETA (LDAEP-sLORETA). Given some evidence for a correlation between the two, we expected comparable results. Finally, we probed the effect of sex on AEPs and LDAEPs; we predicted steeper LDAEP slopes in females.

2. Methods

2.1. Participants

Fifty-three ($N = 53$) adults with a primary diagnosis of MDD (Table 1) were recruited from the Mood Disorders Research Unit at the University of Ottawa Institute of Mental Health Research Center. Patients were diagnosed by trained psychiatrists using the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) IV-TR Diagnoses, Axis I, Patient Version (SCID-IV-I/P; First et al., 1997). The 17 and 29 item versions of the Hamilton

Table 1
Major depressive disorder (MDD) and control group characteristics & demographics (Means ± S.D.).

	MDD females ($N = 29$)	MDD males ($N = 24$)	Control females ($N = 23$)	Control males ($N = 20$)
Age (M ± S.D.)	43.2 ± 11.6*	37.7 ± 11.6	37.2 ± 7.8	35.8 ± 11.9
Education years (M ± S.D.)	15.6 ± 2.4	16.5 ± 2.5	16.4 ± 2.0	16.4 ± 1.9
Smoker	4	7	1	2
HAMD-17 (M ± S.D.)	22.4 ± 5.1*	19.1 ± 4.7	–	–
HAMD-29 (M ± S.D.)	32.5 ± 5.4	29.5 ± 6.7	–	–
MADRS (M ± S.D.)	30.8 ± 5.1	30.8 ± 5.4	–	–
BDI-II (M ± S.D.)	–	–	4.4 ± 5.0	3.1 ± 4.8
Ethnicity	27 Caucasian; 1 Asian; 1 South Asian	21 Caucasian; 2 Asian; 1 African	20 Caucasian; 2 South Asian; 1 African	19 Caucasian; 1 Asian

HAMD-17/29: Hamilton Rating Scale for Depression, 29 & 17 item versions; MADRS: Montgomery–Åsberg Depression Rating Scale; BDI-II: Beck Depression Inventory-II.
* $p < .05$, MDD females had higher HAMD-17 versus MDD males; MDD females were older than control females.

Rating Scale for Depression (HAMD-17/29; Hamilton, 1960) and the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) were administered to index symptom severity. All patients had MADRS scores ⩾22 at time of enrollment. Notable exclusion criteria were: Bipolar Disorder (BP-I/II or NOS) diagnosis, history of psychosis, current (<6 months) substance abuse/dependence (except nicotine/smoking), history of seizures or known increased seizure risk (e.g. brain trauma/lesion, pro-convulsant medication use), unstable medical condition (i.e., unstabilized for ⩾3 months), life-time history of anorexia/bulimia and having a significant risk for suicide. Individuals with significant hearing loss (i.e., using hearing aids and/or unable to hear 60 dB SPL, 1000 Hz) were excluded. Patients were not taking antidepressants at the time of testing as they were enrolled in a clinical trial and were tested prior to starting study medication. Washout consisted of five times the t½ of medication(s) previously taken.

Forty-three ($N = 43$) non-depressed, healthy controls were recruited and matched to patients on gender, age and education (Table 1). Controls had no personal psychiatric history and substance abuse/dependence (assessed with a modified non-patient version of the SCID [SCID-IV-I/NP]), history of seizures, brain trauma/lesion(s) or significant hearing loss. Controls completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and were included in the study if they scored ⩽13. Only controls without a psychiatric history in first-degree relatives were tested (assessed with the Family Interview for Genetic Studies [FIGS]; Maxwell, 1992).

Prior to testing, participants abstained for >3 h from caffeine and/or smoking/nicotine, as well as from alcohol/drugs (other than contraceptives and medication required for a stabilized physical condition) beginning at midnight. All participants were compensated $30.00 CDN/session (patients participated in multiple sessions as part of a larger study). This study was approved by the Royal Ottawa Health Care Group and the University of Ottawa Social Sciences and Humanities Research Ethics Boards; informed consent was obtained from all participants.

2.2. Subjective mood ratings

Upon arrival, subjective mood was assessed with the Profile of Mood States (POMS; McNair et al., 1992) on which mood is rated using 65 adjectives, from which values are aggregated to form seven mood dimensions (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment, total mood disturbance).

2.3. LDAEP paradigm

Participants were seated in a sound- and light-attenuated testing chamber with their eyes open and fixed on a point ~1 m in front of them. Auditory stimuli (1000 Hz, 30 ms duration, 10 ms rise/fall) were binaurally presented (Neurobehavioral Systems Inc, Albany, CA, USA; via a PC) through headphones (TDH-49, Northeastern Technologies, Glen Cove, NY, USA). Stimuli at five intensities (60, 70, 80, 90, 100 dB SPL) were presented 80 times each in a pseudo-randomized order (no identical tones presented back-to-back) with ISIs randomized at 1200–1800 ms.

2.4. Electrophysiological recordings & data reduction

EEG was recorded (500 Hz) with a cap embedded with 32 Ag/AgCl electrodes (EasyCap, Herrsching-Breitbrunn, Germany) positioned according to the 10–10 system (Chatrian et al., 1985). Electrodes on the supra-orbital ridges and external eye canthi monitored electrooculographic (EOG) activity. An AFz electrode served as the ground. Impedance was maintained at ⩽5 KΩ and EEG was recorded with an amplifier bandpass filter set at 0.1–80 Hz (BrainVision Recorder, Richardson, TX, USA). Acquired signals were stored for subsequent analyses (BrainVision Analyzer, Richardson, TX, USA).

EEG was referenced to the average of the left and right mastoids ($TP_{9/10}$). Signals were filtered (0.1–30 Hz) and ocular-corrected (Gratton et al., 1983). Data were segmented into 600 ms epochs/intensity (-100–500 ms post-stimulus). This was followed by artifact rejection, which excluded epochs of ±75 μV. Epochs were baseline corrected (using mean activity 100 ms prior to stimulus onset) and averaged for each participant/intensity. A minimum of >40 epochs/intensity were included in the ERP analysis; two MDD patients were excluded from ERP analyses due to insufficient epochs and one for hearing loss ($N = 27$ MDD females, $N = 23$ MDD males; $N = 23$ control females, $N = 20$ control males).

2.5. ERP and LDAEP extraction

N1 and P2 peak time windows were established from grand-averages (groups collapsed) at Cz. N1 was the most negative peak 70–140 ms post-stimulus and P2 was the most positive peak 110–260 ms post-stimulus. N1 and P2 amplitudes and latencies were picked from the mean of all epochs at each intensity/participant. The peak-to-peak amplitude difference between the N1 and P2 (N1/P2) was calculated at each intensity/participant. For each participant, a mean slope (least squares linear regression) was constructed for N1, P2 (in accordance with Linka et al., 2009) and N1/P2, with intensity being the independent and amplitude the dependent variables (i.e., three scalp LDAEP slopes were calculated: N1 LDAEP, P2 LDAEP, N1/P2 LDAEP). Median slopes (Hegerl and Juckel, 1994) were significantly correlated with mean slopes (data not shown), thus, only mean slopes are presented and discussed.

2.6. Source localization

sLORETA was used to estimate current density values in the primary auditory corticex (BA 41) for the scalp-derived N1, P2, N1/P2

components at each intensity/participant (artifact- and ocular-corrected averaged epochs from 28 electrodes from each participant were used for sLORETA computations). sLORETA estimates neuronal activity as current density ($\mu A/mm^2$) based on the Montreal Neurological Institute 152 template creating a low-resolution activation image. The sLORETA solution space consists of 6239 voxels ($5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi. Its validation has been independently replicated (Phillips et al., 2002) and cross-validated with fMRI (Mulert et al., 2004), MRI (Worrell et al., 2000) and PET (Pizzagalli et al., 2004).

For each participant, the average current density for 70–140 ms post-stimulus (N1 activation), 110–260 ms post-stimulus (P2 activation) and 70–260 ms post-stimulus (N1/P2 activation) was determined in the primary auditory cortex [i.e., region of interest (ROI)]. The ROI was based on a probabilistic map of the primary auditory cortex (Penhune et al., 1996) and precedent work (Mulert et al., 2002; Park et al., 2011). It consisted of a volume of 1500 mm^3 on the left (12 voxels) and 1375 mm^3 on the right side (11 voxels). Average current source density values for each of the N1-sLORETA, P2-sLORETA and N1/P2-sLORETA were used to generate LDAEP slopes (N1, P2, N1/P2 LDAEP-sLORETA). Several participants were excluded from the sLORETA analysis due to faulty channels, with 48 MDD ($N = 25$ females) and 40 controls ($N = 22$ females) included.

2.7. Statistical analyses

Analyses of variances (ANOVAs) were carried out (SPSS Inc., Chicago, IL, USA) on each POMS dimension with group (MDD; controls) and sex (males; females) as between-subject factors. N1 and P2 amplitudes and latencies were separately assessed with repeated-measures ANOVAs with group and sex as between-subject and intensity (50, 60, 70, 80, 90, 100 dB) as within-subject factors. Similar analyses were carried out for N1/P2 amplitude and N1, P2 and N1/P2-sLORETA activity values. For analysis of N1, P2, N1/P2 LDAEP slopes, two-way ANOVAs were applied, with group and sex as between-subject factors. Mean N1, P2, N1/P2 LDAEP-sLORETA slopes were analyzed in a similar manner. Main effects and interactions were Greenhouse-Geisser corrected ($p < .05$) and Bonferroni adjustments (built into SPSS) were applied to account for multiple comparisons. Pearson's correlations were carried out between the N1, P2, N1/P2 LDAEP-sLORETA and equivalent LDAEP slopes (sex collapsed), to assess if sLORETA slopes correlated with the scalp ones. Correlations were carried out between N1, P2 N1/P2 LDAEP and LDAEP-sLORETA slopes and clinical ratings (MADRS, HAMD-17/29) for the MDD group. Separate correlations were subsequently run for each sex. Significance was set at $p < .01$ to adjust for multiple comparisons.

3. Results

3.1. Profile of mood states (POMS)

As no sex effects were noted, reported scores are collapsed across sexes. POMS scores were unavailable for one MDD patient ($N = 52$; controls: $N = 43$). A main group effect was noted for the following POMS dimensions: tension-anxiety [$F(1,91) = 110.59$, $p < .001$; MDD: 18.2 ± .8, control: 5.2 ± .9], depression-dejection [$F(1,91) = 243.47$, $p < .001$; MDD: 35.4 ± 1.4, control: 3.4 ± 1.5], anger-hostility [$F(1,91) = 71.36$, $p < .001$; MDD: 16.9 ± 1.0; control: 3.9 ± 1.1], fatigue [$F(1,91) = 216.76$, $p < .001$; MDD: 20.2 ± .7; control: 4.4 ± .8], confusion-bewilderment [$F(1,91) = 155.18$, $p < .001$;

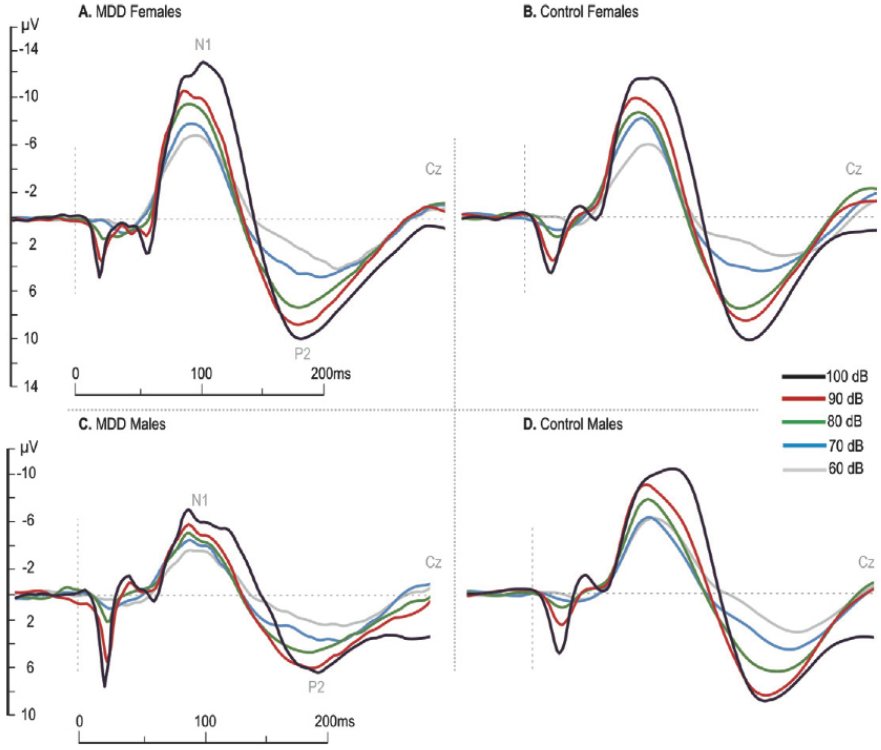


Fig. 1. Mean N1 and P2 auditory evoked potentials (at Cz) in males and females with major depressive disorder (MDD) and controls to increasing sound intensities.

MDD: 16.5 ± .7, control: 4.1 ± .7] and total mood disturbance [$F(1,91) = 300.20$, $p < .001$; MDD: 102.5 ± 3.9, control: 1.6 ± 4.3], with scores being greater for the MDD versus control group. Vigor-activity [$F(1,91) = 169.29$, $p < .001$] scores were lower for the MDD (5.0 ± .7) versus control group (19.4 ± .8).

3.2. N1 amplitude & latency

A main effect of intensity existed [$F(4,356) = 85.91$, $p < .001$], with an N1 amplitude difference between all intensities (min $p < .001$). The most pronounced N1 was to 100 dB (−12.9 μV ± .7) and was least pronounced to 60 dB (−6.5 μV ± .3). A main effect of sex was noted [$F(1,89) = 15.37$, $p < .001$], with greater amplitudes for females (−10.6 μV ± .5) versus males (−7.7 μV ± .6). A group × sex interaction existed [$F(1,89) = 4.75$, $p = .032$], with smaller amplitudes for MDD (−6.3 μV ± .8) versus control males (−9.1 μV ± .8; $p = .013$). MDD females (−10.9 μV ± .7) had larger N1 amplitudes than MDD males (−6.3 μV ± .8, $p < .001$; Fig. 1).

Regarding N1 latency, a main effect of intensity existed [$F(4,356) = 14.43$, $p < .001$], with latency differences between most intensities (min $p < .001$; no difference between 70 and both 80 and 90 dB; no difference between 80 and 90 dB; trend for a difference between 60 and 100 dB, $p = .092$). Latency was longest for 100 dB (104.0 ms ± 1.8) and shortest for 80 dB (−95.2 ms ± 1.10).

3.3. P2 amplitude & latency

A main effect of intensity existed [$F(4,356) = 119.18$, $p < .001$], with P2 amplitude differences between all intensities (min $p < .005$). The largest P2 emerged for 100 dB (10.4 μV ± .6) and the smallest for 60 dB (4.1 μV ± .3). A main effect of sex was found [$F(1,89) = 5.41$, $p = .02$], with a greater P2 for females (8.2 μV ± .5) than males (6.6 μV ± .50; Fig. 1).

For P2 latency, a main effect of intensity was found [$F(4,356) = 9.35$, $p < .001$], with differences between most intensities (min $p < .05$; no difference between 80 versus 70, 90 and 100 dB; no difference between 70 and 100 dB). Latency was longest for 60 dB (200.5 ms ± 2.9) and shortest for 90 dB (184.3 ms ± 2.2). An intensity × sex interaction existed [$F(4,356) = 3.02$, $p = .026$], with females having shorter P2 latencies than males at 80 dB ($p = .005$), with a similar trend for 60 dB and 70 dB ($p = .07$, $p = .074$, respectively). A trend for a main effect of sex existed [$F(1,89) = 3.37$, $p = .07$], with shorter latencies for females (187.4 ms ± 2.4) than males (193.7 ms ± 2.5). A group × sex interaction was found [$F(1,89) = 4.46$, $p = .037$], with MDD females (192.9 ms ± 3.2) having longer latencies than control females (181.8 ms ± 3.5, $p = .02$).

3.4. N1/P2 amplitude

A main effect of intensity existed [$F(4,356) = 177.80$, $p < .001$], with an N1/P2 amplitude difference between all intensities (min $p < .001$). The largest amplitude was to 100 dB (23.3 μV ± 1.0) and smallest to 60 dB (10.6 μV ± .4). A main effect of sex was found [$F(1,89) = 5.41$, $p = .022$], with a greater amplitude for females (18.8 μV ± .8) versus males (14.3 μV ± .8). A group × sex interaction was noted [$F(1,89) = 4.56$, $p = .035$], with larger amplitudes for control (16.3 μV ± 1.2) versus MDD males (12.2 μV ± 1.1, $p = .013$).

3.5. N1, P2, N1/P2 LDAEP slopes

A main effect of sex was noted for N1 LDAEP [$F(1,87) = 3.96$, $p = .05$], with steeper slopes for females (−.17 ± .02) than males (−.12 ± .02). For N1/P2 LDAEP, a main effect of sex existed [$F(1,87) = 5.61$, $p = .020$], with steeper slopes for females (.35 ± .03) than males (.26 ± .03; Fig. 2).

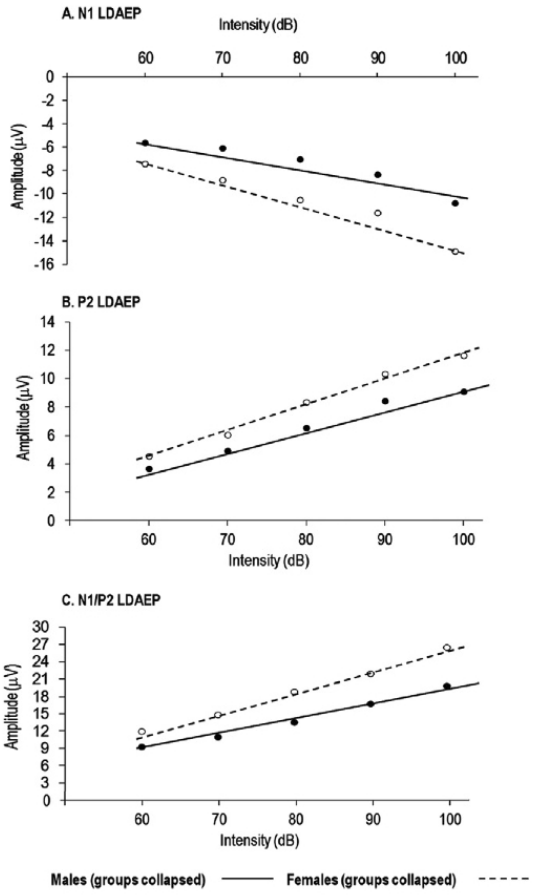


Fig. 2. Mean N1, P2 and N1/P2 amplitudes plotted against increasing sound intensity (dB), constituting the loudness dependence of the auditory evoked potential (LDAEP) slopes (at Cz), in males and females (groups collapsed).

3.6. Current source density

A main effect of intensity existed for N1-sLORETA activity [$F(4,336) = 101.71$, $p < .001$], with differences between all intensities (min $p < .001$). Greatest activity was found for 100 dB (2.3 ± .2) and smallest for 60 dB (.75 ± .05; Fig. 3). A main effect of sex was also noted [$F(1,84) = 5.10$, $p = .027$], with greater N1-sLORETA activity for females (1.5 ± .1) than males (1.1 ± .1).

A main effect of intensity was found for P2-sLORETA [$F(4,336) = 102.29$, $p < .001$], with differences between all intensities (min $p < .001$). Greatest P2-sLORETA activity existed for 100 dB (1.3 ± .07) and least activity for 60 dB (.49 ± .03).

Finally, a main intensity effect existed for N1/P2-sLORETA activity [$F(4336) = 132.51$, $p < .001$], with differences between all intensities (min $p < .001$); greatest activity existed for 100 dB (1.5 ± .08) and least activity for 60 dB (.55 ± .03).

3.7. N1, P2, N1/P2 LDAEP-sLORETA slopes

No significant findings were noted for any of the LDAEP-sLORETA slopes.

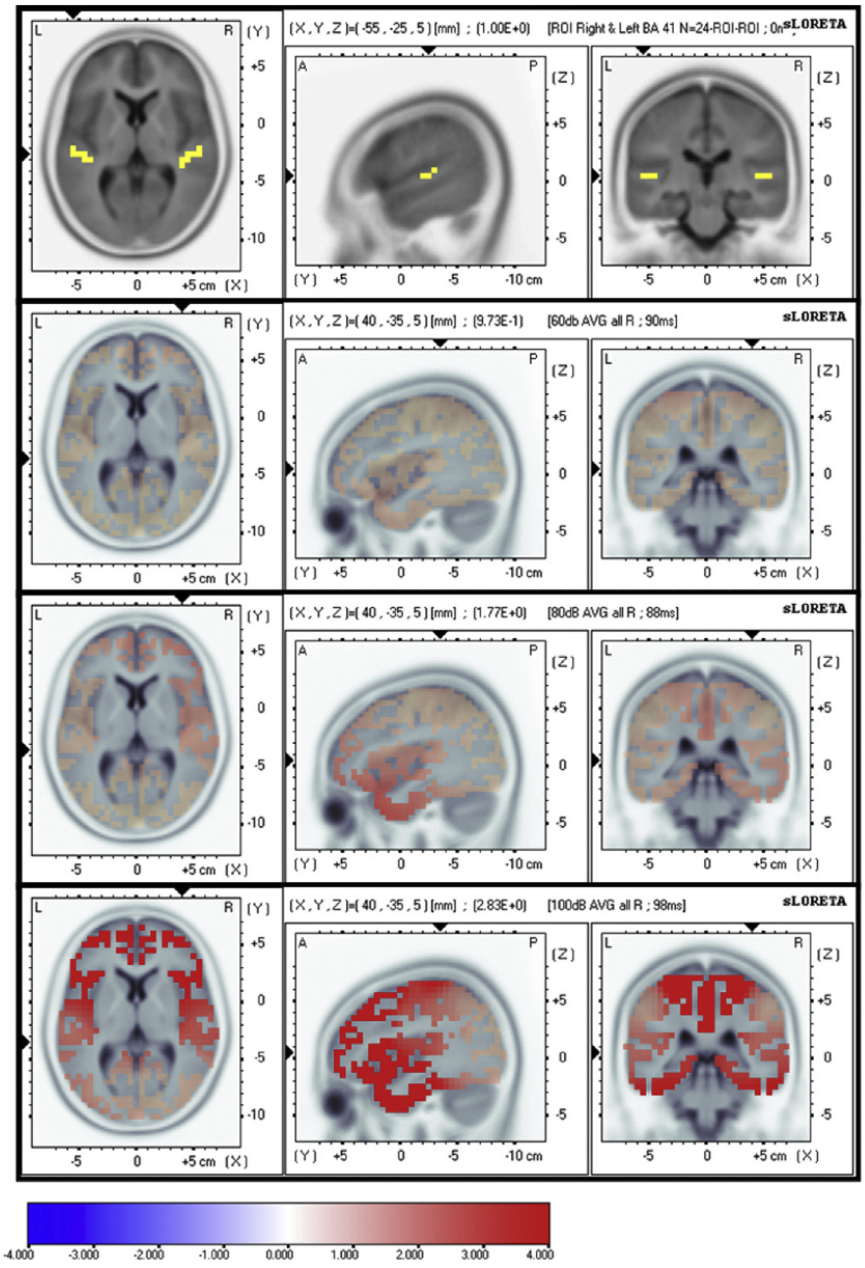


Fig. 3. Grand average (groups and sexes collapsed) of sLORETA current source density activation related to 60 dB (second panel), 80 dB (third panel) and 100 dB (fourth panel) during the time frame corresponding to the N1. The first panel identifies the region of interest in the superior temporal gyrus (BA 41) used in the sLORETA analyses.

3.8. Correlations

All scalp derived LDAEPs correlated with their LDAEP-sLORETA counterparts for both groups [MDD: N1: $r(47) = -.56$, $p < .001$; P2: $r(47) = .35$, $p = .017$; N1/P2: $r(40) = .43$, $p = .006$; control: N1: $r(40) = -.40$, $p < .01$; P2: $r(40) = .33$, $p = .04$; N1/P2: $r(47) = .54$, $p < .001$].

P2 LDAEP tended to correlate negatively with MADRS scores [$r(48) = -.32$, $p = .026$; sex collapsed]. Similarly, P2 LDAEP-sLORETA correlated negatively with MADRS scores [$r(48) = -.41$,

$p = .004$]; the same trend was noted for N1/P2 LDAEP-LORETA slope [$r(48) = -.35$, $p = .016$]. When correlations were broken down by sex, P2 LDAEP-sLORETA correlated negatively with both HAMD-17 [$r(25) = -.55$, $p = .004$] and MADRS scores [$r(25) = -.71$, $p < .001$] in females. Similarly, N1/P2 LDAEP-sLORETA correlated negatively with HAMD-17 [$r(25) = -.50$, $p = .010$] and MADRS [$r(25) = -.55$, $p = .004$] scores in females. In males, P2 LDAEP tended to correlate negatively with MADRS scores [$r(23) = -.46$, $p = .027$].

4. Discussion

We examined whether intensity-dependent AEPs and LDAEP slope differences existed in MDD versus controls, and between the sexes. We also assessed if LDAEP slopes from sLORETA-indexed activity in the primary auditory cortex parallel scalp-derived ones. Consistent with diagnosis and hypotheses, the MDD group exhibited POMS-indexed mood disturbances. Subtle group differences in specific scalp AEPs were noted. Steeper scalp LDAEP slopes, increased scalp- and sLORETA-derived AEP amplitudes and activation, respectively, and decreased AEP latencies existed in females versus males. Scalp- and sLORETA-derived LDAEP slopes were weakly-moderately correlated. These results and their implications are discussed below.

In line with our hypothesis, we noted greater N1, P2 and N1/P2 amplitudes and concomitantly steeper N1 and N1/P2 LDAEPs in females. Of the handful of studies specifically assessing intensity-dependent AEPs and LDAEP slopes between the sexes, several have noted no sex differences in these measures (Hegerl and Juckel, 1994; Linka et al., 2009; Park et al., 2010; Simmons et al., 2011), though others have documented findings consistent with ours (Hensch et al., 2008; Oliva et al., 2011). Thus, females appear to exhibit greater cortical resource allocation to auditory sensory processing than males. This may reflect baseline differences in 5-HT neurotransmission between the sexes, consistent with some PET work indicating lower 5-HT synthesis in females in various cortical regions (Nishizawa et al., 1997; Okazawa et al., 2000; Sakai et al., 2006). Cyclical variations in female sex hormones have been also been shown to affect AEPs (Yadav et al., 2002) and forebrain 5-HT activity (Fink et al., 1998). However, given the paucity of clinical evidence directly linking 5-HT activity with LDAEPs, as well as the various neurochemical differences in the male and the female brain (Cosgrove et al., 2007), we cannot unequivocally attribute the slope differences between the sexes to baseline 5-HT neurotransmission differences. Future work should further probe the relationship between sex hormones, 5-HT function and AEPs/LDAEP.

Consistent with precedent research (Neukirch et al., 2002; Linka et al., 2007), a main effect of intensity, with the expected maximal amplitudes to 100 dB, was found for AEP amplitudes. For both the N1 and P2, latency progressively decreased with increasing intensity until the highest intensities, at which point it increased. Though this U-shaped relationship is inconsistent with some literature (Neukirch et al., 2002), others have noted similar latency distributions as us (Adler and Adler, 1989). Increased AEPs latencies are thought to index slowing of neuronal processing, likely related to altered balance in excitatory/inhibitory neurotransmission. Highly intense stimuli may elicit greater activation of inhibitory (neuroprotective) mechanisms, which may be reflected by longer latencies. Finally, an intensity by sex interaction existed for P2 latency, with females demonstrating speeded processing of auditory stimuli than males at all but the highest intensities. These findings indicate that females exhibit greater cortical processing of auditory stimuli and faster processing of moderately intense sounds as indexed by the attention-sensitive P2.

Smaller N1 and N1/P2 amplitudes were noted in MDD versus control males. This suggests either impaired sensory processing or potentiated inhibitory mechanisms to auditory stimuli processing in MDD males. If the latter is endorsed, it may point to enhanced inhibitory 5-HT neurotransmission in the primary auditory cortex in MDD males. However, given the mixed clinical evidence for a direct inverse relationship between 5-HT activity and intensity-dependent AEPs, as well as research suggesting the involvement of other neurotransmitter systems in the relationship, this interpretation is tenuous. Decreased N1 amplitudes been noted in clinical disorders with psychotic features (Umbricht et al., 2003; Rosburg et al., 2008). However, since patients with psychotic features were excluded from this study, it is unlikely that psychosis accounted for the reduced N1 in MDD males. MDD females exhibited larger N1 amplitudes than males, consistent with the aforementioned sex effect on AEPs.

Previous work assessing AEPs in MDD have yielded mixed findings, and most studies have noted no AEP amplitudes differences in MDD, though greater N1/P2 amplitudes with increasing intensity in MDD have been found (Gopal et al., 2004). Others, using auditory oddball paradigms, also noted a larger P2 in MDD than controls, which may reflect attenuated 5-HT neurotransmission (Vandoolaeghe et al., 1998). A trend for longer AEP latencies in MDD (Himani et al., 1999) and in depressed melancholic patients has been reported in auditory oddball tasks (Urretavizcaya et al., 2003). This suggests slower auditory stimuli processing in the disorder, consistent with our P2 latency findings in MDD versus control females, though the opposite has also been noted (Kähkönen et al., 2007). Thus, depression may be associated with delayed processing of auditory information (and perhaps impaired inhibitory mechanisms), though the latter may be sex-specific.

Much like Linka et al. (2007) we noted no group differences on scalp N1, P2 and N1/P2 LDAEP slopes. Given that certain MDD features, such as suicide history, melancholy and specific somatic symptoms have been associated with LDAEP modulations, it is feasible that certain aspects of MDD, versus the disorder in general, may underlie the relationship. However, it is difficult to speculate which depression features may be associated with altered LDAEPs and there is scant theoretical rationale linking specific MDD aspects and/or sub-types with LDAEP modulations.

Similarly to the scalp-derived ERPs, a main effect of intensity existed for N1, P2 and N1/P2-sLORETA current source densities and females exhibited greater N1-sLORETA activity than males. However, the smaller N1 and N1/P2 scalp-derived AEPs noted in MDD versus control males did not extend to the sLORETA indices, suggesting that the two methods are not equitable. This is consistent with the weak-moderate correlations between scalp- and sLORETA-derived LDAEP for each group, though correlations were greater (i.e., greater shared variance) for the MDD group (with the exception of N1/P2) and stronger for the N1 than P2 LDAEP. Previous work has also found a limited relationship between scalp- and source-derived LDAEP slopes (Mulert et al., 2002; Hagenmuller et al., 2011). This may be related to the fact that scalp AEP generators extend beyond the primary auditory cortex (Rosburg et al., 2008), while current source density measures are confined to it. Additionally, source analysis has localized the N1 to the primary auditory cortex and planum temporale, while P2 sources may be more diffuse (Godey et al., 2001). Thus, increased P2 LDAEP variability may have accounted for the limited relationship between scalp- and sLORETA-derived P2 slopes, though this requires further investigation.

Several correlations were noted between LDAEP slopes and clinical MDD ratings. With sex collapsed, the scalp P2 LDAEP tended to correlate negatively with MADRS scores. Similarly, P2 LDAEP-sLORETA correlated negatively with MADRS scores; the same trend was noted for the N1/P2 LDAEP-LORETA slope. If an inverse relationship between the P2 LDAEP slope and 5-HT neurotransmission is assumed, this outcome suggests that patients with more

effective 5-HT systems (i.e., shallower slopes) exhibit greater depression symptoms pre-treatment. One study has previously reported significant correlations between the N1 LDAEP (at Fz) and MDD somatic symptoms, including appetite/weight loss, insomnia and sexual dysfunction (Linka et al., 2009). Others noted no associations between LDAEP and MDD-related baseline clinical ratings (Chen et al., 2005; Beucke et al., 2010). However, consistent with our results, Fitzgerald et al. (2009) noted a trend towards a significant inverse relationship between individual MADRS scores and LDAEP slopes.

Individuals with MDD tend to be characterized by disturbances in monoamine, including 5-HT, system function and antidepressant drugs tend to increase 5-HT neurotransmission with chronic use. Thus, the relationship between increased 5-HT system activity and increased depression scores, if we endorse the inverse relationship between 5-HT and LDAEP, is counterintuitive. It is feasible that individuals with higher clinical scores were those with a longer MDD history (and/or more treatment-resistant MDD) who may have been treated with antidepressants for longer periods or had a more aggressive treatment history. This, in turn, may have induced neuronal alterations that might account for shallower LDAEP slopes. However, this explanation is speculative. The negative correlations were noted regardless of sex, though they tended to be stronger in females, who also exhibited negative correlations between both the P2 and N1/P2 LDAEP-sLORETA slopes and $HAMD_{17}$ scores.

Precedent work indicates that LDAEP slopes may be associated with specific personality aspects. Hensch et al. (2007) noted a negative correlation between the LDAEP and hyperthymic temperament and hypomanic personality. Others noted that a steep LDAEP was associated with an action-oriented and extroverted personality style (Juckel et al., 1995) and impulsiveness (Norra et al., 2003). Exploratory correlational analysis between LDAEP slopes (both scalp- and sLORETA-derived) and Eysnyck Personality Questionnaire dimensions in the current study did not reveal any significant relationships (data not shown), though other personality factors common to the MDD group, may mediate the relationship between the clinical depression symptoms and the LDAEP.

4.1. Study limitations & conclusions

Several limitations must be acknowledged. Firstly, we used scalp- and sLORETA-derived measures to construct LDAEP slopes, rather than the perhaps more sensitive dipole source analysis (DSA) method. Secondly, we did not control for menstruation cycle phase, thus, it is difficult to comment on whether certain menstrual cycle phases may have a specific effect on the observed AEPs and associated LDAEP slopes. Thirdly, we did not assess whether specific MDD subtypes, such as melancholic or atypical depression, may be specifically related to the LDAEP. Finally, though smokers did not constitute a large proportion of our sample and their exclusion did not alter the LDAEP outcome measures (though significance was reduced; data not shown), smoking has been shown to reduce the LDAEP (Gallinat et al., 2005). As such, future work should attempt to control for and examine these parameters.

In conclusion, females exhibited greater cortical allocation and speeded processing of auditory information compared with males. Impaired sensory processing or potentiated inhibitory mechanisms to auditory processing were noted in MDD versus control males. Conversely, MDD versus control females exhibited longer scalp P2 latencies suggesting longer processing auditory information in depressed females. Scalp-derived LDAEPs correlated weak-moderately with their sLORETA counterparts. Several LDAEP slope measures correlated negatively with depression ratings, suggesting attenuated auditory processing in MDD.

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