

The combined and differential effects of monophasic and biphasic repetitive transcranial magnetic stimulation on ERP-indexed attentional processing in treatment-resistant depression

by

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Abstract

In addition to low mood, major depressive disorder (MDD) is characterized by persistent cognitive deficits that impair daily functioning and resist improvement with conventional pharmacotherapies. Repetitive transcranial magnetic stimulation (rTMS) holds promise as an efficacious alternative, offering better outcomes than medication for patients with treatment-resistant depression (TRD). Yet, current rTMS protocols that administer sinusoidal biphasic pulses achieve remission in less than the majority. However, monophasic pulses may yield higher success rates based on greater cortical excitation/neuromodulation strength. MDD is associated with altered P300 event-related potentials (ERPs), indexing decreased attentional resource allocation and slower cortical processing speed.

Using a cohort of 20 TRD patients who received high-frequency rTMS, this study aimed to assess the impact of monophasic and biphasic stimulation on attention-related P300 measures and their utility as correlates of clinical/cognitive response. Based on baseline and post-treatment change in P300 components, rTMS-induced increases in automatic attention/passive information processing differed by pulse type and predicted greater clinical improvement in depressed individuals. This study represents an important step towards identifying cognitive changes and underlying cortical mechanisms associated with rTMS response and targeted MDD treatment.

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List of Abbreviations

5-HT	Serotonin
BDNF	Brain-Derived Neurotrophic Factor
CEN	Central Executive Network
DMN	Default Mode Network
DLPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5 th Edition
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
ERP	Event-Related Potential
FED	First-Episode Depression
GABA	Gamma-Aminobutyric Acid
HFL	High Frequency Left-Sided
HPA	Hypothalamic-Pituitary-Adrenal
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MEP	Motor Evoked Potential
m-Ino	Myoinositol
NDRI	Norepinephrine-Dopamine Reuptake Inhibitor
PFC	Prefrontal Cortex
PSP	Postsynaptic Potential
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
sgACC	Subgenual Anterior Cingulate Cortex
SN	Salience Network
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant

TRD Treatment-Resistant Depression
WHO World Health Organization

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Chapter 1: Introduction

1.1 Major Depressive Disorder

1.1.1 Overview

Ranked as the leading cause of disability worldwide by the World Health Organization, (WHO) (Marcus et al., 2012), Major Depressive Disorder (MDD) is a debilitating psychiatric condition associated with substantial impairment in quality of life (Ishak et al., 2013). MDD is a clinically heterogenous disorder characterized by profound sadness or loss of interest for a 2-week period, accompanied by 200 possible symptom combinations that fulfill criteria for diagnosis, including: disturbed sleep, psychomotor agitation or retardation, weight fluctuation, feelings of worthlessness, diminished energy and concentration, and recurrent thoughts of death (American Psychiatric Association, 2013). MDD imposes a major economic impact owing to high occupational, medical service, and suicide-related costs; in 2010, the economic burden of MDD in the United States was estimated at over \$200 billion (Greenberg et al., 2015).

1.1.2 Prevalence

MDD is a pervasively common disorder, affecting approximately 350 million individuals worldwide and showing a lifetime prevalence of 15% in North America alone (Marcus et al., 2012). A descriptive epidemiology report by Patten et al. indicated a lifetime MDD prevalence rate of 9.9% in Canada and determined more than 1.5 million Canadians experienced a major depressive episode (MDE) in 2012. Despite increased awareness and greater provision of mental health services in Canada, there have been no changes in annual prevalence of MDE across recent years (4.8% in 2002 vs. 4.7% in 2012; Patten et al., 2015). Demographically, greater annual MDD prevalence rates are observed in women (3.8%) than men (2.8%) and subgroups at a disproportionate risk for depression include: individuals with low socio-economic status, ethnic

minorities, aging adults, and clinical populations facing chronic or terminal illness (Hegeman et al., 2017; Patten et al., 2015; Perrino et al., 2015).

1.1.3 Etiology

The etiological complexity of MDD is showcased by the multitude and heterogeneity of interacting risk factors (genetic, epigenetic, endocrine, and environmental) that increase vulnerability. The most significant risk factor affecting susceptibility to depression is acute traumatic or chronic stress (Duman et al., 2016); stress exposure can occur during early childhood, resulting in long-lasting biological consequences (e.g., epigenetic alterations) (Menke and Binder, 2014; Sun et al., 2013), or during adulthood. The development of MDD in response to trauma or stress is influenced by physiological features and previous exposure to stressful life experiences, as well as genetic composition which accounts for 35-40% of the variance in depression (Sullivan et al., 2000).

Other risk factors that increase MDD susceptibility include sex steroid fluctuations (Bloch et al., 2003; Borrow and Cameron, 2014), elevated inflammatory cytokines, and dysfunctional activation of the hypothalamic-pituitary-adrenal (HPA) axis and abnormal cortisol release (Duman et al., 2016). These pathological determinants alter gene transcription and translation, intracellular signalling, and neurotransmitter systems, leading to disruptions in neuronal function and behavior (Duman et al., 2016). Dysfunction in cellular respiration (Gardner and Boles, 2011), loss of neurotrophic support (Duman and Aghajanian, 2012), imbalanced gut microbiome-interactions (Petra et al., 2015), and metabolic disorders (i.e., obesity, diabetes) (Leone et al., 2012; Mansur et al., 2015) are also associated with increased depression risk.

1.1.4 First-Line Treatment Strategies

Various MDD treatment options have been made available, the most common of which being psychotherapeutic and pharmacological interventions, including: first-generation (i.e., tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (i.e., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]), and norepinephrine-dopamine reuptake inhibitors [NDRIs]. Although often used as a primary intervention strategy, antidepressant medications (alone and in combination) show high rates of partial or non-responsiveness, delayed response onset (weeks to months), and limited duration of efficacy (Gaynes et al., 2009).

Despite variable symptom clustering in MDD, current practices rely on trial-and-error treatment provision, resulting in suboptimal clinical outcomes. Only 30-40% of patients achieve remission during the first antidepressant trial (Gaynes et al., 2009; Rush et al., 2006) and findings from the large-scale (3,671 MDD outpatients) Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project indicate steadily declining remission rates and higher relapse rates after subsequent medication attempts (Rush et al., 2006).

1.1.5 Treatment-Resistant Depression (TRD)

An estimated 15-35% of depressed patients fail to reach remission and are classified as treatment-resistant (Nemeroff, 2007). Although the definition of treatment-resistant depression (TRD) has faced considerable debate, the general consensus now classifies a depressive episode as treatment-resistant if adequate response is not attained following two trials of different classes of antidepressants (Berlim and Turecki, 2007). TRD carries disabling consequences for the individual by increasing functional impairment in domains of occupation, physical health and social relationships (Lam et al., 2016). Furthermore, TRD is commonly linked to poor quality of

life and increased suicidal behavior (Al-Harbi, 2012). Medical expenses are six times more costly in TRD (vs. non-TRD) patients (Crown et al., 2002), underscoring the significant economic burden associated with treatment resistance. Low remission rates in patients following successive courses of medication (10-15% per attempt; Rush et al., 2006) and intensive TRD-focused psychotherapy (20%; Schatzberg et al., 2005) indicate an urgent need for: a) precision medicine with treatments that are uniquely tailored to the individual; and b) more potent intervention strategies to improve depressive outcomes.

1.2 Cognitive Dysfunction in Depression

1.2.1. Overview

Though depression is traditionally characterized by clinical symptomatology, cognitive impairment is considered a core feature of the disease and is reported by 94% of patients in a current MDE (Conradi et al., 2011). The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5) lists deficits in concentration and decision-making as criteria for determining cognitive dysfunction in MDD (American Psychiatric Association, 2013); however, these do not comprise the full spectrum of cognitive symptoms associated with depressive disorders, which also include disturbances in: attention, processing speed, memory, and executive function (Lam et al., 2016).

Cognitive deficits in MDD worsen as a function of illness severity and episode length/frequency. Moreover, greater cognitive impairment has been linked to female gender, lower intelligence, and older age (Pan et al., 2017; Porter et al., 2007). Following symptomatic remission, deficits remain in 44% of MDD patients (Conradi et al., 2011) and contribute to failures in full functional recovery (Woo et al., 2016). Although neuropsychological dysfunction is a common residual symptom in the absence of low mood, its relationship with TRD has yet to

be conclusively elucidated. One study by Spronk et al. (2011) determined that pre-treatment memory scores were positively associated with antidepressant outcomes; these findings corroborate those from numerous studies reporting that enhanced cognitive performance (i.e., executive function, working memory, psychomotor function) contributes to better treatment outcomes (Bogner et al., 2007; Dunkin et al., 2000; Gorlyn et al., 2008; Kalayam and Alexopoulos, 1999; Taylor et al., 2006). Conversely, Herrera-Guzmán et al. (2008) showed successful response was linked to worse pre-treatment cognitive performance.

There exists a bidirectional relationship between cognition and daily functioning, whereby functional impairments contribute to the persistence of deficits (Pan et al., 2017) and cognitive impairment powerfully predicts poor psychosocial/occupational functioning (McIntyre et al., 2013; Woo et al., 2016). In contrast to overall illness severity, cognitive function has a greater impact on quality of life and is more indicative of self-reported health measures in MDD (McIntyre and Lee, 2016). Furthermore, workplace productivity is differentially affected by individual MDD symptoms; coupled with depressed mood, occupational impairment is most closely associated with concentration difficulties (Fried and Nesse, 2014). Specific targeting of cognitive deficits is needed to elevate occupational performance and overall daily functioning in MDD patients.

1.2.2. Attentional Processing Deficits

While controversy exists over the nature of cognitive impairment in MDD, there is evidence that specific domains (i.e., attentional and executive dysfunction) exist independently from fluctuating symptomatology and may be important trait-markers of MDD (Lee et al., 2012; Paelecke-Habermann et al., 2005; Vinberg et al., 2013). Previous studies have specifically depicted attentional processing as persistently deficient in MDD and a significant contributor of

diminished functional performance (Hasselbalch et al., 2011; McIntyre et al., 2013). In a meta-analysis of 24 studies, Rock et al. (2014) examined the degree of cognitive impairment in MDD and, compared to healthy controls, found moderate deficits in sustained attention (as measured by the Rapid Visual Performance task) in both remitted and currently depressed patients. Moreover, in their systematic review of remitted patients, Hasselbalch et al. (2011) found residual dysfunction in sustained and selective attention, in accordance with Douglas and Porter (2009) who revealed that attention remained impaired during treatment. To date, only two meta-analyses have examined cognitive processing in first-episode depression (FED): Ahern and Semkovska (2017) revealed moderate (effect size 0.35) auditory attentional deficits in FED patients (relative to controls) and their findings are consistent with Lee et al. (2012) who showed similar levels of attentional impairment (effect size 0.36). Overall, these findings underscore the persistence of neuropsychological dysfunction within attentional processing and support the hypothesis that impairments in certain cognitive domains develop and increase during the course of depression.

1.2.3 Neurocognitive Correlates

Although the neural processes underlying the pathophysiology of MDD have been extensively investigated, the exact mechanistic features of implicated brain structures and neurotransmitter pathways remain inconclusive. Reduced gray matter in the bilateral hippocampus and prefrontal cortex (PFC) has emerged as the most common finding from reports of structural abnormalities in depression and this volumetric loss is positively associated with illness duration and severity (Lener and Iosifescu, 2015; MacQueen et al., 2008; Malykhin et al., 2010). Additionally, MDD is commonly characterized by morphometric changes in the amygdala and subgenual anterior cingulate cortex (sgACC) (Bora et al., 2012; Drevets et al.,

2008; Lener and Iosifescu, 2015). Neurobiological research has traditionally focused on monoamine systems (i.e., serotonergic, noradrenergic, dopaminergic) in MDD pathophysiology and treatment (aan het Rot et al., 2009); however, other neurotransmitters (e.g., GABA, glutamate), brain-derived neurotrophic factor (BDNF), and various neural pathways have also been investigated as targets for intervention strategies (Duman et al., 2016; Lee and Kim, 2010)

Although not fully elucidated, the pathoetiology of neuropsychological impairment in MDD involves disturbances to brain structure and function, as well dysconnectivity between several distinct neural networks linked to clinical symptoms (e.g., anhedonia, mood, fatigue, suicidality) that contribute to cognitive fluctuations (McIntyre et al., 2016, 2015). The presence of proinflammatory cytokines, glucocorticoid imbalances, obesity and metabolic syndromes, decreased BDNF, and catecholamine dysregulation have all been associated with cognitive symptoms in MDD (Bortolato et al., 2015; Hidese et al., 2018; Millan et al., 2012; Stahl et al., 2003). Importantly, aberrations within the amygdala-ACC-PFC pathway have been strongly implicated in neurocognitive impairment (Duman et al., 2016; Pizzagalli, 2011). Depression is associated with overactivity in the amygdala and volumetric loss in the ACC, an integration point bridging affective and attentional information by assessing the significance of external stimuli. Abnormal projections from the amygdala are received by the ACC and the dorsolateral prefrontal cortex (DLPFC) (Davidson et al., 2002; Drevets, 2000), thereby contributing to disordered executive networks that are reliant upon these neuroanatomical regions (Cabeza and Nyberg, 2000). It has therefore been postulated that the perpetual attentional deficits observed in MDD are directly associated with amygdala-ACC-PFC dysfunction (Paelecke-Habermann et al., 2005). Sustained pathological input to the DLPFC can result in an enduring hypoactive state and decreased ability to cognitively override automatic emotional responses, resulting in persevering

negative affect. Further investigation is required to address and adequately treat the neurobiological abnormalities related to clinical and cognitive dysfunction observed in MDD, specifically for recurrent-episode and treatment-resistant patients.

1.2.4. Pharmacotherapeutic Effectiveness

Currently, evidence of the cognitive-enhancing effects of pharmacological treatment in MDD is conflicted. Although conventional antidepressants (e.g., bupropion, escitalopram, sertraline) have reportedly improved some aspects of neuropsychological processing (Ragguett et al., 2016; Schrijvers et al., 2009; Soczynska et al., 2014), these changes are largely attributed to diminished depressive symptom severity. Most medications appear to offer minimal direct cognitive benefit, with the exception of duloxetine (SNRI) and vortioxetine, a multimodal, atypical antidepressant that modulates serotonin (5-HT) receptors (Pan et al., 2017). The paucity of available pro-cognitive medications highlights the urgent need for alternative treatments that specifically target and enhance cognitive processing and psychosocial functioning in MDD patients.

1.3. Repetitive Transcranial Magnetic Stimulation

1.3.1. Overview

The lack of responsiveness to traditional pharmacotherapies warrants improved clinical methods of treating refractory depression and the personalization of treatment for the individual. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive, stimulus-based technology involving the induction of a transient magnetic field to stimulate neuronal electric current flow. Compared with electroconvulsive therapy (ECT), a more invasive brain stimulation modality that can produce significant cognitive deficits, rTMS is associated with minimal side effects; light-headedness, headache, and transient pain or discomfort are the most commonly

experienced adverse events, with the greatest risk being the rare occurrence of fainting or seizure (Rossi et al., 2009).

By administering repeated pulses via an inductor coil held over the scalp, rTMS can induce lasting changes in cortical excitability; the duration of after-effect is influenced by several variables, including: length of application period, magnetic pulse shape, total number of stimuli, pulse intensity, and pulse frequency (Rossi et al., 2009; Taylor and Loo, 2007). Neural activation patterns are modulated by stimulation frequency: rTMS applied at a low frequency (1 Hz or lower) induces inhibitory activity, whereas high-frequency (HF-)rTMS (faster than 1 Hz) generates cortical excitability (Houdayer et al., 2008).

The finding that rTMS produces durable increases or decreases in cortical activity raised the possibility of its use as a therapeutic tool to normalize dysfunctional signaling in psychiatric patients. Indeed, the DLPFC was proposed as an effective stimulation target after early functional neuroimaging studies identified prefrontal abnormalities in MDD patients (George et al., 1994; George and Wassermann, 1994). Pioneering trials revealed improvement in depressive symptoms in medication-resistant patients receiving 10 Hz (Pascual-Leone et al., 1996) and 20 Hz (George et al., 1995) prefrontal stimulation, introducing the clinical utility of HF-rTMS directed at the left DLPFC. To date, the left DLPFC remains the most common therapeutic target region, representing the gold standard for delivering rTMS at a high frequency.

1.3.2 Neural Mechanisms of Action

Although unclear, the mechanisms by which rTMS normalizes disrupted functional connectivity involves focal increases in cortical activity and propagated downstream effects on PFC-subcortical circuitry (Paus and Barrett, 2004). During stimulation, cortical areas are activated transsynaptically (i.e, perpendicular to descending pyramidal neurons, parallel to

GABAergic interneurons); it is the orientation between the inductor coil and the underlying neural tissue that determines which groups of neurons are selectively activated (Rothwell, 1997). High frequency left-sided (HFL)-rTMS can generate repeated and consistent cell firing to induce long-term potentiation (LTP) of plasticity, the strengthening of synaptic connections and adaptive rewiring of neurons (Fitzgerald and Daskalakis, 2013). Furthermore, some studies have found evidence of post-rTMS increases in BDNF concentrations (Yukimasa et al., 2006; Zanardini et al., 2006), an important mediator of neuroplasticity that is decreased in patients with untreated depression (Lee and Kim, 2010).

In conjunction with induced neuroplasticity, the therapeutic effects of HF-rTMS in depression are likely associated with relevant biochemical changes. For example, MDD studies have found increased DLPFC glutamate levels in rTMS treatment responders that corresponded with reduced depressive symptom scores (Luborzewski et al., 2007; Yang et al., 2014). Similarly, Mingli et al. (2009) detected significantly lower post-treatment salivary cortisol concentrations across patient groups that were positively correlated with depression severity measures, whereas Zwanzger et al. (2003) found decreased cortisol only in rTMS responders. Excitatory left hemisphere (L-)rTMS has been linked to increased levels of neurochemicals, such as norepinephrine (Yukimasa et al., 2006), choline (Luborzewski et al., 2007), and myo-inositol (m-Ino), a sugar molecule involved in cellular signal transduction (Zheng et al., 2010). By stimulating the cortex, neurochemical changes can also be induced in subcortical brain regions: following HFL-rTMS, Strafella et al. (2001) reported striatal dopamine release, indicating that stimulation effects are produced both locally and distally through interconnected circuitry. By upregulating neuronal outputs and altering the strength of connections between neural substrates,

rTMS may function therapeutically by reorganizing pathological patterns of activity seen in depression.

1.3.3. Treatment of Cognitive Deficits

There is ample evidence to suggest that HF-rTMS exerts pro-cognitive effects (Guse et al., 2010; Martis et al., 2003; Siebner et al., 2009) and improvements in neuropsychological processing have specifically been observed in MDD subpopulations (Serafini et al., 2015). Interestingly, a 30-study systematic review by Guse et al. (2010) involving both patients and controls revealed that the effects of rTMS on cognitive function are laterality-dependent and are likely to appear only when stimulating the left, but not the right PFC. Additionally, they found that cognitive domains are differentially affected by excitatory stimulation. With respect to attentional processing, results were largely inconsistent; some studies assessing post-treatment changes in selective and sustained attention detected statistically relevant improvements (Hausmann et al., 2004; Martis et al., 2003; Rektorova et al., 2005), whereas several others failed to find significant effects (Avery et al., 2006; Mogg et al., 2008; Speer et al., 2001; Vanderhasselt et al., 2006). Conversely, robust ameliorations in working memory were consistently observed following HFL-rTMS (Hausmann et al., 2004; Martis et al., 2003; Vanderhasselt et al., 2009). The neural mechanisms subserving rTMS-induced cognitive improvements in depression are not fully understood, but evidence strongly implicates white matter changes in PFC-subcortical networks (Peng et al., 2012). The strengthening of connections along this pathway could potentially allow for increased prefrontal executive control to regulate abnormal activity in subcortical mood circuitry. Further investigation into the neurobiological basis of cognitive modulation with rTMS, as well as the impact of various stimulation parameters (e.g, intensity, frequency, train duration), is necessary to identify novel

targets for therapeutic intervention as a means of optimizing neuropsychological outcomes in MDD patients.

1.3.4. Therapeutic Outcomes in Depression

rTMS has been robustly recognized as a safe, tolerable and effective treatment option for TRD, with response and remission rates comparing favorably to antidepressant medications at ~50% and ~30%, respectively (Berlim et al., 2014; Connolly et al., 2012; Fitzgerald et al., 2011; Loo et al., 2008). In accordance with initial reports, large-scale randomized controlled trials indicate that prefrontal rTMS can outperform sham stimulation to consistently and markedly reduce depressive symptoms (George et al., 2010; O'Reardon et al., 2007). Though, despite its recognition as a useful intervention for treating TRD, up to 45% of patients who undergo rTMS do not achieve a clinically significant response (Fitzgerald et al., 2011). Findings from Fitzgerald et al. (2016) showed that the likelihood of antidepressant response to rTMS is variable among individuals; responders exhibited lower pre-treatment depression scores, shorter illness duration, and later age of onset. Interestingly, response rates were disproportionately lower in patients with a single compared to multiple episodes of depression. Moreover, the degree of treatment resistance reportedly influences clinical improvement: antidepressant effects were substantially better in patients who failed to respond to only one medication in the current episode compared to those with several treatment failures (O'Reardon et al., 2007).

Recently, clinicians and researchers have developed novel treatment parameters in an attempt to boost its therapeutic potential in depression. Superior results were obtained by increasing the number of rTMS sessions: studies that included 20-30 treatments reported a doubling of response and remission rates (up to 58% and 43%, respectively) (Berlim et al., 2014). Over time, researchers manipulated additional dosage parameters to enhance clinical

response: a) stimulation intensity was progressively raised from 90-100 % to 120% of the recipient's resting motor threshold (RMT), and b) the number of pulses per session applied during initial trials (~10 trains) was increased to 75 trains or more in recent studies (Fitzgerald and Daskalakis, 2013). Strategies for stimulation site targeting were also modernized and shifted away from the conventionally used '5 cm method' (Pascual-Leone et al., 1996), an ambiguous measurement technique that misses the DLPFC in a third of cases (George et al., 2010). Increased target precision has been achieved using structural image-guided neuronavigation (Schönfeldt-Lecuona et al., 2005) and Beam F3 methodology (Beam et al., 2009). Despite these rTMS parameter modifications, remission is achieved in less than the majority, warranting alternative treatment protocols to improve antidepressant outcomes for medication-resistant patients.

1.3.4.1. Monophasic Pulses

The presently accepted rTMS practice utilizes biphasic waveforms; however, monophasic magnetic pulses may be more effective based on the homogenous activation of neurons compared to the complex cortical activation pattern observed during biphasic stimulation (Arai et al., 2005). The monophasic waveform is a unidirectional pulse that rises rapidly from zero then slowly decays (Fitzgerald and Daskalakis, 2013); in contrast, the sinusoidal biphasic pulse is shorter in duration and has empirically demonstrated lower neuromodulation strength (Arai et al., 2007, 2005; Hosono et al., 2008; Taylor and Loo, 2007). Recently, Goetz et al. (2016) compared the inhibitory strength of novel pulse shapes to biphasic by applying 1 Hz stimulation to the primary motor cortex (M1) and observing the amplitudes of elicited motor evoked potentials (MEPs). The unidirectional pulse shape generated greater inhibition of MEP amplitude than the biphasic pulse, which did not produce a significant change

in cortical activity. Current literature indicates greater cortical excitability with monophasic pulses in healthy volunteers, but there is no work to date examining clinical or cognitive outcomes compared to biphasic stimulation in MDD patients.

1.3.5 Predicting rTMS Response

With the techniques currently available, up to half of patients undergoing rTMS fail to achieve a clinical response. Research indicates a bimodal distribution of antidepressant outcome, suggesting that distinctions in response to rTMS can be reflected categorically as groups of responders and non-responders, rather than a continuum of change in treatment response (Fitzgerald et al., 2016). Despite the identification of MDD subpopulation characteristics that relate to rTMS response, these clinical variables (e.g., depression severity, treatment resistance, illness duration) demonstrate insignificant strength in accurately parsing responders from non-responders (Avery et al., 2008; Berlim et al., 2014; Fitzgerald et al., 2016).

Early prediction of successful rTMS outcomes in individual TRD patients could prove useful by sparing non-responders from undergoing unnecessary weeks of treatment. Furthermore, accurate prediction methods may reduce systemic health care costs by dramatically reducing the proportion of futile treatment attempts. Investigative approaches have turned towards measurable biological markers (biomarkers) as a potential avenue for treatment prediction; for example, a recent neuroimaging study retrospectively determined that rTMS responders showed increased functional connectivity in limbic and frontostriatal networks, including the left DLPFC, ACC, and amygdala (Drysdale et al., 2017). These encouraging findings warrant replication using accessible, cost-effective methodology to practically and reliably identify biomarkers predictive of therapeutic outcomes in depression.

1.4 Electroencephalography

1.4.1 Overview

Electroencephalography (EEG) is a non-invasive electrophysiological tool that measures neural network activity using scalp-placed electrodes. The EEG signal is generated by a number of summed postsynaptic potentials (PSPs) occurring primarily at apical dendrites of pyramidal neurons oriented perpendicular to the surface of the cortex (Olejniczak, 2006). Electrical activity associated with a single action potential event does not contribute to the measured signal, as it is too small and quick to be detected (Shibasaki, 2008). The characteristic oscillation pattern of the EEG wave reflects synchronized interactions between thalamocortical neurons that form cyclical current loops to produce rhythmic cortical activity (Olejniczak, 2006). Neural oscillatory activity is sensitive to cognitive and emotional states; EEG waveforms will change in frequency and amplitude with the altering state of the individual. Oscillations within specific frequency ranges are divided according to bands that reflect varying levels of arousal: delta (< 4 Hz; sleep), theta (4-8 Hz; drowsy), alpha (8-12 Hz; relaxed), and beta (13-30 Hz; alert).

1.4.2. Event-Related Potentials

Event-related potentials (ERPs) are positive (P) or negative (N) voltage deflections evoked by the brain in anticipation of or in response to internal or external events (Luck, 2012). ERP waveforms are time-locked to the onset of a stimulus; they are extracted from averaged EEG data and mirror the perception of sensory information, as well as higher-order cognitive operations. The amplitude of an ERP peak indexes the extent of neural resources devoted to processing specific cognitive information, whereas its latency tracks the timing of mental processing with millisecond precision (Duncan et al., 2009). ERP components can be classified based on polarity (P or N), latency (short or long), and scalp distribution (anterior or posterior);

they can also be categorized as either: a) exogenous components that are obligatorily elicited during the preconscious sensory processing of stimuli (peaks occurring <200 ms) and are highly determined by raw stimulus features (e.g, intensity, rate of presentation); or b) endogenous components that are influenced by cognitive factors (e.g., attention, stimulus relevancy) and reflect later (~200-1000 ms) neural processing stages (Luck, 2012). With their exceptional temporal resolution, ERPs are an effective method for assessing the neural correlates of dysfunctional sensory/cognitive processing in MDD and may provide insight into outcomes of various intervention strategies.

1.4.3. P300 ERP

The auditory evoked P300 waveform is the most extensively studied ERP and represents cognitive information processing in the realms of context-updating and attention shifting/orienting (Polich and Kok, 1995). P300 potentials are generated during the oddball paradigm as a positive deflection peaking at approximately 300 ms in response to infrequent and/or task-relevant auditory stimuli (Polich, 2007). The most distinctive property of the P300 component is its sensitivity to task-defined probability, resulting in the elicitation of larger amplitudes by rare oddball stimuli than frequently-presented standard stimuli (Luck, 2012). The size of the P300 wave reflects the amount of attentional neuronal resources allocated to an incoming stimulus; it also indexes neural representations of working memory performance when a stimulus environment changes in the presence of novel sensory input (Polich, 2007, 2004). P300 latency is tied to cortical processing speed and predominantly mirrors the time taken to perceive and evaluate a stimulus (Luck, 2012); it is independent from overt behavioral response generation and typically correlates negatively with cognitive function (Polich, 2004).

The P300 (P3) ERP encompasses two distinct subcomponents that emerge during the three-stimulus auditory oddball paradigm, the most common being the P3b waveform. The P3b peak is maximally activated at parietal regions (~250-600 ms) by task-related target tones and is thought to reflect cognitive capabilities associated with conscious, sustained attention (Polich, 2007). An earlier (~250-300 ms) P3a subcomponent is elicited fronto-centrally when distractor sounds are presented within a train of standard tones and infrequent target stimuli; the P3a wave can be characterized as a cortical measure of novelty discrimination and involuntary attention capture (Luck, 2012; Polich, 2004). Other observable ERP components are elicited by the auditory oddball paradigm and precede the onset of P300 waveforms as indices of earlier perceptual processing. For example, the N100 (N1) is a negative potential with a latency around 100 ms that reportedly represents the unconscious sensory analysis of physical stimulus features (Barry et al., 2003), whereas the P200 (P2) component (positive; ~200 ms) corresponds with cortical network activation and the initial differentiation of incoming task-relevant/irrelevant stimuli (Barry et al., 2003; Rennie et al., 2002). The N200 (N2) complex detects deviations from auditory memory traces; it reflects cognitive evaluation of stimuli and occurs earlier (~200 ms) than more advanced P3-indexed task-processing (Luck, 2012). As seen for P300, N200 can be subdivided into overlapping subcomponents; the novelty-associated N2a component is associated with automatic mismatch detection among stimuli, whereas the later N2b is elicited while categorizing and processing target stimuli (Bruder et al., 2012).

Although the precise neurobiological substrates underlying the P300 are unknown, recordings show peaks emerging simultaneously across the scalp, suggesting contributions by multiple neural generators that are either operating within a widespread, interconnected system or independently of one another (Duncan et al., 2009). Major foci have been identified in the

PFC, hippocampus, superior temporal sulcus, and intraparietal sulcus; thus, it has been postulated that P300 generation relies on the integrity of the PFC and its connections with the limbic system and temporoparietal brain regions (Duncan et al., 2009; Polich, 2004). In addition to studies of basic information processing, the P300 component has been used extensively as a measure of attentional impairment in neuropsychiatric research and has emerged as an illness marker of MDD (Duncan et al., 2009).

1.5 Electrophysiological Findings in MDD

1.5.1 Overview

Neuroimaging modalities such as functional magnetic resonance imaging (fMRI) have proven useful for detecting biologically meaningful markers of depression (Drysdale et al., 2017); however, EEG is an advantageous candidate for widespread use in clinical settings as a less complex, low-cost alternative. The clinical utility of EEG is showcased by its potential to aid with diagnosis, classification, and response prediction by directly capturing ongoing neuronal activity (versus proxy measurement) (Olbrich and Arns, 2013). Numerous resting EEG alterations have been observed in MDD, though certain pertinent findings have emerged consistently, including: increased cortical theta power (Knott et al., 2000; Ricardo-Garcell et al., 2009), diminished sgACC theta activity (Jaworska and Protzner, 2013; Saletu et al., 2010), and elevated global alpha activity/asymmetry (Jaworska et al., 2012; Olbrich and Arns, 2013; Towers and Allen, 2009). Whether EEG can reliably differentiate between treatment response groups has not been properly established. Previous work has been largely contradictory, with some studies supporting the predictive value of alpha/theta activity in MDD, and others depicting these measures as insignificant for determining antidepressant response (Arns et al., 2016; Bailey et al., 2018; Wade and Iosifescu, 2016; Widge et al., 2019). Investigation into additional

electrophysiological endophenotypes that are reflective of clinical status in depression is warranted to uncover markers that effectively classify individuals as treatment responders/non-responders.

1.5.2 P300 Abnormalities

The P300 ERP has been extensively used in depression research, with most, but not all, studies reporting attenuated amplitudes in patients compared to healthy controls (Bruder et al., 2012; Van Dinteren et al., 2015; Zhou et al., 2019). Despite conflicting findings, Bruder et al. (2012) calculated a moderate group difference (mean effect size: 0.85) among P300 studies in MDD, indicating an overall trend of smaller potentials and deficient attentional allocation in depressed patients. Concordantly, findings of P300 latency in MDD are equivocal, though studies predominantly report delayed peak onset (Tripathi et al., 2015; Zhou et al., 2019) which suggests inefficient perceptual processing in depression.

Heterogeneity among P300 findings in MDD may be influenced by differences among patients. For example, amplitude reductions and latency delays reportedly correspond to illness severity (Tripathi et al., 2015; Van Dinteren et al., 2015), thus classifying the P300 ERP as at least partially state-dependent. Furthermore, several studies comparing MDD patients to controls have failed to differentiate P300 subcomponents (P3a and P3b) embedded within a more cognitively challenging three-stimulus auditory oddball paradigm. Importantly, one study by Bruder et al. (2009) found smaller novelty and target P300 amplitudes in patients; however, the difference between controls had a larger effect size for novelty P3a (1.0) than target P3b (0.61). The P3a and P3b reflect distinct cognitive operations and underlying neurophysiological mechanisms; therefore, individual examination of each subcomponent could yield new insight into the nature of attentional deficits in MDD (Bruder et al., 2012).

Compared to P300, there is considerably less agreement regarding ERP-indexed early sensory processing in depression; though deficits have been reported, results have been inconsistent. In MDD patients, some studies have found abnormal N1 latencies/amplitudes (Coffman et al., 1989; Greimel et al., 2015; Kemp et al., 2009; Van Dinteren et al., 2015), whereas others detected no significant differences from controls (Bruder et al., 1998; Kawasaki et al., 2004; Kemp et al., 2010). Similarly, for P200, both decreased amplitudes/prolonged latencies and no group differences have been reported (Anderer et al., 2002; Greimel et al., 2015; Kemp et al., 2010, 2009; Zhou et al., 2019). N200 results have been particularly variable, with some researchers finding increased amplitudes (Bruder et al., 1998; Giese-Davis et al., 1993), and others finding no differences (Blackwood et al., 1987; Kaiser et al., 2003) or reduced amplitudes in depressed subjects (Deldin et al., 2000; el Massioui et al., 1996). Though attentional deficits are prevalent in depressive states, further investigation of auditory oddball ERP subcomponents is required to draw more definitive conclusions regarding sensory processing, task-relevance evaluating, mismatch detecting, and context updating capabilities in MDD.

1.5.3 Effects of rTMS on P300

A large body of work has already demonstrated the pro-cognitive effects of HFL-rTMS (Guse et al., 2010; Martis et al., 2003); thus, it may be hypothesized that HF-rTMS applied to the left DLPFC should produce P300 alterations associated with enhanced attentional processing. Yet, a meta-analysis of the effects of rTMS on P300 components yielded conflicting results among 3 studies administering left-sided stimulation at a high frequency (Rêgo et al., 2012). In samples of healthy controls, Jing et al. (2001) used 10 Hz L-rTMS and reported increases in P3 latency, whereas Evers et al. (2001) found decreased latencies when using left-sided stimulation

at 20 Hz. One study recorded P300 data from 10 patients diagnosed with a depressive disorder before and after 5 sessions of HFL-rTMS (10 Hz) and reported a significant post-treatment increase in amplitude, but no change in latency (Möller et al., 2006). More recently, Choi et al. (2014) explored the effects of 10 Hz L-rTMS on ERP components in medication-resistant depression. Following 3 weeks of stimulation, results from an auditory oddball task showed significant increases in P2 amplitude and P3 latency, albeit no changes in P3 amplitude were detected (Choi et al., 2014). Notably, clinical improvement was achieved after 3 weeks of HFL-rTMS (Choi et al., 2014), but not after 5 consecutive days of treatment (Möller et al., 2006). Given the overall paucity of findings from studies with limited treatment duration, ERP changes should be evaluated after longer therapeutic regimens of HFL-rTMS to adequately determine the effects of high-frequency stimulation on P300 parameters in TRD.

1.5.4. P300 Biomarkers

Emerging evidence indicates that auditory oddball ERP measurements may serve as biomarkers predictive of treatment outcomes in depression. Reduced P300 potentials and prolonged latencies at baseline have been detected in individuals who respond poorly to antidepressants (Bruder et al., 1995; Işintaş et al., 2012; Vandoolaeghe et al., 1998); studies suggest these non-responders may comprise a subgroup with ‘pre-frontal dysfunction’ (Dunkin et al., 2000; Kalayam and Alexopoulos, 1999). Furthermore, the N100 component has been proposed as an illness marker based on findings of larger pre-treatment amplitudes in medication responders (Olbrich and Arns, 2013; Spronk et al., 2011). These findings were recently replicated by Van Dinteren et al. (2015); baseline N1 amplitudes correlated with percentage improvement on depressive symptom rating scales and were increased in male SNRI responders.

With the establishment of the efficacy of rTMS, there has been increased interest in uncovering potential neural correlates of treatment response. Though the P300 wave has shown considerable promise as a biomarker in MDD, research examining its specific association with rTMS outcomes is exceptionally limited. In a pioneering trial investigating P300 components as predictors of rTMS response, Arns et al. (2012) measured ERP parameters in 90 depressed patients treated with left DLPFC HF-rTMS. Treatment responders elicited marginally ($p = .054$) diminished P300 amplitudes at baseline, contrary to previous findings (Bruder et al., 1995; Vandoolaeghe et al., 1998); however, there were no differences between response groups with respect to P300 latency. A follow-up study by Krepel et al. (2018) failed to replicate these findings, though trending reductions in pre-treatment P300 amplitudes among rTMS responders were detected.

1.5.5 Summary

MDD literature assessing HFL-rTMS effects on various auditory oddball features (i.e., N1/200, P2/P300 amplitudes and latencies) and their utility as response classifiers is unclear, underscoring the need for further investigation into the cognitive impacts of rTMS and the neurophysiology underlying ERP-indexed attentional processing in depression.

Electrophysiological endophenotypes that are reflective of clinical status and cognitive dysfunction may be important in providing insight into the prediction of antidepressant response in TRD patients.

Chapter 2: Research Objectives and Hypotheses

2.1. Objectives

Two primary objectives were defined for this project:

1. To examine the impact of HFL-rTMS therapy and monophasic vs. biphasic pulse type on attentional processing in TRD as indexed by P3 potentials and clinician-rated concentration scores
2. To assess P300 ERP components as biomarkers predictive of clinical and cognitive response to monophasic and biphasic HFL-rTMS as a means of targeting and personalizing antidepressant treatment

In an effort to expand upon the current literature base, a secondary objective was defined for this project:

3. To investigate differences in novelty and target detection between healthy controls and treatment-resistant MDD patients using pre- and post-treatment P3a/P3b measures

Finally, two exploratory objectives were defined for this project:

4. To compare the efficacy of monophasic versus biphasic HFL-rTMS in improving clinician-rated antidepressant outcomes
5. To assess the effects of monophasic versus biphasic HFL-rTMS on early sensory and perceptual processing in TRD as assessed by N100, P200, and N200 ERP components.

2.2. Hypotheses

In relation to these research objectives, three primary and two secondary hypotheses were proposed:

1. Both target detection and novelty discrimination are expected to improve following 6 weeks of rTMS therapy in MDD patients

2. Compared to the biphasic condition, patients in the monophasic treatment condition will demonstrate improved attentional processing reflected by increased P3a/P3b amplitudes and reductions in reported concentration difficulties
3. Baseline P300 amplitudes and latencies will differ significantly between HFL-rTMS treatment response groups and will correlate with degree of symptomatic (clinical and cognitive) improvement in patients
4. TRD patients will produce attenuated P3a and P3b amplitudes and slower latencies compared to healthy controls at baseline
5. Contrary to the post-rTMS improvement predicted in patients, healthy controls will display little to no change in attentional processing as indexed by follow-up ERP measurements

Chapter 3: Methods

The clinical and electrophysiological data for this study were derived from a larger double blind, randomized controlled trial comparing monophasic to biphasic rTMS in treatment-resistant depression (TRD).

3.1. Participants

TRD patients were recruited from clinician referrals of registered outpatients at the Royal Ottawa Mental Health Centre (a teaching psychiatric hospital providing specialized mental health care as a tertiary referral centre across Eastern Ontario). Patients were also recruited externally through public online postings; external candidates were admitted as outpatients of the Royal Ottawa Mental Health Centre prior to treatment initiation. Healthy volunteers were recruited through public online postings and word of mouth. Written informed consent was

obtained from all study participants (forms approved by the Research Ethics Board of The Royal’s Institute of Mental Health Research; Appendix A).

3.1.1 Screening Procedure

The eligibility criteria for study participation are listed in Table 1. Interested candidates were administered a pre-screen telephone interview to assess initial eligibility. Subsequently, a referral was requested from the patient’s primary physician, whereby further information regarding the length and onset of the current depressive episode was obtained. Following referral, patients underwent a psychiatric consultation with a study psychiatrist (Pierre Blier, Lisa McMurray, Asif Khan, or Ahmed Rostom) to review medication history, confirm a diagnosis of major depressive episode, and assess any DSM-IV comorbidities. During a final in-person screening session with research personnel, patients underwent a blood draw to rule out significant laboratory abnormalities, a urine toxicology screen to confirm substance abstinence, and an auditory test to ensure adequate hearing thresholds. Following the informed consent process and prior to EEG recording, healthy volunteers were subject to screening during the baseline session, which included a urine toxicology screen and an auditory test.

Table 1. Eligibility Criteria for Patients and Healthy Controls

	Inclusion Criteria	Exclusion Criteria
Patients	<ul style="list-style-type: none"> (1) A confirmed DSM-IV diagnosis of unipolar major depressive disorder (2) Were voluntary, competent to consent to treatment, and able to adhere to the treatment schedule (3) Between the ages of 18-75 (4) Failed to achieve a clinical response to an antidepressant of adequate dose and duration in the current episode; or were unable to tolerate at least 2 antidepressant trials of inadequate dose and duration (5) Maintained a stable regimen of medication and/or psychotherapy for at least 4 weeks prior 	<ul style="list-style-type: none"> (1) A history of substance dependence or abuse in the last 3 months; or current substance indicated by a urine screen (2) Any significant neurological disorder or insult (3) Any rTMS contraindications including implanted devices, foreign metal bodies in or around the head, any unstable medical conditions, and/or a history of seizures (3) Pregnant (4) Active suicidal intent (5) A lifetime DSM-IV diagnosis of bipolar I or II, schizophrenia, or other psychotic disorder; or

	<p>to screening with no anticipated changes during treatment</p> <p>(6) Scored ≥ 22 on the MADRS</p> <p>(7) Passed the TMS Adult Safety Screen (TASS) (Wasserman et al. 2000)</p> <p>(8) Normal thyroid functioning based on pre-treatment blood work</p>	<p>any other current primary Axis I or Axis II diagnoses causing greater impairment than MDD</p> <p>(6) Failed a course of ECT during the current episode or episode prior</p> <p>(7) Received rTMS for any previous indication</p> <p>(8) Had taken lorazepam (>2 mg) or any anticonvulsant in the 4 weeks prior to screening</p> <p>(9) Failed 3 or more adequate trials of medications of different drug classifications in the current episode</p>
Healthy Controls	<p>(1) Were voluntary and competent to consent to treatment</p> <p>(2) Between the ages of 18-75</p> <p>(3) Patient-matched by age, gender, education, and smoking status</p>	<p>(1) A history of substance dependence or abuse in the last 3 months; or current substance indicated by a urine screen</p> <p>(2) Any significant neurological disorder or insult</p> <p>(3) Any current or history of psychiatric illness based on the Structured Clinical Interview Non-Patient (SCID-NP) version for DMS-IV (Spitzer et al., 1995)</p>

3.1.2 Treatment Protocol

Eligible TRD patients (N=20) were stratified at random to one of two treatment protocols, receiving either high-frequency (20 Hz) monophasic or biphasic stimulation of the left dlPFC. Treatment allocation of enrolled patients was conducted using a computer algorithm (www.randomizer.org) and a sealed randomization list was generated. Experimenters, symptom raters and patients were blind to the treatment allocation. By necessity, treatment technicians accessed the randomization list immediately before treatment initiation; they were instructed to abstain from discussing treatment allocation with patients and research staff. The study timeline of events is illustrated in Figure 1.

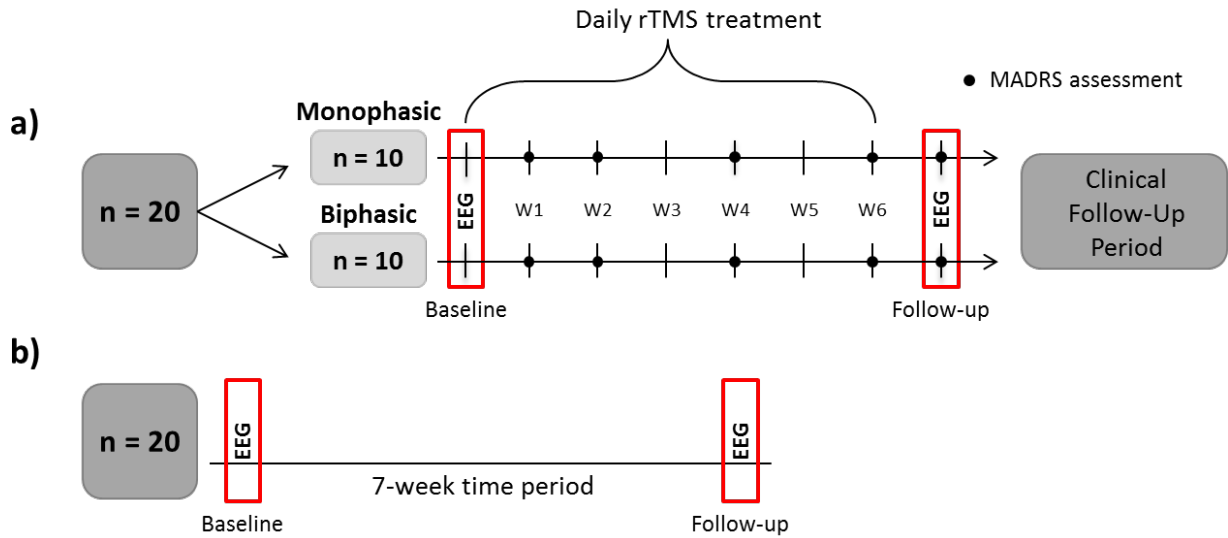


Figure 1. Study Timeline. a) Eligible TRD patients were randomly assigned to receive either monophasic or biphasic stimulation over a six-week treatment period consisting of five rTMS sessions per week (Monday to Friday, 30 sessions total). EEG recordings were acquired twice for each subject: 1) during the week prior to treatment initiation; and 2) at one week post-treatment termination. Clinician-rated MADRS assessments were completed at baseline, during treatment (weeks 1, 2, 4, and 6), and at three follow-up points (1 week, 4 weeks, and 12 weeks post-treatment); b) Patient-matched healthy controls underwent two separate EEG recordings: 1) at baseline; and 2) after 7 weeks post-baseline.

3.2 rTMS Technique

Each patient received 30 sessions of rTMS (monophasic or biphasic) at 120% motor threshold (MT) once per day, 5 days per week (Monday to Friday), over a span of 6 consecutive weeks. All treatments were administered at the Royal's Institute of Mental Health Research using a NeuroQore Investigational TMS Device (NeuroQore, Ottawa, ON) equipped with a cooled Figure-8 70 mm coil; rTMS stimulation parameters are summarized in Table 2. Patients were monitored for both short-term (over 24 hours) and acute adverse events using a self-report

checklist (Appendix B) administered prior to and immediately following daily rTMS treatment, respectively. Patients were compensated \$10 daily for travel expenses.

Table 2. Stimulation Parameters

	Monophasic	Biphasic
Effective pulse width	Fall time 60 μ s	Rise and fall time 60 μ s
Ineffective pulse width	Rise time 200 μ s	-
Frequency	20 Hz	20 Hz
Pulse interval	1s	1s
Silent interval	5s	5s
Pulses per session	3,000	3,000
Stimulation duration	15 minutes	15 minutes

3.2.1 Neuronavigation

Neuronavigation was accomplished using Beam F3 methodology (Beam et al., 2009) to locate the optimal stimulation target. Three measurements were obtained for this method: 1) the distance from tragus to tragus, 2) the distance from nasion to inion, and 3) the head circumference. To identify site F3 over the DLPFC, two coordinates were calculated according to the 10/20 EEG system (Trans Cranial Technologies Ltd, 2012): 1) distance along the circumference from midline and 2) distance from the vertex.

3.2.2 Motor Threshold Calibration

Resting MT was assessed prior to treatment initiation by stimulating the primary motor cortex according to published methods (Schutter and van Honk, 2006). The stimulation intensity for each patient was defined by the technician’s visual observance of a twitch in the first dorsal interosseous (FDI) muscle in the hand. If the individual MT could not be determined for any anatomical-physiological reason, the stimulation intensity was set according to the lower 95% confidence interval of the average MT value from previously enrolled patients.

3.3 Clinical Assessment

Patients were administered the Montgomery-Asberg Depression Rating Scale (MADRS), a semi-structured interview indexing depression severity, by study psychiatrists during scheduled clinical assessments (see Figure 1). MADRS score was recorded at each assessment point and used as the primary outcome measure. Treatment response was defined as a $\geq 50\%$ reduction in MADRS score from baseline and the scoring criterion for remission was < 10 at one-week post-treatment (primary endpoint).

3.3.1 Adverse Events

Adverse events were recorded using a self-report checklist consisting of varied items clustered into psychological, physical, and psychomotor symptoms (Table 3). TRD patients completed this checklist twice per daily treatment session: once prior to receiving rTMS to assess short-term adverse stimulation effects (over the preceding 24-hour period) and once immediately following treatment to assess acute effects.

Table 3. Symptom Clusters of Adverse Events Associated with rTMS Treatment

Physical	Psychological	Psychomotor
Light headedness	Agitated	Seizure
Headache	Irritated	Tremors
Drowsy	Fatigue	Dizziness
Nausea	Depressed	Spinning sensation
Jaw/muscle pain	Anxious	Lack of coordination
Heart palpitations	Mood swings	Disorientation
Chest pain	Difficulty concentrating	Weakness/lack of energy
Difficulty breathing	Hallucinations	
Dry mouth		
Blurred vision		

3.4 EEG Procedure

EEG assessments occurred during a single 1-hour session between 9:00 am and 4:00 pm on weekdays. Participants were asked to abstain overnight from caffeine and alcohol, and at least 2 hours from food and nicotine; any medications consumed the morning of were noted.

Participants were seated in a dimly lit, sound-attenuated chamber and subjected to various task paradigms while EEG activity was recorded. Embedded within the paradigms, the active auditory P300 task consisted of 4 blocks of randomized stimuli binaurally presented through headphones. Auditory stimuli included high-pitched (1000 Hz) standard tones (336 ms duration; 70 dB), low-pitched (700 Hz) target tones (336 ms duration; 70 dB), and novel distractor sounds (169-399 ms duration; 65-75 dB) (e.g., horn honking, dog barking). Participants were instructed to respond as quickly and accurately as possible via mouse-button click to the infrequently-presented (10%) target tones, while ignoring the frequent (80%) standard tones and rare (10%) distractor sounds (e.g., barking dog). To ensure adequate task comprehension, participants completed a short practice block (6 target tones) without EEG recordings. Hits (% of correct target clicks), false alarms (standard or distractor clicks), and reaction time (ms) were recorded as measures of behavioral performance. Healthy volunteers were compensated \$30 per EEG session for a total of \$60; similarly, patients received \$15 per session (\$30 total).

3.4.1 Recordings

EEG activity was acquired with Brain Vision Recorder[®] and a Brain Vision QuickAmp[®] amplifier (Brain Products; bandpass filter: 0.1-70 Hz, sampling rate: 500 Hz) with Ag/AgCl passive electrodes placed according to the 10/20 international EEG system (Trans Cranial Technologies Ltd, 2012)(see Figure 2). Two electrodes were placed on left and right mastoids (sites TP9 and TP10), in addition to a ground electrode (site AFz) and two reference electrodes placed on either side of the nose. Vertical and horizontal electrooculographic activity was recorded by electrodes on the supraorbital ridges and outer canthi, respectively. Electrode impedance was maintained at ≤ 5 k Ω .

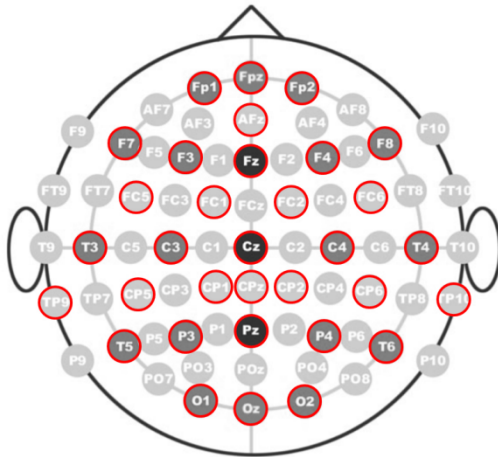


Figure 2. EEG Electrode Montage. Recordings obtained from 32 scalp sites (circled in red).

3.5 ERP Processing

Using Brain Vision Analyzer 2® software (Brain Products), EEG recordings were re-referenced to mastoids, digitally filtered (0.1-30 Hz), ocular corrected (Gratton et al., 1983), and segmented by stimulus type (standard, novelty, target) into 1000 ms epochs, beginning 150 ms pre-stimulus onset. Segments were baseline corrected (150 ms pre-stimulus) and subject to artifact rejection; segments with voltages exceeding $\pm 70 \mu\text{V}$ were excluded from further analysis. Remaining segments were averaged and used to derive amplitude and latency measurements for each stimulus waveform. Novelty P3a and target P3b amplitudes and latencies were chosen at maximally positive peaks between 200-700 ms at sites Fz/Cz (P3a) and Pz (P3b). N1 (standard, novelty, target), N2 (target), and P2 (standard, target) measurements were derived from site Fz for exploratory investigation. Amplitude and latency information was exported with 5 points to the left and right of the peak values for statistical analysis.

3.6 Statistical Analysis

3.6.1 Clinical Outcome

A restricted maximum likelihood (REML) mixed-model of repeated measures (MMRM) approach was used for the primary outcome analysis with MADRS score as the dependent variable. The MMRM statistical model effectively handles missing data, unequal variances, and correlated data that is common in repeated measurements of subjects. The model included visit (week 0/1/2/4/6/7) as the repeated measure; and treatment (monophasic/biphasic), and treatment-by-visit interaction as fixed effect variables. Using Bayesian Index Criterion (BIC) values, a first-order autoregressive (AR1) covariance structure was determined as the best fit and was therefore included in the model. An identical model was subsequently used to examine the effects of treatment type and duration on concentration in TRD patients; Concentration Difficulties (MADRS: item #6) score served as the dependent variable. To assess patient outcome rates, a test of two proportions analyzed monophasic vs. biphasic group differences in the proportion of responders and remitters at the primary endpoint (Fisher's exact test was run due to small sample sizes).

3.6.2 ERP Components

ERP data was statistically analyzed using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL). Mixed analysis of variance (ANOVA) procedures were used to analyze ERP amplitude, latency, and behavioral performance measures among TRD patient and healthy control groups, with session (baseline/follow-up) as the within-subject factor. Electrode site (Fz/Cz) was used as an additional within-subject factor in the P3a and target N2 analyses, as peak amplitudes were differentially maximal between patients (Cz) and healthy controls (Fz). Significant effects ($p < .05$) and planned comparisons were examined with Bonferroni-corrected

t-tests. One-way analysis of covariance (ANCOVA) was used to analyze stimulation (monophasic/biphasic) group differences in TRD patients. Baseline amplitude, latency, and behavioral performance values were used as covariates with post-treatment ERP measures serving as the dependent variable.

3.6.3 Response Prediction

Independent t-tests were used to assess the utility of ERP components as predictors of rTMS treatment response in TRD. Patients were stratified into responder or non-responder groups based on MADRS score at one week post-treatment; differences in baseline ERP features (amplitude/latency) between response groups were analyzed. As exploratory analyses, Pearson's correlations examined the association between baseline P300 components and the percent change in MADRS score (difference in primary endpoint score from baseline); relationships between baseline ERP features and the change in the Concentration Difficulties item score were analyzed using Spearman's ranked-order correlation.

3.6.4 Adverse Events

Fisher's exact test was used to examine proportional differences in clustered adverse symptoms experienced both short-term and acutely within each treatment week (1-6) by patients receiving monophasic versus biphasic rTMS.

Chapter 4: Results

4.1 Clinical Outcomes

Of the 20 TRD patients enrolled to undergo rTMS, 18 completed the 6-week treatment protocol; two patients dropped out after week 1 and week 4, respectively, and could not be classified as treatment responders or non-responders. Differences in patient demographics and baseline characteristics between monophasic and biphasic groups were analyzed using

independent t-tests. Fisher’s exact test was used to compare proportion of sexes between groups; treatment groups did not significantly differ in sex, age, baseline MADRS score, length of current depressive episode, or number of current antidepressant medications (see Table 4 for a summary of results).

Table 4. Demographics/Baseline Characteristics of Monophasic and Biphasic Patients who Completed Treatment ($N = 18$)

Item	Monophasic ($N = 9$)	Biphasic ($N = 9$)	p-value
Sex (Male/Female)	4/5	3/6	.500
Mean Age (Years)	52.8 ± 11.0	41.2 ± 15.3	.072
Mean Baseline MADRS Score	29.6 ± 4.5	29.4 ± 4.5	.926
Mean Current Episode Length (Months)	57.9 ± 82.6	38.0 ± 40.1	.489
Mean # Current Medications	1.4 ± 1.2	1.3 ± 1.1	.747

Note: mean ± standard deviation, unless otherwise stated

4.1.1 Treatment Response

At one-week post-rTMS treatment, 5 patients (55.6%) responded to monophasic stimulation compared to 7 patients (77.8%) in the biphasic group; there was no significant difference in proportions between the two stimulation types ($p = .620$). Comparison of remission rates at the primary endpoint revealed no significant difference ($p = .153$) in the proportions of remitters who received monophasic stimulation (2 patients; 22.2%) versus biphasic stimulation (6 patients; 66.7%).

A mixed model of repeated measures (MMRM) was used to assess the significance of treatment (monophasic/biphasic) and visit (weeks 1/2/4/6/7) as predictors of antidepressant response (change in depression severity as indexed by MADRS score); this analysis used all available data from patients who received at least one week (5 consecutive days) of rTMS treatment ($N = 20$). A significant time effect emerged, with all patients demonstrating clinical

improvement (decreased scores from baseline) across visits [$F(5, 75) = 11.82, p < .001$] (see Figure 3a). Both treatment [$F(1, 23) = .000, p = .990$] and treatment-by-visit [$F(5, 75) = .86, p = .512$] were non-significant predictors of antidepressant response. Parameter estimates revealed significant differences between baseline MADRS scores and scores at each subsequent visit (Week 1: $p < .05$; Week 2: $p < .01$; Week 4-7: $p < .001$). MADRS scores are summarized for each visit in Table 5.

To estimate treatment effect on cognitive changes, an MMRM analysis was performed on Concentration Difficulties score (MADRS: item #6). Results indicated a significant improvement in concentration over time [$F(5, 63.76) = 10.03, p < .001$] (see Figure 3b); scores were significantly reduced from baseline at each visit (Week 2: $p < .05$; Weeks 4-7: $p < .001$), except for Week 1. Treatment emerged as a trending predictor [$F(1, 27.08) = 3.81, p = .061$]; however, the between-groups difference (0.66; monophasic > biphasic) was not significant ($p = .124$). A significant treatment-by-visit interaction effect was found [$F(5, 63.76) = 2.46, p = .042$]. Least square mean differences indicated significantly reduced Concentration Difficulties scores in biphasic patients ($M = 1.13, SE \pm .30$) compared to monophasic patients ($M = 2.56, SE \pm .30$) at treatment conclusion (Week 6).

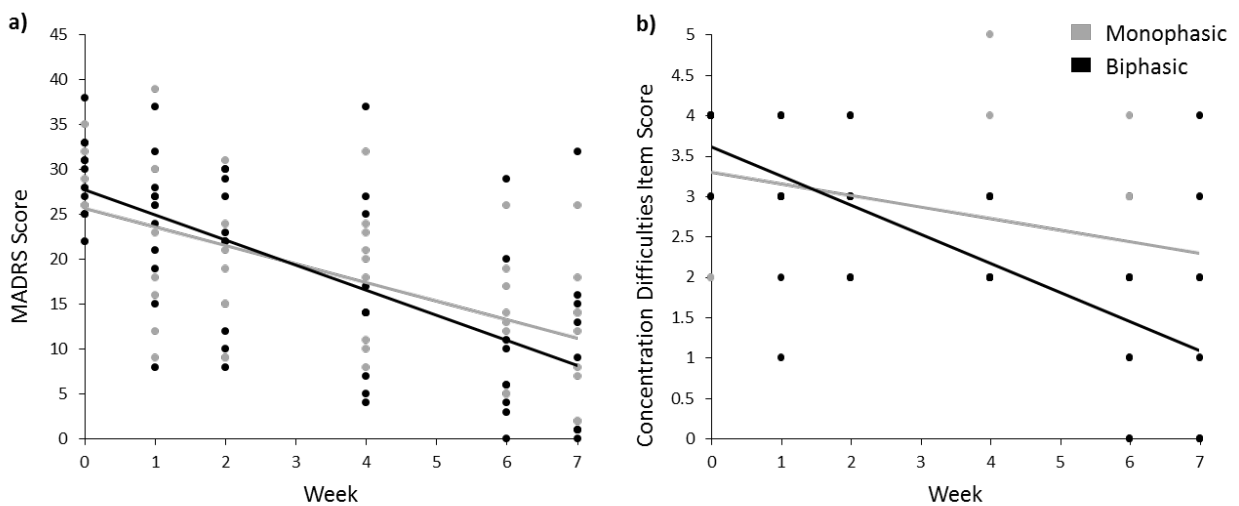


Figure 3. Treatment Effects on Clinical Response. a) Raw MADRS scores significantly decreased across time but did not differ between stimulation groups; b) Concentration Difficulties scores significantly improved across time and greater improvement was observed post-biphasic stimulation than monophasic

Table 5. Summary of MADRS Scores by Visit

	Monophasic (N = 9)	Biphasic (N = 11)*
Baseline		
Mean (SD)	28.4 (4.2)	29.4 (4.5)
Week 1		
Mean (SD)	22.6 (9.7)	24.0 (8.0)
Δ from Baseline	-5.8	-5.4
Week 2		
Mean (SD)	18.3 (7.2)	21.3 (8.4)
Δ from Baseline	-10.1	-8.1
Week 4		
Mean (SD)	18.6 (7.7)	15.4 (8.7)
Δ from Baseline	-9.8	-14
Week 6		
Mean (SD)	13.6 (6.6)	9.9 (9.2)
Δ from Baseline	-14.8	-19.5
Week 7		
Mean (SD)	11.4 (7.7)	9.8 (10.6)
Δ from Baseline	-17	-19.6

*Week 2-4 (N = 10), Week 6-7 (N = 9)

4.1.2 Adverse Events

Analyses using Fisher’s exact test indicated no significant differences in the proportion of reported physical, psychological, or psychomotor symptoms between stimulation groups (see Table 6 and Table 7 for acute and short-term adverse event frequencies, respectively).

Table 6. Proportion of Patients who Experienced Acute Adverse Events

Week	Physical		Psychological		Psychomotor	
	Monophasic	Biphasic	Monophasic	Biphasic	Monophasic	Biphasic
1	6 (66.7)	7 (63.6)	4 (44.4)	4 (36.4)	2 (22.2)	4 (36.4)
2	4 (44.4)	3 (30)	5 (55.6)	3 (30)	2 (22.2)	3 (30)
3	3 (33.3)	3 (30)	3 (33.3)	0	2 (22.2)	1 (10)
4	3 (33.3)	2 (20)	2 (22.2)	3 (30)	1 (11.1)	1 (10)
5	3 (33.3)	2 (22.2)	3 (33.3)	1 (11.1)	0	1 (11.1)
6	3 (33.3)	2 (22.2)	1 (11.1)	0	0	1 (11.1)

Note: N (%)

Table 7. Proportion of Patients who Experienced Short-Term Adverse Events

Week	Physical		Psychological		Psychomotor	
	Monophasic	Biphasic	Monophasic	Biphasic	Monophasic	Biphasic
1	7 (87.5)	7 (70)	6 (75)	8 (80)	5 (62.5)	4 (40)
2	3 (37.5)	4 (44.4)	5 (62.5)	5 (55.6)	3 (37.5)	4 (44.4)
3	5 (62.5)	3 (33.3)	5 (62.5)	4 (44.4)	2 (25)	2 (22.2)
4	3 (37.5)	3 (33.3)	5 (62.5)	4 (44.4)	1 (12.5)	1 (11.1)
5	2 (25)	2 (25)	4 (50)	2 (25)	1 (12.5)	2 (25)
6	4 (50)	2 (25)	4 (50)	2 (25)	1 (12.5)	2 (25)

Note: *N* (%)

4.2 ERP Results

The properties (i.e., amplitude and latency) of ERPs indexing attention-related neural processes were statistically analyzed to compare differences between TRD patients/healthy controls and monophasic/biphasic conditions over time. All 20 enrolled healthy controls completed both EEG sessions; however, controls matched to the 2 patient dropouts were removed from analysis to ensure consistency between samples. Differences in age and education level between patients and controls were assessed using independent t-tests; no significant results were detected. Chi-square analyses revealed non-significant proportional differences in handedness, smoking status and sex between groups (see Table 8 for a summary of results).

Table 8. Demographic Comparison of TRD Patients and Healthy Controls (*N* = 18)

Item	Patients (<i>N</i> = 9)	Controls (<i>N</i> = 9)	p-value
Sex (Male/Female)	7/11	8/10	.735
Mean Age (Years)	47.3 ± 14.3	45.7 ± 12.2	.708
Handedness (Right/Left/Ambidextrous)	14/3/1	14/3/1	1.000
Smoking Status (Smoker/Non)	2/16	1/17	.546
Education Level (Years)	17.7 ± 1.9	17.7 ± 1.4	1.000

Note: mean ± standard deviation, unless otherwise stated

4.2.1 Standard N1/P2 Amplitude and Latency

NI: Data are mean ± SE, unless otherwise stated. A two-way mixed ANOVA revealed no main effects of session (baseline/follow-up), group (patient/control), or session-by-group

interaction on N1 features. One-way ANCOVA results indicated that N1 amplitude and latency did not significantly differ between treatment groups (monophasic/biphasic).

P2: Analysis of frontal P2 components showed a main group effect [$F(1, 34) = 7.95, p = .008$] with healthy volunteers displaying increased amplitudes ($3.37 \pm .36 \mu\text{V}$) compared to TRD patients ($1.95 \pm .36 \mu\text{V}$). Conversely, P2 latency did not significantly differ between groups; there were no main effects of session or session-by-group-interaction for either P2 component. Exploratory follow-up comparisons revealed significantly attenuated P2 amplitudes in patients ($1.58 \pm .36 \mu\text{V}$; controls: $3.39 \pm .36 \mu\text{V}$) at baseline ($p = .001$) with non-significant group differences at Week 7. Following rTMS treatment, TRD patients exhibited significantly increased P2 amplitudes ($2.32 \pm .41 \mu\text{V}, p = .021$) and longer latencies ($218.78 \pm 8.53 \text{ ms}, p = .045$) compared to baseline (amplitude: $1.58 \pm .36 \mu\text{V}$; latency: $206.11 \pm 7.62 \text{ ms}$). Healthy controls showed no significant amplitude or latency differences between sessions.

No significant group differences existed in P2 amplitude or latency between patients receiving monophasic versus biphasic rTMS. Given the significant findings indicating post-treatment (versus baseline) differences in amplitude and latency within patients, exploratory independent t-tests were conducted examining baseline P2 components as predictors of treatment response. Although baseline latency was not a significant predictor of clinical response, there was a trend towards significantly reduced baseline amplitudes [$t(16) = 1.98, p = .065$] in responders ($1.11 \pm .43 \mu\text{V}$; non-responders: $2.30 \pm .33 \mu\text{V}$). This trend reached statistical significance [$t(7) = 2.84, p = .029$] within the biphasic group (responders: $.76 \pm .48 \mu\text{V}$; non-responders: $2.49 \pm .30 \mu\text{V}$). Furthermore, biphasic treatment responders exhibited significantly shorter [$F(1, 7) = 7.47, p = .029$] baseline P2 latencies ($184.80 \pm 11.32 \text{ ms}$) than non-responders ($222.50 \pm 5.74 \text{ ms}$). No significant differences emerged within the monophasic group.

4.2.2 Novelty N1/P3a Amplitude and Latency

N1: No main effects of group (patient/control), session (baseline/follow-up) or group-by-session interaction were noted with N1 novelty amplitude or latency. Similarly, no significant N1 differences existed between monophasic and biphasic conditions (Figure 5).

P3a: Mixed ANOVAs of P3a amplitude in patients versus controls (factors: session and site as within; group as between) revealed no main effects of session, site, or group. No main interaction effects were detected; however, a trending session-by-group interaction effect emerged [$F(1, 34) = 3.95, p = .055$]. Planned comparisons revealed a significant amplitude difference ($p = .041$) between pre- ($6.64 \pm 1.11 \mu\text{V}$) and post-treatment ($8.22 \pm 1.23 \mu\text{V}$) sessions in patients, but not in healthy controls. No significant differences in baseline amplitude were detected between patients and controls (see Figure 4a). Exploratory follow-up comparisons indicated a site-dependent effect, with patients exhibiting significantly increased post-treatment amplitudes ($8.38 \pm 1.30 \mu\text{V}$; pre-treatment: $6.46 \pm 1.22 \mu\text{V}$) at site Cz ($p = .029$; Figure 4c), but not site Fz (Figure 4b). Analysis of P3a latency showed no main session effect. A main effect of group was detected [$F(1, 34) = 8.49, p = .006$], with patients exhibiting significantly longer latencies ($350.67 \pm 9.51 \text{ ms}$) than controls ($311.47 \pm 9.51 \text{ ms}$). A main site effect [$F(1, 34) = 6.81, p = .013$] revealed slower latencies at Cz ($336.36 \pm 7.16 \text{ ms}$) compared to Fz ($325.78 \pm 6.89 \text{ ms}$). A significant time-by-group interaction [$F(1, 34) = 9.28, p = .004$] emerged, with follow-up comparisons showing slower ($p < .001$) post-treatment latencies in TRD patients ($358.33 \pm 9.66 \text{ ms}$) versus controls at week 7 ($303.89 \pm 9.66 \text{ ms}$); group differences did not exist at baseline. Compared to baseline, both groups exhibited significant P3a latency differences at week 7 (patients: $p = .037$; controls: $p = .039$); patients displayed significantly longer post-treatment latencies ($358.33 \pm 9.66 \text{ ms}$; baseline: $344.00 \pm 10.61 \text{ ms}$), whereas controls exhibited

shorter follow-up latencies (303.89 ± 9.66 ms; baseline: 319.06 ± 10.61 ms). No other two- or three-way interaction effects emerged.

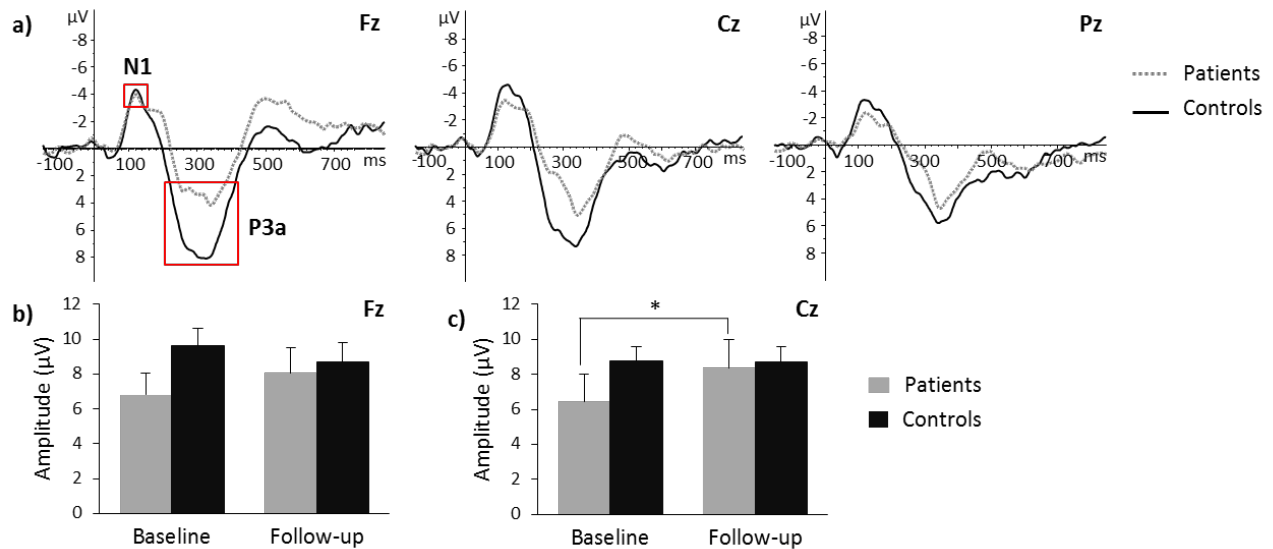


Figure 4. ERP-Indexed Novelty Processing in TRD Patients and Healthy Controls. a) Grand averaged N1 and P3a auditory evoked potentials elicited at baseline; mean \pm standard error of P3a amplitudes at baseline and Week 7, at b) site Fz and c) site Cz ($*p < .05$).

Analysis of stimulation (monophasic/biphasic) effects on post-treatment P3a amplitude at site Fz and Cz found no significant differences between patient groups. Assessment of post-treatment P3a latency between groups indicated significantly longer [$F(1, 15) = 36.86, p = .006$] latencies in monophasic patients (383.78 ± 31.41 ms; biphasic: 346.22 ± 47.27 ms) at site Cz. There was no significant group difference at site Fz (see Figure 5).

Mixed ANOVAs (factors: site, response, site \times response) were performed to assess baseline P3a amplitude and latency as predictors of post-rTMS treatment response. Overall, baseline P3a features were non-significant predictors of response in TRD patients; however, planned comparisons revealed a significant difference ($p = .023$) in P3a latency between response groups at site Fz (but not Cz), with responders eliciting longer latencies at baseline

(355.64 ± 13.29 ms) compared to non-responders (302.00 ± 16.66 ms). In biphasic patients, a main group effect existed for both baseline P3a amplitude [$F(1, 7) = 19.74, p = .003$] and latency [$F(1, 7) = 6.06, p = .043$], with treatment responders showing significantly smaller amplitudes (6.14 ± 1.07 μ V) and longer latencies (373.00 ± 17.68 ms) at baseline than non-responders (amplitude: 13.29 ± 1.20 μ V; latency: 307.75 ± 19.76 ms). Neither baseline P3a amplitude nor latency emerged as significant predictors of rTMS response in monophasic patients. Exploratory one-way ANOVAs revealed a significant group (responders/non-responders/healthy controls) effect on baseline P3a amplitude [$F(2, 39) = 3.32, p = .047$] and latency [$F(2, 39) = 4.84, p = .014$] at site Fz. Post-hoc comparisons indicated significantly smaller ($p = .043$) baseline amplitudes in responders (5.86 ± 3.61 μ V) than healthy controls (10.34 ± 4.54 μ V); neither responders nor healthy controls differed from non-responders. Baseline latencies exhibited by responders (364.31 ± 57.99 ms) were longer than both non-responders (300.86 ± 53.13 ms; $p = .025$) and healthy controls (321.00 ± 43.25 ; $p = .05$), with no observed difference between non-responders/healthy controls.

Relationships between baseline P3a features and clinical improvement were examined using Pearson correlations. A significant negative correlation between percent change in MADRS score and baseline P3a latency emerged, $r(16) = -.57, p = .014$, with longer latencies at baseline associated with greater reductions in MADRS score at one week post-treatment (Figure 6a). Furthermore, there existed a strong negative correlation, $r(16) = -.89, p < .001$, between prolonged P3a latency at baseline and greater reduction in post-treatment Concentration Difficulties item score (MADRS-assessed) (Figure 6b). Neither overall Δ MADRS score (%), nor Δ Concentration Difficulties item score (%), was significantly correlated with baseline P3a amplitude.

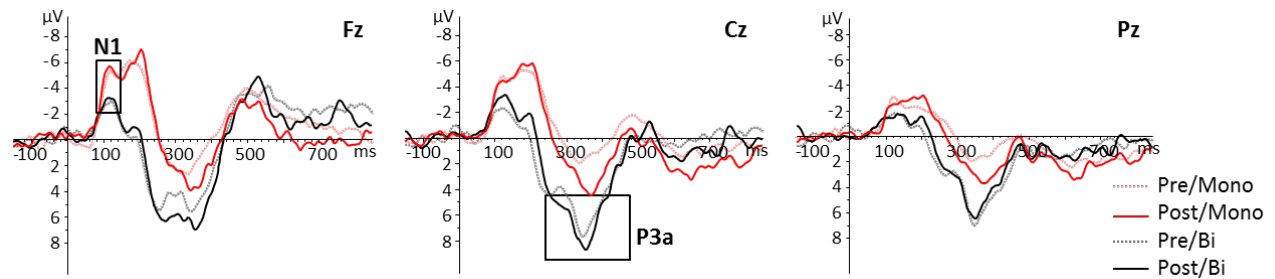


Figure 5. ERP-Indexed Novelty Processing in TRD patients Receiving Monophasic or Biphasic rTMS. Grand averaged N1 and P3a auditory evoked potentials at baseline and post-treatment.

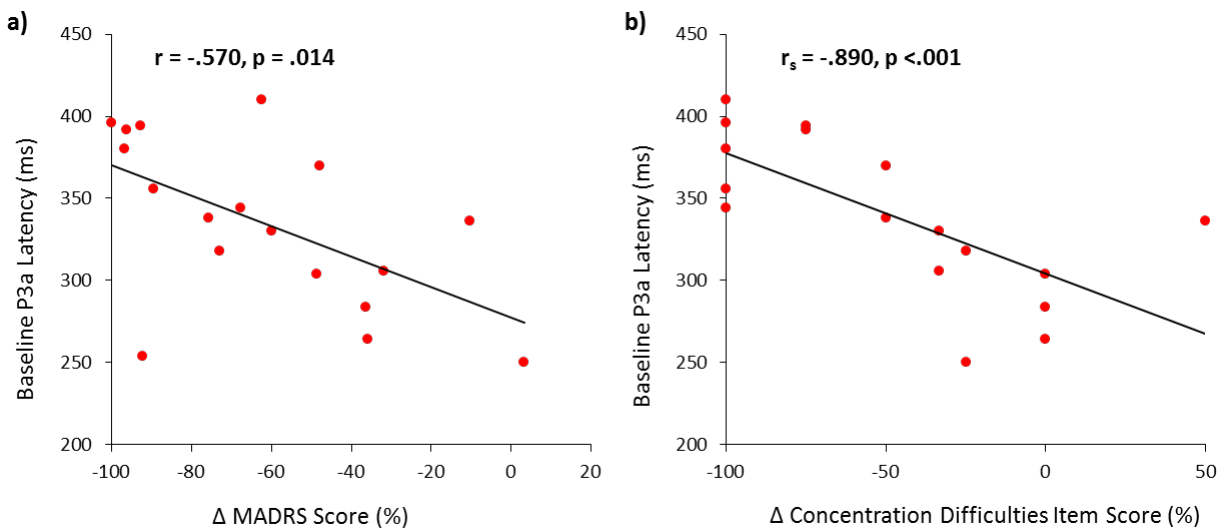


Figure 6. Relationship Between ERP-Indexed Novelty Processing and Clinical Improvement in TRD Patients. a) Baseline P3a latency correlation with percent Δ MADRS score [(post-treatment score – baseline score)/baseline score x 100]; b) baseline P3a latency correlation with percent Δ Concentration Difficulties Item score.

4.2.3 Target N1/N2/P2/P3b Amplitude and Latency

NI: Analysis of target N1 amplitude revealed no main group (patient/healthy control), session (baseline/follow-up), or group x session effects. There existed a main session effect on N1 latency [$F(1, 34) = 6.22, p = .018$]; shorter latencies were present at baseline (108.06 ± 2.56

ms) compared to follow-up (113.17 ± 2.32 ms). A main group effect also emerged [$F(1, 34) = 4.86, p = .034$] with TRD patients exhibiting longer latencies (115.50 ± 3.14 ms) than controls (105.72 ± 3.14 ms). Although no two-way interaction effect emerged, planned comparisons showed significantly longer latencies in patients (118.67 ± 3.29 ; controls: 107.67 ± 3.29) at follow-up, but not at baseline. Furthermore, patients displayed significantly longer latencies post-rTMS (118.67 ± 3.29 ; baseline: 112.33 ± 3.62), whereas healthy controls showed no change between sessions. After controlling for baseline latency values, one-way ANCOVAs revealed no significant differences in post-treatment N1 amplitude or latency between patients receiving monophasic or biphasic rTMS (Figure 8).

N2: Mixed ANOVAs indicated no main effects of group (patients/healthy controls), site (Fz/Cz), or session (baseline/follow-up) on target N2 components. Furthermore, no main two- or three-way interaction effects were revealed. Post-treatment N2 amplitude and latency means did not significantly differ between stimulation groups (monophasic/biphasic) at either site (Figure 8).

P2: Assessment of target P2 features between patients and healthy controls yielded no main effects of group, site, or session; no two- or three-way interaction effects existed. No significant differences in P2 amplitude were detected between monophasic/biphasic patients. Monophasic patients trended [$F(1, 15) = 3.99, p = .064$] towards longer post-treatment latencies (191.43 ± 6.29 ms; biphasic: 173.32 ± 6.29 ms) at site Fz, but not Cz (Figure 8).

P3b: Analysis of P3b features yielded no main group or session effects in patients versus healthy controls. A trending session x group interaction effect existed for both P3b amplitude [$F(1, 34) = 3.51, p = .069$] and latency [$F(1, 34) = 3.11, p = .087$]. Planned comparisons revealed

no significant differences in P3b amplitude or latency between patients and controls at baseline or follow-up (see Figure 7a, 7c).

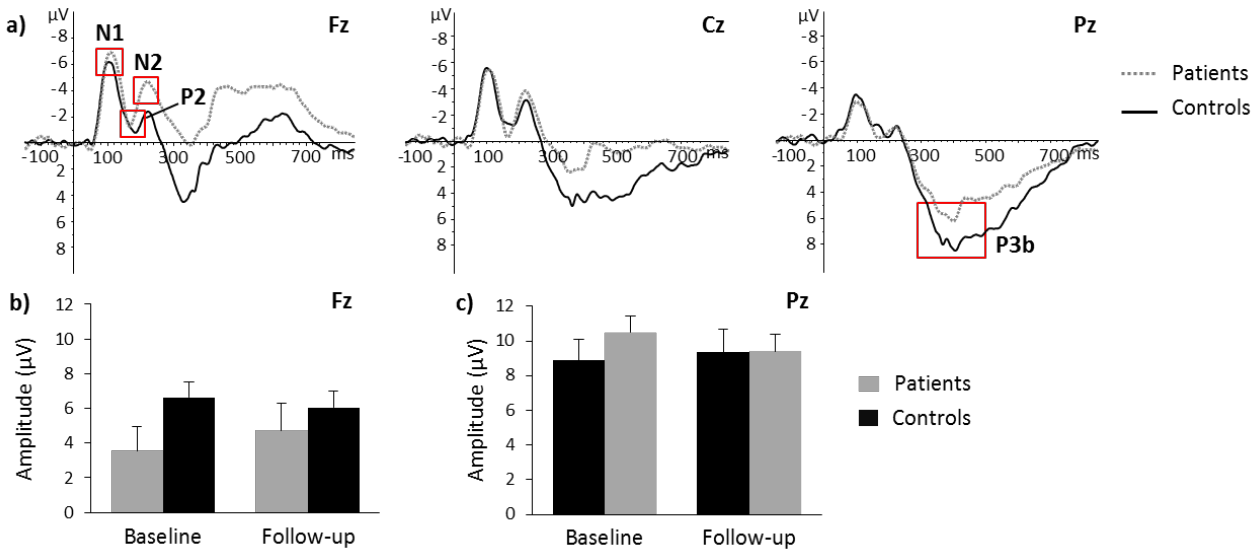


Figure 7. ERP-Indexed Target Processing in TRD Patients and Healthy Controls. a) Grand averaged N1, N2, P2 and P3b auditory evoked potentials elicited at baseline; mean \pm standard error of P3b amplitudes at baseline and Week 7, at b) site Fz and c) site Pz.

Post-treatment P3b amplitudes did not significantly differ between monophasic and biphasic conditions (Figure 8). A trend towards significantly longer post-rTMS latencies [$F(1, 15) = 3.53, p = .080$] existed in monophasic (496.64 ± 18.56 ms) versus biphasic patients (447.14 ± 18.56 ms). Independent t-tests were used to assess baseline P3b features as predictors of treatment response in TRD patients. Analyses indicated no significant differences in baseline amplitude or latency between treatment responders and non-responders (overall and within monophasic/biphasic groups). Exploratory one-way ANOVAs of baseline P3b features revealed no group differences between responders/non-responders/healthy controls.

Pearson correlations were used to assess associations between baseline P3b features and clinical response following rTMS. Although baseline P3b features did not significantly correlate

with clinical improvement in TRD patients (Figure 9a), there existed a significant negative relationship, $r(16) = -.49, p = .048$, between baseline P3b amplitude and percent change in MADRS-assessed Concentration Difficulties item score (Figure 9b); larger amplitudes were correlated with greater concentration improvement at one week post-treatment.

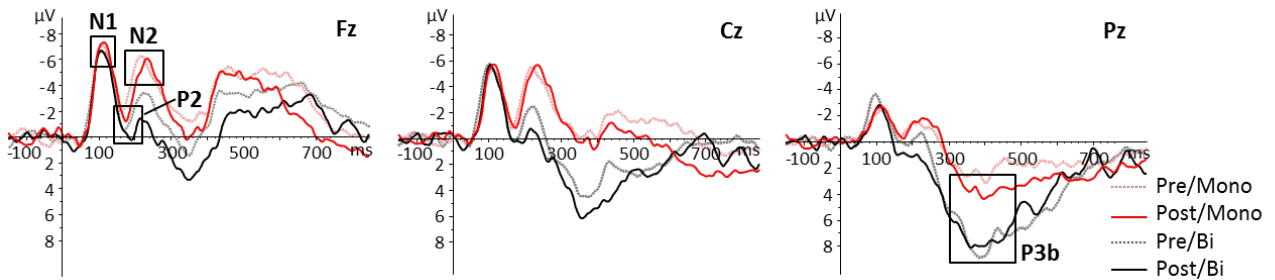


Figure 8. ERP-Indexed Target Processing in TRD Patients Receiving Monophasic or Biphasic rTMS. Grand averaged N1, N2, P2 and P3b auditory evoked potentials at baseline and post-treatment.

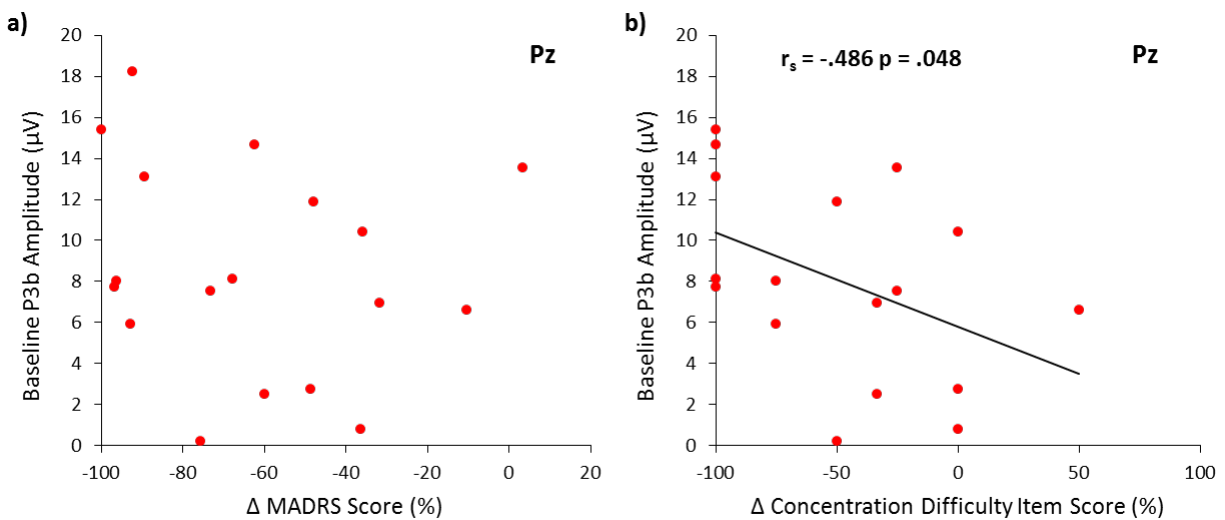


Figure 9. Relationship Between ERP-Indexed Target Processing and Clinical Improvement in TRD Patients. a) Baseline P3b amplitude correlation with percent Δ MADRS score [(post-treatment score – baseline score)/baseline score x 100]; b) baseline P3b amplitude correlation with percent Δ Concentration Difficulties Item score.

4.2.4 Behavioral Performance

There were no main session (baseline/follow-up), group (patients/healthy controls), or session x group effects on correct responses (CRs) or false alarms (FAs). A main session effect on average reaction time (RT) emerged [$F(1, 33) = 5.25, p = .028$] with shorter post-treatment RTs than baseline. Planned comparisons showed significantly decreased RTs at follow-up (vs. baseline) in patients ($p = .044$), but not in controls (Table 9). Behavioral performance measures did not significantly differ between monophasic and biphasic groups (Table 9).

Table 9. Behavioral Performance Measures on Target P300 Task

Group	Correct Response (%)		False Alarm (n)		Avg. Response Time (ms)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
TRD Patients ($N = 18$)	99.1 ± 1.7	97.8 ± 3.6	1.5 ± 1.6	1.2 ± 1.4	487.0 ± 101.5	450.6 ± 83.7
Healthy Controls ($N = 18$)	98.5 ± 2.6	98.5 ± 2.6	1.4 ± 2.2	1.4 ± 2.0	488.8 ± 107.2	469.6 ± 98.9
Monophasic ($N = 9$)	99.8 ± .44	98.9 ± 3.1	1.5 ± 1.9	1.5 ± 1.7	462.3 ± 95.7	444.3 ± 62.6
Biphasic ($N = 9$)	98.3 ± 2.2	97.4 ± 3.8	1.6 ± 1.5	.89 ± 1.2	509.0 ± 106.9	456.3 ± 102.4

Note: mean ± standard deviation

Chapter 5: Discussion

5.1 Study Summary and Significance

The key objectives from this project were to compare the cognitive effects of monophasic and biphasic HFL-rTMS in TRD patients and evaluate the utility of ERPs reflective of attentional processing as correlates and/or predictors of clinical response. Our findings contribute towards enhanced understanding of several factors that contribute to optimizing clinical and cognitive rTMS outcomes for TRD patients. First, the results demonstrate that monophasic and biphasic rTMS are equally effective at improving depressive symptoms. Additionally, these findings highlight the procognitive impacts of monophasic/biphasic HFL-rTMS and provide insight into electrophysiological features of baseline attentional (and pre-attentional) processing that are associated with clinical improvement.

5.2 Evaluation of Clinical Outcomes

In an effort to markedly improve rTMS treatment for TRD patients, this project is the first to evaluate the clinical efficacy of monophasic versus biphasic stimulation (the presently accepted practice). Monophasic pulses generate uniform neuronal activation patterns that purportedly induce greater cortical excitability than biphasic waveforms in studies with healthy volunteers (Arai et al., 2005). On this basis, we explored whether monophasic rTMS exerts greater antidepressant effects than biphasic rTMS in patients with TRD.

Clinical ratings of depressive symptomatology (MADRS score) showed a marked decrease following 6 weeks of HFL-rTMS treatment (overall response rate of 67%). Concordant with previous literature (Berlim et al., 2014), antidepressant outcomes were influenced by the length of treatment administration: greater improvement was accomplished with increased rTMS sessions. Overall, response/remission rates did not differ between stimulation groups and pulse type (monophasic vs. biphasic) was not a significant predictor of clinical improvement. Furthermore, MADRS score did not differ between stimulation groups at any time point throughout treatment. Ratings of concentration difficulties significantly improved over the course of treatment, consistent with previous reports of enhanced neuropsychological function following HFL-rTMS (Guse et al., 2010; Serafini et al., 2015). Contrary to our hypothesis, concentration scores did not differ between groups at most assessment points, though improvements were more pronounced in biphasic than monophasic patients at treatment termination (week 6).

As no treatment differences emerged, monophasic and biphasic rTMS regimens appeared equally effective at reducing symptom severity. To our knowledge, no previous studies have assessed the antidepressant outcomes of monophasic stimulation. However, given that HFL-

rTMS putatively exerts therapeutic effects via sustained alterations in synaptic plasticity, our findings are inconsistent with preliminary data showing greater neuromodulatory strength with unidirectional pulses applied to M1 (Arai et al., 2005). A possible explanation for this discrepancy relates to critical differences among stimulation targets and their underlying cytoarchitectonic features; monophasic stimulation of M1 may not be directly comparable to DLPFC, which possesses distinct neuronal geometric and physiological properties. Furthermore, whereas conclusions drawn from earlier research relied on easily quantified MEP outputs, findings from clinical protocols are multifaceted and exceedingly complex in their interpretation. However, this explanation warrants further scrutiny and more comprehensive evaluations of these outcomes will be explored in upcoming publications by the primary investigators of the RCT.

5.3 Evaluation of ERP Outcomes

5.3.1. Pre-to-Post Treatment Changes in P300 Features

Deficits in attention reflected by P3 abnormalities have been consistently observed in depression (Bruder et al., 2012). Therefore, of particular interest in this project were the effects of HFL-rTMS on markers of attentional processing (i.e., pre- to post-treatment changes in P300 amplitude and latency) in TRD patients. Functional neuroimaging studies in MDD cohorts have depicted hypoactivity in the DLPFC (George et al., 1995), an important node within the central executive network (CEN) implicated in cognitive control functions (e.g., attention) that modulate emotion regulation (Dolcos et al., 2011). On this basis, we predicted that P300 potentials indexing attentional dysfunction (attenuated amplitudes/prolonged latencies) in TRD patients would normalize in response to left-sided HF-rTMS; in particular, we expected greater improvement post-monophasic (vs. biphasic) stimulation.

Compared to controls, smaller P3a/P3b amplitudes and longer latencies were observed in depressed patients at baseline, though differences were not significant. We did not observe any significant changes in post-treatment P3b features, contrary to previous findings (Möller et al., 2006) and our prediction that HFL-rTMS would enhance neural processing associated with contextual updating and sustained attention in TRD patients. Consistent with expectations, depressed individuals exhibited larger P3a amplitudes post-rTMS, indicating an increase in attention allocation to novel stimuli that was absent in controls. We noted slower post-treatment P3a latencies in depressed individuals, with monophasic rTMS producing longer latencies than biphasic. These findings are somewhat in line with other studies that similarly detected post-rTMS increases in P3 amplitude/latency (Choi et al., 2014; Möller et al., 2006). We identified a trend towards significantly prolonged P3b latencies in the monophasic group only, indicating an overall delay in attentional processing post-monophasic stimulation. Our hypothesis that monophasic stimulation would generate more robust P3a/P3b waveforms was not supported, as no post-treatment differences existed between stimulation groups. Regarding behavioral performance, average RTs were significantly reduced in TRD patients following rTMS treatment, though no stimulation differences were noted.

Aberrations in preconscious ERP components that correlate with higher-order attentional processing have been depicted in depressed individuals (Greimel et al., 2015; Kemp et al., 2009). On this basis, we explored the impact of monophasic and biphasic HFL-rTMS on N1, N2, and P2-indexed sensory/perceptual processing in TRD patients. Interestingly, at baseline, patients (vs. controls) elicited smaller P2 amplitudes in response to standard tones that significantly increased following rTMS treatment; similarly, standard P2 latencies were increased post-treatment. With respect to target stimuli, we found prolonged post-treatment N1 latencies in

TRD patients in the absence of P2/N2 changes. However, no N1 differences were noted in response to novelty stimuli. We did not detect any pulse-specific effects on early sensory/perceptual ERP components in depressed individuals.

Overall, our findings support the notion that HFL-rTMS strengthens cortical resources devoted to automatic attentional processing in TRD patients. The P2 potential has been linked to early attention allocation and initial conscious stimulus awareness (Näätänen, 1992), whereas the P3a wave is thought to index involuntary attention orienting (Bruder et al., 2012); therefore, our detection of larger post-treatment P2/P3a amplitudes reflects enhanced passive processing of incoming auditory information. This suggests that left DLPFC-rTMS may normalize MDD-induced disruptions in functional connectivity within and between frontocortical circuits that play a crucial role in executive function and attentional allocation [i.e., the CEN, the default mode network (DMN), and the salience network (SN)]. Comprising the ACC and amygdala, the SN mediates dynamic switching between internal and external attention, largely subserved by the DMN and CEN, respectively (Bressler and Menon, 2010; Sha et al., 2019). Evidently, MDD is associated with impaired modulation of DMN activity and subsequent inability to shift attention from introspective processes to external stimuli (Duman et al., 2016). In line with findings from Liston et al. (2014), our results suggest that HFL-rTMS may alleviate MDD symptoms by suppressing abnormal DMN hyperactivity, in conjunction with engagement of SN/CEN nodes to increase environmental saliency and attentional control over negative mood states. This explanation is further bolstered by evidence that P3a generation is related to ACC activity when incoming stimuli replace working memory contents and command frontal lobe attention (Polich, 2004). In contrast, we determined that HFL-rTMS did not increase P2/P3b amplitudes elicited by target stimuli. However, this discrepancy may be attributed to higher-order attentional demands,

as these ERPs reflect conscious allocation of neural resources for stimulus evaluation (Polich, 2004). Pronounced improvements in voluntary attention in MDD may require more intensive rTMS protocols that include increasing the overall number of sessions or treating with multiple sessions per day. Curiously, prolonged P3 latencies (indexing slower attentional processing) were detected post-rTMS, with longer latencies elicited by monophasic patients. Taken together with our findings of increased P3a amplitudes, delayed peak onset at baseline may reflect cortical inefficiency in MDD, whereas longer post-treatment latencies could represent enhanced analysis of elicited stimuli features in response to increased allocation of attentional resources. Though P3 latency is putatively tied to RT (Luck, 2012), reactions to target stimuli were quicker post-rTMS treatment than baseline in TRD patients, which may be explained by faster motor response generation that is unrelated to stimulus classification speed. Collectively, these results support the notion that HFL-rTMS potentiates cortical changes that reflect enhanced involuntary attentional processing in patients with depression.

5.3.2. Predicting Response with Baseline P300 Features

The value of clinical features in predicting antidepressant outcome is limited, warranting the noticeable shift towards uncovering neurobiological markers of response and a ‘personalized medicine’ approach to alleviating MDD symptoms. Pre-treatment ERP measures have shown promising results in aiding treatment prediction in depression. Thus, we hypothesized that baseline P3 amplitudes and latencies would serve as effective predictors of rTMS response and correlates of clinical/cognitive improvement in TRD patients.

The handful of studies assessing P300 measurements as predictors of rTMS outcomes in depression have yielded mixed findings (Arns et al., 2012; Krepel et al., 2018; Möller et al., 2006). In partial concordance with a study by Arns et al. (2012), we observed smaller P3a

amplitudes and longer latencies in TRD patients who successfully responded to biphasic treatment. Interestingly, pre-treatment P3a features were not predictive of monophasic rTMS outcomes. Though, regardless of stimulation type received, MADRS-assessed clinical and cognitive improvement was significantly correlated with prolonged P3a latencies at baseline. Contrary to our predictions, HFL-rTMS treatment response was not predicted by pre-treatment P3b features; however, larger baseline P3b amplitudes were associated with greater alleviation of concentration difficulties. The observed change in standard P2 parameters (pre- to post-treatment) gave us justification to examine its utility as a neurophysiological marker of response. We found that attenuated amplitudes and shorter latencies at baseline predicted better antidepressant outcomes post-biphasic, but not monophasic, rTMS treatment.

Overall, the majority of neural predictors/correlates of response appeared in one domain of interest: deficient automatic information processing was associated with better treatment outcomes. Previous MDD studies have linked prolonged P3 latency with poor response to antidepressant medication (Işintaş et al., 2012; Jaworska et al., 2013). In contrast, we determined that attenuated/delayed P2 and P3a components were predictive of successful response. Our use of HFL-rTMS as a treatment modality (vs. pharmacotherapy) may account for this discrepancy in findings. The generation of sensory/perceptual and early attentional ERP components (i.e., P2, P3a) relies in part on the functional integrity of the DLPFC (Bruder et al., 2012; Sato et al., 2013), a critical component of the CEN which also comprises the ACC and posterior parietal cortex. Disrupted in MDD patients, the CEN regulates the operations of overlapping cognitive and emotional systems. It has been postulated that HFL-rTMS exerts its antidepressant effects by normalizing CEN function and enhancing cognitive control, allowing for adequate engagement of attentional resources in response to changing environmental demands (i.e., orientation to

novel/involuntary stimuli) (Niendam et al., 2012). Thus, our findings may suggest that treatment responders were characterized by pathological interactions between attentional/affective circuitry and HF-rTMS of the DLPFC may beneficially impact cortical CEN modulation in this patient subgroup. Conversely, non-responders presumably represent a proportion of depressed individuals with intact frontal neurocognitive network connectivity for whom HFL-rTMS may not be therapeutically useful. Interestingly, early ERP components were less predictive of monophasic stimulation response, indicating that rTMS pulse types may be differentially sensitive to poor automatic attentional processing in MDD. Moreover, baseline P3 subcomponents differentially modulated HFL-rTMS treatment response; larger P3b amplitudes were associated with greater reductions in concentration difficulties. Evidently, TRD patients who are better able to consciously direct attentional resources acquire procognitive benefits from rTMS treatment within the realm of sustained attention/concentration. Consistent with our findings that P3b measures showed negligible change post-treatment, it appears that electrophysiological indices of higher-order attentional processing are less sensitive in predicting rTMS outcomes in TRD than ERPs that reflect passive information processing.

5.4. Limitations and Future Directions

Despite this study's novel findings, there are several limitations that must be acknowledged. Most notably, sample size is limited, thus interpretations of these preliminary results should be treated with caution. As a next step, this research should be replicated with a larger sample size to ensure adequate statistical power. Another important limitation in the project's design involved the absence of sham stimulation. Although the intent behind this trial's design was to compare the efficacy of monophasic pulses to the standard of care (biphasic stimulation), a sham condition must be present to adequately rule out non-specific treatment

effects on neural function and clinical response. However, this limitation is somewhat mediated by the inclusion of a patient-matched healthy control group. This direct comparator group provided benchmark values that allowed us to better assess whether treatment was in fact normalizing brain activity in TRD patients.

Though we collected clinician-rated concentration scores, our conclusions are also limited by the absence of any self-report cognitive measures that have been psychometrically validated. The Montreal Cognitive Assessment (MoCA) was administered to rule out substantial neuropsychological impairment; however, it has been described as insufficiently sensitive to detect cognitive deficits in depression (Mcintyre et al., 2013). Thus, future rTMS investigations in MDD would benefit from the use of a highly sensitive cognitive battery to explore potential correlations with objective measures of brain activity. We must also acknowledge that the three-stimulus auditory oddball paradigm is a relatively simple, low-demand cognitive task and there is a need to assess neural correlates of other attentional domains, including selective and divided attention. Notably, we did not assess whether clinical outcomes or ERP measures were influenced by specific MDD subtypes (e.g., melancholic) or the presence of secondary anxiety symptoms. Further, though we ensured that medication status was stable prior to initiating treatment, we did not examine pharmacological effects in our analysis. Future work should control for these parameters, as evidence exists that rTMS efficacy varies when administered under different medication conditions (Slotema et al., 2010).

Certain limitations inherent to EEG methodology must be noted. As a neuroimaging tool, EEG enables visualization of functional cortical activity that underlies basic sensory and cognitive processing. However, our conclusions regarding brain-behavior relationships are limited by the fact that post-treatment changes in electrophysiological features cannot be causally

connected with improvement in depressive symptomatology. Indeed, numerous external factors that affect electrocortical recordings have been elucidated, with P3 characteristics specifically impacted by fatigue, heart rate, intelligence, and substance exposure (Polich, 2004). Though we attempted to control for nicotine and caffeine consumption, compliance was verified through self-report and cannot be guaranteed. Finally, the validity of ERP measurement is hindered by the inherently poor spatial resolution of EEG recordings; using a combined EEG/fMRI or source localization approach would provide more detailed insight into the cortical and subcortical effects of monophasic and biphasic rTMS in medication-resistant depression.

5.5 Conclusions

Monophasic pulses generate increased cortical excitability and provide a novel opportunity for optimizing rTMS outcomes in TRD patients. Therapeutic rTMS has been shown to exert network-level effects, modulating cortical-subcortical circuitry involved in cognition and emotion regulation. Alterations in P300 characteristics have been identified across a wide spectrum of psychiatric cohorts, including depressive patients. Attenuated P3 amplitudes appear to reflect deficits in regulating appropriate functional responses to salient stimuli, exemplified by an inability to voluntarily sustain attention, in addition to impaired contextual updating and involuntary orientation to unexpected stimuli. Prolonged P3 latencies index delayed information processing and could represent a bias towards internal stimuli in depression. These neurophysiological markers of deficient attentional processing may reflect critical disruptions in cognitive control pathways implicated in the pathophysiology of MDD and may serve as correlates of clinical improvement in patients who undergo monophasic and conventional (biphasic) HFL-rTMS.

Our study found that monophasic stimulation shows equal clinical effectiveness to biphasic rTMS. Overall, HFL-rTMS reduced depressive symptoms and cognitive difficulties, and strengthened discriminability of novel stimuli and passive listening in depressed patients. We identified early attentional ERP predictors of response that applied to patients receiving biphasic stimulation (or either type of stimulation, in some cases). Superior antidepressant outcomes were predicted by P2/P3a-indexed deficiencies in automatic information processing. On the contrary, cognitive improvement in TRD was associated with greater ability to direct attention at baseline, as reflected by P3b potentials. In addition to elucidating clinical and cognitive outcomes of monophasic/biphasic rTMS therapy in treatment-resistant MDD patients, these findings yield insight into a) electrophysiological correlates of HFL-rTMS response and b) potential neural mechanisms underlying its therapeutic effects. It is our hope that future work will build upon our findings by further identifying neurocognitive correlates of response to innovative rTMS protocols and increasing targeted treatment for MDD patients.

References

- aan het Rot, M., Mathew, S.J., Charney, D.S., 2009. Neurobiological mechanisms in major depressive disorder. *Can. Med. Assoc. J.* 180, 305–13. <https://doi.org/10.1503/cmaj.080697>
- Ahern, E., Semkovska, M., 2017. Cognitive Functioning in the First-Episode of Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Neuropsychology* 31, 52–72. <https://doi.org/10.1037/neu0000319.supp>
- Al-Harbi, K.S., 2012. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer. Adherence* 6, 369–88. <https://doi.org/10.2147/PPA.S29716>
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. American Psychiatric Publishing, Arlington, VA.
- Anderer, P., Saletu, B., Semlitsch, H. V., Pascual-Marqui, R.D., 2002. Structural and energetic processes related to P300: LORETA findings in depression and effects of antidepressant drugs. *Methods Find. Exp. Clin. Pharmacol.* 24 Suppl D, 85–91.
- Arai, N., Okabe, S., Furubayashi, T., Mochizuki, H., Iwata, N.K., Hanajima, R., Terao, Y., Ugawa, Y., 2007. Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. *Clin. Neurophysiol.* 118, 2227–2233. <https://doi.org/10.1016/j.clinph.2007.07.006>
- Arai, N., Okabe, S., Furubayashi, T., Terao, Y., Yuasa, K., Ugawa, Y., 2005. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clin. Neurophysiol.* 116, 605–613. <https://doi.org/10.1016/j.clinph.2004.09.020>
- Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D.M., Etkin, A., Fallahpour, K., Gatt, J.M., Hirshberg, L., Gordon, E., 2016. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clin. Neurophysiol.* 127, 509–519. <https://doi.org/10.1016/j.clinph.2015.05.032>
- Arns, M., Drinkenburg, W.H., Fitzgerald, P.B., Kenemans, J.L., 2012. Neurophysiological predictors of non-response to rTMS in depression. *Brain Stimul.* 5, 569–576. <https://doi.org/10.1016/j.brs.2011.12.003>
- Avery, D.H., Holtzheimer, P.E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D.L., Haynor, D.R., Claypoole, K.H., Wajdik, C., Roy-Byrne, P., 2006. A Controlled Study of Repetitive Transcranial Magnetic Stimulation in Medication-Resistant Major Depression. *Biol. Psychiatry* 59, 187–194. <https://doi.org/10.1016/j.biopsych.2005.07.003>
- Avery, D.H., Isenberg, K.E., Sampson, S.M., Janicak, P.G., Lisanby, S.H., Maixner, D.F., Loo, C., Thase, M.E., Demitrack, M.A., George, M.S., 2008. Transcranial Magnetic Stimulation in the Acute Treatment of Major Depressive Disorder: Clinical Response in an Open-Label Extension Trial, *J Clin Psychiatry*.
- Bailey, N.W., Hoy, K.E., Rogasch, N.C., Thomson, R.H., McQueen, S., Elliot, D., Sullivan, C.M., Fulcher, B.D., Daskalakis, Z.J., Fitzgerald, P.B., 2018. Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. *Brain Stimul.* 11, 190–203. <https://doi.org/10.1016/j.brs.2017.10.015>
- Barry, R.J., Johnstone, S.J., Clarke, A.R., 2003. A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clin. Neurophysiol.* 114, 184–98.
- Beam, W., Borckardt, J.J., Reeves, S.T., George, M.S., 2009. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul.* 2, 50–4.

- <https://doi.org/10.1016/j.brs.2008.09.006>
- Berlim, M.T., Turecki, G., 2007. Definition, Assessment, and Staging of Treatment—Resistant Refractory Major Depression: A Review of Current Concepts and Methods. *Can. J. Psychiatry* 52, 46–54. <https://doi.org/10.1177/070674370705200108>
- Berlim, M.T., van den Eynde, F., Tovar-Perdomo, S., Daskalakis, Z.J., 2014. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol. Med.* 44, 225–239. <https://doi.org/10.1017/S0033291713000512>
- Blackwood, D., Whalley, L., Christie, J., Blackburn, I., St Clair, D., McInnes A., 1987. Changes in auditory P3 event-related potential in schizophrenia and depression. *Br. J. Psychiatry* 150, 154–160.
- Bloch, M., Daly, R.C., Rubinow, D.R., 2003. Endocrine factors in the etiology of postpartum depression. *Compr. Psychiatry* 44, 234–246. [https://doi.org/10.1016/S0010-440X\(03\)00034-8](https://doi.org/10.1016/S0010-440X(03)00034-8)
- Bogner, H.R., Bruce, M.L., Reynolds III, C.F., Mulsant, B.H., Cary, M.S., Morales, K., Alexopoulos, G.S., PROSPECT Group, T., 2007. The Effects of Memory, Attention, and Executive Dysfunction on Outcomes of Depression in a Primary Care Intervention Trial: The PROSPECT Study. *Int. J. Geriatr. Psychiatry* 22, 922–929. <https://doi.org/10.1002/gps.1767>
- Bora, E., Harrison, B.J., Davey, C.G., Yücel, M., Pantelis, C., 2012. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychol. Med.* 42, 671–81. <https://doi.org/10.1017/S0033291711001668>
- Borrow, A.P., Cameron, N.M., 2014. Estrogenic mediation of serotonergic and neurotrophic systems: implications for female mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 54, 13–25. <https://doi.org/10.1016/j.pnpbp.2014.05.009>
- Bortolato, B., Carvalho, A.F., Soczynska, J.K., Perini, G.I., McIntyre, R.S., 2015. The Involvement of TNF- α in Cognitive Dysfunction Associated with Major Depressive Disorder: An Opportunity for Domain Specific Treatments. *Curr. Neuropharmacol.* 13, 558–76.
- Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn. Sci.* 14, 277–290. <https://doi.org/10.1016/j.tics.2010.04.004>
- Bruder, G.E., Kayser, J., Tenke, C.E., 2012. Event-Related Brain Potentials in Depression: Clinical, Cognitive and Neurophysiologic Implications, in: Luck, S.J., Kappenman, E.S. (Eds.), *The Oxford Handbook of Event-Related Potential Components*. Oxford University Press, New York, pp. 563–592.
- Bruder, G.E., Kropfmann, C.J., Kayser, J., Stewart, J.W., Mcgrath, P.J., Tenke, C.E., 2009. Reduced brain responses to novel sounds in depression: P3 findings in a novelty oddball task. *Psychiatry Res.* 170, 218–223. <https://doi.org/10.1016/j.psychres.2008.10.023>
- Bruder, G.E., Tenke, C.E., Stewart, J.W., Towey, J.P., Leite, P., Voglmaier, M., Quitkin, F.M., 1995. Brain event-related potentials to complex tones in depressed patients: Relations to perceptual asymmetry and clinical features. *Psychophysiology* 32, 373–381.
- Bruder, G.E., Tenke, C.E., Towey, J.P., Leite, P., Fong, R., Stewart, J.E., Mcgrath, P.J., Quitkin, F.M., 1998. Brain ERPs of depressed patients to complex tones in an oddball task: Relation of reduced P3 asymmetry to physical anhedonia. *Psychophysiology* 35, 54–63.
- Cabeza, R., Nyberg, L., 2000. *Imaging Cognition II: An Empirical Review of 275 PET and fMRI*

- Studies. *J. Cogn. Neurosci.* 12, 1–47.
- Choi, K.M., Jang, K.-M., Jang, K.I., Um, Y.H., Kim, M.-S., Kim, D.-W., Shin, D., Chae, J.-H., 2014. The effects of 3 weeks of rTMS treatment on P200 amplitude in patients with depression. *Neurosci. Lett.* 577, 22–27. <https://doi.org/10.1016/j.neulet.2014.06.003>
- Coffman, J.A., Torello, M.W., Lewis, C.E., Fortin, L.D., Martin, D.J., 1989. Event-related brain potentials in depressed patients treated with electroconvulsive therapy. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 13, 687–692.
- Connolly, K.R., Helmer, A., Cristancho, M.A., Cristancho, P., O’Reardon, J.P., 2012. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *J. Clin. Psychiatry* 73, e567-73. <https://doi.org/10.4088/JCP.11m07413>
- Conradi, H.J., Ormel, J., de Jonge, P., 2011. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol. Med.* 41, 1165–74. <https://doi.org/10.1017/S0033291710001911>
- Crown, W.H., Finkelstein, S., Berndt, E.R., Ling, D., Poret, A.W., Rush, A.J., Russell, J.M., 2002. The impact of treatment-resistant depression on health care utilization and costs. *J. Clin. Psychiatry* 63, 963–71.
- Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: Perspectives from Affective Neuroscience. *Annu. Rev. Psychol.* 53, 545–574. <https://doi.org/10.1146/annurev.psych.53.100901.135148>
- Deldin, P.J., Keller, J., Gergen, J.A., Miller, G.A., 2000. Right-posterior face processing anomaly in depression. *J. Abnorm. Psychol.* 109, 116–21.
- Dolcos, F., Iordan, A.D., Dolcos, S., 2011. Neural correlates of emotion–cognition interactions: A review of evidence from brain imaging investigations. *J. Cogn. Psychol.* 23, 669–694. <https://doi.org/10.1080/20445911.2011.594433>
- Douglas, K.M., Porter, R.J., 2009. Longitudinal Assessment of Neuropsychological Function in Major Depression. *Aust. New Zeal. J. Psychiatry* 43, 1105–1117. <https://doi.org/10.3109/00048670903279887>
- Drevets, W.C., 2000. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog. Brain Res.* 126, 413–431.
- Drevets, W.C., Ae, J.L.P., Furey, M.L., Price, J.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct. Funct.* 213, 93–118. <https://doi.org/10.1007/s00429-008-0189-x>
- Drysdale, A.T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., Fetcho, R.N., Zebley, B., Oathes, D.J., Etkin, A., Schatzberg, A.F., Sudheimer, K., Keller, J., Mayberg, H.S., Gunning, F.M., Alexopoulos, G.S., Fox, M.D., Pascual-Leone, A., Voss, H.U., Casey, B., Dubin, M.J., Liston, C., 2017. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat. Med.* 23, 28–38. <https://doi.org/10.1038/nm.4246>
- Duman, R.S., Aghajanian, G.K., 2012. Synaptic Dysfunction in Depression: Potential Therapeutic Targets. *Science* (80-.). 338, 68–72. <https://doi.org/10.1126/science.1222939>
- Duman, R.S., Aghajanian, G.K., Sanacora, G., Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat. Med.* 22, 238–249. <https://doi.org/10.1038/nm.4050>
- Duncan, C.C., Barry, R.J., Connolly, J.F., Fischer, C., Michie, P.T., Näätänen, R., Polich, J.,

- Reinvang, I., Van Petten, C., 2009. Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400 q. *Clin. Neurophysiol.* 120, 1883–1908. <https://doi.org/10.1016/j.clinph.2009.07.045>
- Dunkin, J.J., Leuchter, A.F., Cook, I.A., Kasl-Godley, J.E., Abrams, M., Rosenberg-Thompson, S., 2000. Executive dysfunction predicts nonresponse to fluoxetine in major depression, *Journal of Affective Disorders*.
- el Massioui, F., Everett, J., Martin, M.T., Jouvent, R., Widlöcher, D., 1996. Attention deficits in depression: an electrophysiological marker. *Neuroreport* 7, 2483–6.
- Evers, S., Böckermann, I., Nyhuis, P.W., 2001. The impact of transcranial magnetic stimulation on cognitive processing: An event-related potential study. *Neuroreport* 12, 2915–2918. <https://doi.org/10.1097/00001756-200109170-00032>
- Fitzgerald, P.B., Daskalakis, Z.J., 2013. *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders: A Practical Guide*. Springer-Verlag Berlin Heidelberg. <https://doi.org/10.1007/978-3-642-36467-9>
- Fitzgerald, P.B., Hoy, K., Gunewardene, R., Slack, C., Ibrahim, S., Bailey, M., Daskalakis, Z.J., 2011. A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. *Psychol. Med.* 41, 1187–1196. <https://doi.org/10.1017/S0033291710001923>
- Fitzgerald, P.B., Hoy, K.E., Anderson, R.J., Daskalakis, Z.J., 2016. A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION. *Depress. Anxiety* 33, 746–753. <https://doi.org/10.1002/da.22503>
- Fried, E.I., Nesse, R.M., 2014. The Impact of Individual Depressive Symptoms on Impairment of Psychosocial Functioning. *PLoS One* 9, e90311. <https://doi.org/10.1371/journal.pone.0090311>
- Gardner, A., Boles, R.G., 2011. Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 730–43. <https://doi.org/10.1016/j.pnpbp.2010.07.030>
- Gaynes, B.M., Warden, D., Trivedi, M.H., Wisniewski, S.R., Fava, M., Rush, J.A., 2009. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr. Serv.* 60, 1439–45. <https://doi.org/doi:10.1176/ps.2009.60.11.1439>
- George, M.S., Ketter, T.A., Post, R.M., 1994. Prefrontal cortex dysfunction in clinical depression. *Depression* 2, 59–72. <https://doi.org/10.1002/depr.3050020202>
- George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P.E., Schwartz, T., Sackeim, H.A., 2010. Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder. *Arch. Gen. Psychiatry* 67, 507. <https://doi.org/10.1001/archgenpsychiatry.2010.46>
- George, M.S., Wassermann, E.M., 1994. Rapid-rate transcranial magnetic stimulation and ECT. *Convuls. Ther.* 10, 251–4; discussion 255-8.
- George, M.S., Wassermann, E.M., Williams, W.A., Callahan, A., Ketter, T.A., Basser, P., Hallett, M., Post, R.M., 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6, 1853–6.
- Giese-Davis, J.E., Miller, G.A., Knight, R.A., 1993. Memory template comparison processes in anhedonia and dysthymia. *Psychophysiology* 30, 646–56.
- Goetz, S.M., Lubner, B., Lisanby, S.H., Murphy, D.L.K., Kozyrkov, I.C., Grill, W.M., Peterchev,

- A. V., 2016. Enhancement of Neuromodulation with Novel Pulse Shapes Generated by Controllable Pulse Parameter Transcranial Magnetic Stimulation. *Brain Stimul.* 9, 39–47. <https://doi.org/10.1016/j.brs.2015.08.013>
- Gorlyn, M., Keilp, J.G., Grunebaum, M.F., Taylor, B.P., Oquendo, M.A., Bruder, G.E., Stewart, J.W., Zalsman, G., Mann, J.J., 2008. Neuropsychological characteristics as predictors of SSRI treatment response in depressed subjects. *J. Neural Transm.* 115, 1213–1219. <https://doi.org/10.1007/s00702-008-0084-x>
- Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–84.
- Greenberg, P.E., Fournier, A.-A., Sisitsky, T., Pike, C.T., Kessler, R.C., 2015. The Economic Burden of Adults With Major Depressive Disorder in the United States (2005 and 2010). *J. Clin. Psychiatry* 76, 155–162. <https://doi.org/10.4088/JCP.14m09298>
- Greimel, E., Trinkl, M., Bartling, J., Bakos, S., Grossheinrich, N., Schulte-Körne, G., 2015. Auditory selective attention in adolescents with major depression: An event-related potential study. *J. Affect. Disord.* 172, 445–452. <https://doi.org/10.1016/j.jad.2014.10.022>
- Guse, B., Falkai, P., Wobrock, T., 2010. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J. Neural Transm.* 117, 105–122. <https://doi.org/10.1007/s00702-009-0333-7>
- Hasselbalch, B.J., Knorr, U., Kessing, L.V., 2011. Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. *J. Affect. Disord.* 134, 20–31. <https://doi.org/10.1016/j.jad.2010.11.011>
- Hausmann, A., Pascual-Leone, A., Kemmler, G., Rupp, C.I., Lechner-Schoner, T., Kramer-Reinstadler, K., Walpoth, M., Mechtcheriakov, S., Conca, A., Weiss, E.M., 2004. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *J. Clin. Psychiatry* 65, 772–82.
- Hegeman, J.M., van Fenema, E.M., Comijs, H.C., Kok, R.M., van der Mast, R.C., de Waal, M.W.M., 2017. Effect of chronic somatic diseases on the course of late-life depression. *Int. J. Geriatr. Psychiatry* 32, 779–787. <https://doi.org/10.1002/gps.4523>
- Herrera-Guzmán, I., Gudayol-Ferré, E., Lira-Mandujano, J., Herrera-Abarca, J., Herrera-Guzmán, D., Montoya-Pérez, K., Guardia-Olmos, J., 2008. Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. *Psychiatry Res.* 160, 72–82. <https://doi.org/10.1016/j.psychres.2007.04.012>
- Hidese, S., Ota, M., Matsuo, J., Ishida, I., Hiraishi, M., Yoshida, S., Noda, T., Sato, N., Teraishi, T., Hattori, K., Kunugi, H., 2018. Association of obesity with cognitive function and brain structure in patients with major depressive disorder. *J. Affect. Disord.* 225, 188–194. <https://doi.org/10.1016/j.jad.2017.08.028>
- Hosono, Y., Urushihara, R., Harada, M., Morita, N., Murase, N., Kunikane, Y., Shimazu, H., Asanuma, K., Uguisu, H., Kaji, R., 2008. Comparison of monophasic versus biphasic stimulation in rTMS over premotor cortex: SEP and SPECT studies. *Clin. Neurophysiol.* 119, 2538–2545. <https://doi.org/10.1016/j.clinph.2008.07.279>
- Houdayer, E., Degardin, A., Cassim, F., Bocquillon, P., Derambure, P., Devanne, H., 2008. The effects of low- and high-frequency repetitive TMS on the input/output properties of the human corticospinal pathway. *Exp. Brain Res.* 187, 207–217. <https://doi.org/10.1007/s00221-008-1294-z>
- Ishak, W.W., Balayan, K., Bresee, C., Greenberg, J.M., Fakhry, H., Christensen, S., Rapaport,

- M.H., 2013. A descriptive analysis of quality of life using patient-reported measures in major depressive disorder in a naturalistic outpatient setting. *Qual. Life Res.* 22, 585–96. <https://doi.org/10.1007/s11136-012-0187-6>
- Işıntaş, M., Ak, M., Erdem, M., Oz, O., Ozgen, F., 2012. [Event-related potentials in major depressive disorder: the relationship between P300 and treatment response]. *Turk Psikiyatri Derg.* 23, 33–9.
- Jaworska, N., Blier, P., Fusee, W., Knott, V., 2012. Alpha power, alpha asymmetry and anterior cingulate cortex activity in depressed males and females. *J. Psychiatr. Res.* 46, 1483–1491. <https://doi.org/10.1016/j.jpsychires.2012.08.003>
- Jaworska, N., De Somma, E., Blondeau, C., Tessier, P., Norris, S., Fusee, W., Smith, D., Blier, P., Knott, V., 2013. Auditory P3 in antidepressant pharmacotherapy treatment responders, non-responders and controls. *Eur. Neuropsychopharmacol.* 23, 1561–1569. <https://doi.org/10.1016/j.euroneuro.2013.03.003>
- Jaworska, N., Protzner, A., 2013. Electro cortical Features of Depression and Their Clinical Utility in Assessing Antidepressant Treatment Outcome. *Can. J. Psychiatry* 58, 509–514.
- Jing, H., Takigawa, M., Hamada, K., Okamura, H., Kawaika, Y., Yonezawa, T., Fukuzako, H., 2001. Effects of high frequency repetitive transcranial magnetic stimulation on P300 event-related potentials. *Clin. Neurophysiol.* 112, 304–313.
- Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., Weisbrod, M., 2003. Executive control deficit in depression: event-related potentials in a Go/Nogo task. *Psychiatry Res.* 122, 169–84.
- Kalayam, B., Alexopoulos, G.S., 1999. Prefrontal dysfunction and treatment response in geriatric depression. *Arch. Gen. Psychiatry* 56, 713–8.
- Kawasaki, T., Tanaka, S., Wang, J., Hokama, H., Hiramatsu, K., 2004. Abnormalities of P300 cortical current density in unmedicated depressed patients revealed by LORETA analysis of event-related potentials, *Psychiatry and Clinical Neurosciences*.
- Kemp, A.H., Hopkinson, P.J., Hermens, D.F., Rowe, D.L., Sumich, A.L., Clark, C.R., Drinkenburg, W., Abdi, N., Penrose, R., Mcfarlane, A., Boyce, P., Gordon, E., Williams, L.M., 2009. Fronto-Temporal Alterations Within the First 200 ms During an Attentional Task Distinguish Major Depression, Non-Clinical Participants With Depressed Mood and Healthy Controls: A Potential Biomarker? *Hum. Brain Mapp.* 30, 602–614. <https://doi.org/10.1002/hbm.20528>
- Kemp, A.H., Pe Benito, L., Quintana, D.S., Clark, C.R., Mcfarlane, A., Mayur, P., Harris, A., Boyce, P., Williams, L.M., 2010. Impact of depression heterogeneity on attention: An auditory oddball event related potential study. *J. Affect. Disord.* 123, 202–207. <https://doi.org/10.1016/j.jad.2009.08.010>
- Knott, V., Mahoney, C., Kennedy, S., Evans, K., 2000. Pre-Treatment EEG and Its Relationship to Depression Severity and Paroxetine Treatment Outcome. *Pharmacopsychiatry* 33, 201–205. <https://doi.org/10.1055/s-2000-8356>
- Krepel, N., Sack, A.T., Leon Kenemans, J., Fitzgerald, P.B., Drinkenburg, W.H., Arns, M., 2018. Non-replication of neurophysiological predictors of non-response to rTMS in depression and neurophysiological data-sharing proposal. *Brain Stimul.* 11, 639–641. <https://doi.org/10.1016/j.brs.2018.01.032>
- Lam, R.W., McIntosh, D., Wang, J., Enns, M.W., Kolivakis, T., Michalak, E.E., Sareen, J., Song, W.-Y., Kennedy, S.H., Macqueen, G.M., Milev, R. V., Parikh, S. V., Ravindran, A. V., 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines

- for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. *Can. J. Psychiatry* 61, 510–523.
<https://doi.org/10.1177/0706743716659416>
- Lee, B.-H., Kim, Y.-K., 2010. The Roles of BDNF in the Pathophysiology of Major Depression and in Antidepressant Treatment. *Psychiatry Investig.* 7, 231.
<https://doi.org/10.4306/pi.2010.7.4.231>
- Lee, R.S., Hermens, D.F., Porter, M.A., Antoinette Redoblado-Hodge, M., 2012. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *J. Affect. Disord.* 140, 113–124. <https://doi.org/10.1016/j.jad.2011.10.023>
- Lener, M.S., Iosifescu, D. V, 2015. In pursuit of neuroimaging biomarkers to guide treatment selection in major depressive disorder: a review of the literature. *Ann. N. Y. Acad. Sci.* 1344, 50–65. <https://doi.org/10.1111/nyas.12759>
- Leone, T., Coast, E., Narayanan, S., de Graft Aikins, A., 2012. Diabetes and depression comorbidity and socio-economic status in low and middle income countries (LMICs): a mapping of the evidence. *Global. Health* 8, 39. <https://doi.org/10.1186/1744-8603-8-39>
- Liston, C., Chen, A.C., Zebly, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., Voss, H.U., Casey, B.J., Etkin, A., Dubin, M.J., 2014. Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression. *Biol. Psychiatry* 76, 517–526.
<https://doi.org/10.1016/j.biopsych.2014.01.023>
- Loo, C.K., McFarquhar, T.F., Mitchell, P.B., 2008. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int. J. Neuropsychopharmacol.* 11, 131–147. <https://doi.org/10.1017/S1461145707007717>
- Luborzewski, A., Schubert, F., Seifert, F., Danker-Hopfe, H., Brakemeier, E.-L., Schlattmann, P., Anghelescu, I., Colla, M., Bajbouj, M., 2007. Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *J. Psychiatr. Res.* 41, 606–615.
<https://doi.org/10.1016/j.jpsychires.2006.02.003>
- Luck, S.J., 2012. Event-Related Potentials, in: Cooper, H., Camic, P., Long, D., Panter, A., Rindskopf, D., Sher, K. (Eds.), *APA Handbook of Research Methods in Psychology: Volume 1, Foundations, Planning, Measures, and Psychometrics*. American Psychological Association, Washington, DC.
- MacQueen, G.M., Yucel, K., Taylor, V.H., Macdonald, K., Joffe, R., 2008. Posterior Hippocampal Volumes Are Associated with Remission Rates in Patients with Major Depressive Disorder. *Biol. Psychiatry* 64, 880–883.
<https://doi.org/10.1016/j.biopsych.2008.06.027>
- Malykhin, N. V, Carter, R., Seres, P., Coupland, N.J., 2010. Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment. *J. Psychiatry Neurosci.* 35, 337–343. <https://doi.org/10.1503/jpn.100002>
- Mansur, R.B., Brietzke, E., McIntyre, R.S., 2015. Is there a “metabolic-mood syndrome”? A review of the relationship between obesity and mood disorders. *Neurosci. Biobehav. Rev.* 52, 89–104. <https://doi.org/10.1016/j.neubiorev.2014.12.017>
- Marcus, M., Yasamy, M.T., Van Ommeren, M., Chisholm, D., Saxena, S., 2012. *Depression: A Global Public Health Concern*.
- Martis, B., Alam, D., Dowd, S.M., Hill, S.K., Sharma, R.P., Rosen, C., Pliskin, N., Martin, E., Carson, V., Janicak, P.G., 2003. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin. Neurophysiol.* 114, 1125–1132.

- [https://doi.org/10.1016/S1388-2457\(03\)00046-4](https://doi.org/10.1016/S1388-2457(03)00046-4)
- McIntyre, R.S., Cha, D.S., Soczynska, J.K., Woldeyohannes, H.O., Gallagher, L.A., Kudlow, P., Alsuwaidan, M., Baskaran, A., 2013. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress. Anxiety* 30, 515–527. <https://doi.org/10.1002/da.22063>
- McIntyre, R.S., Lee, Y., 2016. Cognition in major depressive disorder: a “Systemically Important Functional Index” (SIFI). *Curr. Opin. Psychiatry* 29, 48–55. <https://doi.org/10.1097/YCO.0000000000000221>
- McIntyre, R.S., Woldeyohannes, H.O., Soczynska, J.K., Maruschak, N.A., Wium-Andersen, I.K., Vinberg, M., Cha, D.S., Lee, Y., Xiao, H.X., Gallagher, L.A., Dale, R.M., Alsuwaidan, M.T., Mansur, R.B., Muzina, D.J., Carvalho, A.F., Jerrell, J.M., Kennedy, S.H., 2016. Anhedonia and cognitive function in adults with MDD: results from the International Mood Disorders Collaborative Project. *CNS Spectr.* 21, 362–366. <https://doi.org/10.1017/S1092852915000747>
- McIntyre, R.S., Xiao, H.X., Syeda, K., Vinberg, M., Carvalho, A.F., Mansur, R.B., Maruschak, N., Cha, D.S., 2015. The Prevalence, Measurement, and Treatment of the Cognitive Dimension/Domain in Major Depressive Disorder. *CNS Drugs* 29, 577–589. <https://doi.org/10.1007/s40263-015-0263-x>
- Menke, A., Binder, E.B., 2014. Epigenetic alterations in depression and antidepressant treatment. *Dialogues Clin. Neurosci.* 16, 395–404.
- Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat. Rev. Drug Discov.* 11, 141–68. <https://doi.org/10.1038/nrd3628>
- Mingli, H., Zhengtian, G., Xinyi, W., Xiaoping, T., 2009. Effects of repetitive transcranial magnetic stimulation on hypothalamic-pituitary-adrenal axis of patients with depression. *J. Med. Coll. PLA* 24, 337–345. [https://doi.org/10.1016/S1000-1948\(10\)60004-4](https://doi.org/10.1016/S1000-1948(10)60004-4)
- Mogg, A., Pluck, G., Eranti, S. V, Landau, S., Purvis, R., Brown, R.G., Curtis, V., Howard, R., Philpot, M., McLoughlin, D.M., 2008. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol. Med.* 38, 323–33. <https://doi.org/10.1017/S0033291707001663>
- Möller, A.L., Hjaltason, Ó., Ívarsson, Ó., Stefánsson, S.B., 2006. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P300 event-related potential. *Nord. J. Psychiatry* 60, 282–285. <https://doi.org/10.1080/08039480600790119>
- Näätänen, R., 1992. Attention and brain function. Lawrence Erlbaum Associates, Inc., Hillsdale, New Jersey.
- Nemeroff, C.B., 2007. Prevalence and management of treatment-resistant depression. *J. Clin. Psychiatry* 68 Suppl 8, 17–25.
- Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn. Affect. Behav. Neurosci.* 12, 241–68. <https://doi.org/10.3758/s13415-011-0083-5>
- O’Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., McDonald, W.M., Avery, D., Fitzgerald, P.B., Loo, C., Demitrack, M.A., George, M.S.,

- Sackeim, H.A., 2007. Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. *Biol. Psychiatry* 62, 1208–1216. <https://doi.org/10.1016/j.biopsych.2007.01.018>
- Olbrich, S., Arns, M., 2013. EEG biomarkers in major depressive disorder: Discriminative power and prediction of treatment response. *Int. Rev. Psychiatry* 25, 604–618. <https://doi.org/10.3109/09540261.2013.816269>
- Olejniczak, P., 2006. Neurophysiologic basis of EEG. *J. Clin. Neuroelectrophysiology* 23, 186–9. <https://doi.org/10.1097/01.wnp.0000220079.61973.6c>
- Paelecke-Habermann, Y., Pohl, J., Leplow, B., 2005. Attention and executive functions in remitted major depression patients. *J. Affect. Disord.* 89, 125–135. <https://doi.org/10.1016/j.jad.2005.09.006>
- Pan, Z., Grovu, R.C., Cha, D.S., Carmona, N.E., Subramaniapillai, M., Shekotikhina, M., Rong, C., Lee, Y., McIntyre, R.S., 2017. Pharmacological Treatment of Cognitive Symptoms in Major Depressive Disorder. *CNS Neurol. Disord. - Drug Targets* 16, 891–899. <https://doi.org/10.2174/1871527316666170919115100>
- Pascual-Leone, A., Rubio, B., Pallardó, F., Catalá, M.D., 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 348, 233–7.
- Patten, S.B., Williams, J.V.A., Dina, J., Lavorato, H., Jian, J., Wang, L., McDonald, K., Andrew, M., Bulloch, G.M., 2015. Descriptive Epidemiology of Major Depressive Disorder in Canada in 2012. *Can. J. Psychiatry* 60, 23–30.
- Paus, T., Barrett, J., 2004. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. *J. Psychiatry Neurosci.* 29, 268–279.
- Peng, H., Zheng, H., Li, L., Liu, Jianbin, Zhang, Y., Shan, B., Zhang, L., Yin, Y., Liu, Jun, Li, W., Zhou, J., Li, Z., Yang, H., Zhang, Z., 2012. High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. *J. Affect. Disord.* 136, 249–57. <https://doi.org/10.1016/j.jad.2011.12.006>
- Perrino, T., Beardslee, W., Bernal, G., Brincks, A., Cruden, G., Howe, G., Murry, V., Pantin, H., Prado, G., Sandler, I., Brown, C.H., 2015. Toward scientific equity for the prevention of depression and depressive symptoms in vulnerable youth. *Prev. Sci.* 16, 642–51. <https://doi.org/10.1007/s11121-014-0518-7>
- Petra, A.I., Panagiotidou, S., Hatziagelaki, E., Stewart, J.M., Conti, P., Theoharides, T.C., 2015. Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation. *Clin. Ther.* 37, 984–95. <https://doi.org/10.1016/j.clinthera.2015.04.002>
- Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology* 36, 183–206. <https://doi.org/10.1038/npp.2010.166>
- Polich, J., 2007. Updating P300: An integrative theory of P3a and P3b. *Clin. Neurophysiol.* 118, 2128–2148. <https://doi.org/10.1016/j.clinph.2007.04.019>
- Polich, J., 2004. Clinical application of the P300 event-related brain potential. *Phys. Med. Rehabil. Clin. N. Am.* 15, 133–161. [https://doi.org/10.1016/S1047-9651\(03\)00109-8](https://doi.org/10.1016/S1047-9651(03)00109-8)
- Polich, J., Kok, A., 1995. Cognitive and biological determinants of P300: an integrative review. *Biol. Psychol.* 41, 103–146.
- Porter, R.J., Bourke, C., Gallagher, P., 2007. Neuropsychological impairment in major

- depression: its nature, origin and clinical significance. *Aust. N. Z. J. Psychiatry* 41, 115–28. <https://doi.org/10.1080/00048670601109881>
- Ragguett, R.-M., Cha, D.S., Kakar, R., Rosenblat, J.D., Lee, Y., McIntyre, R.S., 2016. Assessing and measuring cognitive function in major depressive disorder. *Evid. Based Ment. Heal.* 19, 106–109. <https://doi.org/10.1136/eb-2016-102456>
- Rêgo, S.R.M., Marcolin, M.A., May, G., Gjini, K., 2012. Effects of transcranial magnetic stimulation on the cognitive event-related potential P300: A literature review. *Clin. EEG Neurosci.* <https://doi.org/10.1177/1550059412445657>
- Rektorova, I., Megova, S., Bares, M., Rektor, I., 2005. Cognitive functioning after repetitive transcranial magnetic stimulation in patients with cerebrovascular disease without dementia: a pilot study of seven patients. *J. Neurol. Sci.* 229–230, 157–161. <https://doi.org/10.1016/j.jns.2004.11.021>
- Rennie, C.J., Robinson, P.A., Wright, J.J., 2002. Unified neurophysical model of EEG spectra and evoked potentials. *Biol. Cybern.* 86, 457–471. <https://doi.org/10.1007/s00422-002-0310-9>
- Ricardo-Garcell, J., González-Olvera, J.J., Miranda, E., Harmony, T., Reyes, E., Almeida, L., Galán, L., Díaz, D., Ramírez, L., Fernández-Bouzas, A., Aubert, E., 2009. EEG sources in a group of patients with major depressive disorders. *Int. J. Psychophysiol.* 71, 70–4. <https://doi.org/10.1016/j.ijpsycho.2008.07.021>
- Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol. Med.* 44, 2029–2040. <https://doi.org/10.1017/S0033291713002535>
- Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Bestmann, S., Berardelli, A., Brewer, C., Cantello, R., Chen, R., Classen, J., Di Lazzaro, V., Epstein, C.M., Fregni, F., Karp, B., Lefaucheur, J.-P., Physiologie, S., Fonctionnelles, E., Henri Mondor, H., Sarah Lisanby, F., Miniussi, C., Miranda, P., Paulus, W., Peterchev, A., Porteri, C., Provost, M., Quartarone, A., Rotenberg, A., Rothwell, J., Ruohonen, J., Ltd, N., Hartwig Siebner, F., Zangen, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039. <https://doi.org/10.1016/j.clinph.2009.08.016>
- Rothwell, J.C., 1997. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J. Neurosci. Methods* 74, 113–22.
- Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *Am. J. Psychiatry* 163, 1905–1917. <https://doi.org/10.1176/ajp.2006.163.11.1905>
- Saletu, B., Anderer, P., Saletu-Zyhlarz, G.M., 2010. EEG Topography and Tomography (LORETA) in Diagnosis and Pharmacotherapy of Depression. *Clin. EEG Neurosci.* 41, 203–210. <https://doi.org/10.1177/155005941004100407>
- Sato, A., Torii, T., Nakahara, Y., Iwahashi, M., Itoh, Y., Iramina, K., 2013. The Impact of rTMS Over the Dorsolateral Prefrontal Cortex on Cognitive Processing. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* 2013, 1988–1991. https://doi.org/10.0/Linux-x86_64
- Schatzberg, A.F., Rush, A.J., Arnow, B.A., Banks, P.L.C., Blalock, J.A., Borian, F.E., Howland, R., Klein, D.N., Kocsis, J.H., Kornstein, S.G., Manber, R., Markowitz, J.C., Miller, I., Ninan, P.T., Rothbaum, B.O., Thase, M.E., Trivedi, M.H., Keller, M.B., 2005. Chronic

- depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch. Gen. Psychiatry* 62, 513. <https://doi.org/10.1001/archpsyc.62.5.513>
- Schönfeldt-Lecuona, C., Thielscher, A., Freudenmann, R.W., Kron, M., Spitzer, M., Herwig, U., 2005. Accuracy of stereotaxic positioning of transcranial magnetic stimulation. *Brain Topogr.* 17, 253–9.
- Schrijvers, D., Maas, Y.J., Pier, M.P.B.I., Madani, Y., Hulstijn, W., Sabbe, B.G.C., 2009. Psychomotor Changes in Major Depressive Disorder during Sertraline Treatment. *Neuropsychobiology* 59, 34–42. <https://doi.org/10.1159/000205516>
- Schutter, D.J.L.G., van Honk, J., 2006. A Standardized Motor Threshold Estimation Procedure for Transcranial Magnetic Stimulation Research. *J. ECT* 22, 176–178. <https://doi.org/10.1097/01.yct.0000235924.60364.27>
- Serafini, G., Pompili, M., Belvederi Murri, M., Respino, M., Ghio, L., Girardi, P., Fitzgerald, P.B., Amore, M., 2015. The Effects of Repetitive Transcranial Magnetic Stimulation on Cognitive Performance in Treatment-Resistant Depression. A Systematic Review. *Neuropsychobiology* 71, 125–139. <https://doi.org/10.1159/000381351>
- Sha, Z., Wager, T.D., Mechelli, A., He, Y., 2019. Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders. *Biol. Psychiatry* 85, 379–388. <https://doi.org/10.1016/j.biopsych.2018.11.011>
- Shibasaki, H., 2008. Human brain mapping: Hemodynamic response and electrophysiology. *Clin. Neurophysiol.* <https://doi.org/10.1016/j.clinph.2007.10.026>
- Siebner, H.R., Hartwigsen, G., Kassuba, T., Rothwell, J.C., 2009. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex* 45, 1035–1042. <https://doi.org/10.1016/j.cortex.2009.02.007>
- Slotema, C.W., Blom, J.D., Hoek, H.W., Sommer, I.E.C., 2010. Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)? *J. Clin. Psychiatry* 71, 873–884. <https://doi.org/10.4088/JCP.08m04872gre>
- Soczynska, J.K., Ravindran, L.N., Styra, R., McIntyre, R.S., Cyriac, A., Manierka, M.S., Kennedy, S.H., 2014. The effect of bupropion XL and escitalopram on memory and functional outcomes in adults with major depressive disorder: results from a randomized controlled trial. *Psychiatry Res.* 220, 245–50. <https://doi.org/10.1016/j.psychres.2014.06.053>
- Speer, A.M., Repella, J.D., Figueras, S., Demian, N.K., Kimbrell, T.A., Wasserman, E.M., Post, R.M., 2001. Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *J. ECT* 17, 259–63.
- Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B., 1995. Structured Clinical Interview for the DSM-IV – Non-Patient Edition (SCID-NP, Version 2.0).
- Spronk, D., Arns, M., Barnett, K.J., Cooper, N.J., Gordon, E., 2011. An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study. *J. Affect. Disord.* 128, 41–48. <https://doi.org/10.1016/j.jad.2010.06.021>
- Stahl, S.M., Zhang, L., Damatarca, C., Grady, M., 2003. Brain circuits determine destiny in depression: a novel approach to the psychopharmacology of wakefulness, fatigue, and executive dysfunction in major depressive disorder. *J. Clin. Psychiatry* 64 Suppl 14, 6–17.
- Strafella, A.P., Paus, T., Barrett, J., Dagher, A., 2001. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus.

- J. Neurosci. 21, RC157.
- Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. *Am. J. Psychiatry* 157, 1552–1562. <https://doi.org/10.1176/appi.ajp.157.10.1552>
- Sun, H., Kennedy, P.J., Nestler, E.J., 2013. Epigenetics of the depressed brain: role of histone acetylation and methylation. *Neuropsychopharmacology* 38, 124–37. <https://doi.org/10.1038/npp.2012.73>
- Taylor, B.P., Bruder, G.E., Stewart, J.W., McGrath, P.J., Halperin, J., Ehrlichman, H., Quitkin, F.M., 2006. Psychomotor Slowing as a Predictor of Fluoxetine Nonresponse in Depressed Outpatients, *American Journal of Psychiatry*.
- Taylor, J.L., Loo, C.K., 2007. Stimulus waveform influences the efficacy of repetitive transcranial magnetic stimulation. *J. Affect. Disord.* 97, 271–276. <https://doi.org/10.1016/j.jad.2006.06.027>
- Towers, D.N., Allen, J.J.B., 2009. A better estimate of the internal consistency reliability of frontal EEG asymmetry scores. *Psychophysiology* 46, 132–142. <https://doi.org/10.1111/j.1469-8986.2008.00759.x>
- Trans Cranial Technologies Ltd, 2012. 10/20 Positioning Manual.
- Tripathi, S.M., Mishra, N., Tripathi, R.K., Gurnani, K., 2015. P300 latency as an indicator of severity in major depressive disorder. *Ind. Psychiatry J.* 24, 163–167. <https://doi.org/10.4103/0972-6748.181726>
- Van Dinteren, R., Arns, M., Kenemans, L., Jongsma, M.L.A., Kessels, R.P.C., Fitzgerald, P., Fallahpour, K., Debatista, C., Gordon, E., Williams, L.M., 2015. Utility of event-related potentials in predicting antidepressant treatment response: An iSPOT-D report. *Eur. Neuropsychopharmacol.* 25, 1981–1990. <https://doi.org/10.1016/j.euroneuro.2015.07.022>
- Vanderhasselt, M.-A., De Raedt, R., Baeken, C., Leyman, L., D’haenen, H., 2006. The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Exp. Brain Res.* 169, 279–282. <https://doi.org/10.1007/s00221-005-0344-z>
- Vanderhasselt, M.-A., De Raedt, R., Leyman, L., Baeken, C., Raedt, D., -, L., Vanderhasselt, M., 2009. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes, *Journal of Psychiatry & Neuroscience*.
- Vandoolaeghe, E., Van Hunsel, F., Nuyten, D., Maes, M., 1998. Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude, *Journal of Affective Disorders*.
- Vinberg, M., Miskowiak, K.W., Vedel Kessing, L., 2013. Original Research Impairment of Executive Function and Attention Predicts Onset of Affective Disorder in Healthy High-Risk Twins. *J Clin Psychiatry* 74, 747–753. <https://doi.org/10.4088/JCP.12m08258>
- Wade, E.C., Iosifescu, D. V, 2016. Using Electroencephalography for Treatment Guidance in Major Depressive Disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 1, 411–422. <https://doi.org/10.1016/j.bpsc.2016.06.002>
- Widge, A.S., Taha Bilge, M., Montana, R., Chang, W., Rodriguez, C.I., Deckersbach, T., Carpenter, L.L., Kalin, N.H., Nemeroff, C.B., 2019. Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis. *Am. J. Psychiatry* 176, 44–56. <https://doi.org/10.1176/appi.ajp.2018.17121358>
- Woo, Y.S., Rosenblat, J.D., Kakar, R., Bahk, W.-M., McIntyre, R.S., 2016. Cognitive Deficits as a Mediator of Poor Occupational Function in Remitted Major Depressive Disorder Patients. *Clin. Psychopharmacol. Neurosci.* 14, 1–16. <https://doi.org/10.9758/cpn.2016.14.1.1>

- Yang, X.R., Kirton, A., Wilkes, T.C., Pradhan, S., Liu, I., Jaworska, N., Damji, O., Keess, J., Langevin, L.M., Rajapakse, T., Lebel, R.M., Sembo, M., Fife, M., Macmaster, F.P., 2014. Glutamate alterations associated with transcranial magnetic stimulation in youth depression: A case series. *J. ECT* 30, 242–247. <https://doi.org/10.1097/YCT.0000000000000094>
- Yukimasa, T., Yoshimura, R., Tamagawa, A., Uozumi, T., Shinkai, K., Ueda, N., Tsuji, S., Nakamura, J., 2006. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry* 39, 52–9. <https://doi.org/10.1055/s-2006-931542>
- Zanardini, R., Gazzoli, A., Ventriglia, M., Perez, J., Bignotti, S., Rossini, P.M., Gennarelli, M., Bocchio-Chiavetto, L., 2006. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *J. Affect. Disord.* 91, 83–6. <https://doi.org/10.1016/j.jad.2005.12.029>
- Zheng, H., Zhang, L., Li, L., Liu, P., Gao, J., Liu, X., Zou, J., Zhang, Y., Liu, J., Zhang, Z., Li, Z., Men, W., 2010. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 1189–95. <https://doi.org/10.1016/j.pnpbp.2010.06.009>
- Zhou, L., Wang, G., Nan, C., Wang, H., Liu, Z., Bai, H., 2019. Abnormalities in P300 components in depression: an ERP-sLORETA study. *Nord. J. Psychiatry* 73, 1–8. <https://doi.org/10.1080/08039488.2018.1478991>
- Zwanzger, P., Baghai, T.C., Padberg, F., Ella, R., Minov, C., Mikhael, P., Schüle, C., Thoma, H., Rupprecht, R., 2003. The combined dexamethasone-CRH test before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychoneuroendocrinology* 28, 376–85.

Appendix A: Informed Consent Forms (Patients/Healthy Controls)



PARTICIPANT INFORMED CONSENT FORM

Study Title: NeuroQore Repetitive Transcranial Magnetic Monophasic vs. Biphase Stimulation for Major Depressive Disorder: A Randomized Controlled Pilot Trial

Principle Investigator: Verner J. Knott, Ph.D., C. Psych.

Co-Investigators: Pierre Blier, M.D., Ph.D.; Lisa McMurray, M.D., FRCPC; Ahmed Rostom, M.D., Asif Khan, M.D., FRCPC

Funding Agency: NeuroQore, Inc.

Participation in this study is voluntary. Please read this Information Sheet and Informed Consent Form carefully before you decide if you would like to participate. Ask the study doctor and study team as many questions as you like. We encourage you to discuss your options with family, friends or your healthcare team.

Why am I being given this form?

You are being asked to take part in a research study because you have a diagnosis of Major Depressive Disorder and are interested in pursuing treatment using Repetitive Transcranial Magnetic Stimulation (rTMS). This new technology will be investigated with the use of a recently developed rTMS device by NeuroQore, Inc. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision.

Why is this study being done?

- You have been asked to take part in this research study because you have a diagnosis of Major Depressive Disorder and are interested in pursuing treatment using Repetitive Transcranial Magnetic Stimulation (rTMS). rTMS is a treatment that involves stimulating certain areas of the brain with magnetic field pulses. Over time, the magnetic field pulses can gradually change the activity level of the stimulated brain region. This can be helpful in treating some kinds of psychiatric and neurological disorders.

- One form of rTMS, involves the administration of two-way (bi-phase) magnetic pulses at a frequency of 20 pulses per second (or 20 Hz), with breaks, over a period of 15 minutes per session.
- The problem with the two-way pulses is it generates a complex activation pattern in the brain with short after effects.
- Another form of rTMS involves the administration of one-way (mono-phase) magnetic pulses at a frequency of 20 pulses per second (or 20 Hz), with breaks, over a period of 15 minutes per session. One-way pulses result in greater activation of the brain and could therefore be more effective in producing sustained after effects than two-way pulses.
- This study will compare these two different pulses (two-way versus one-way) within rTMS, using the same overall strength and target, to see if they have the same or better effectiveness in treating major depression.
- The technology used in this study, rTMS, has been approved by Health Canada for investigational research studies like this one. Health Canada does not currently specify what pulse for stimulation should be used to treat major depression. Currently, the standard of care for patients undergoing rTMS involves two-way pulses.
- Forty participants from the Royal Ottawa Mental Health Centre will be enrolled in this study
- If new information emerges about the treatments in this study that alters the risks or benefits of participation you will be notified.

How is the study designed?

This study compares the effectiveness of two different kinds of rTMS: one-way and two-way.

Whether you receive one-way or two-way stimulation will be decided randomly (by chance) like flipping a coin or rolling dice. The number of people getting treatment in each study group will be ~20 so you will have a 1 in 2 chance of receiving one-way stimulation and a 1 in 2 chance of receiving two-way stimulation.

This study will be double-blinded. This means you will not be told if you will be receiving one-way or two-way rTMS. Your study team will also not know. Blinding helps to remove any bias or pre-conceived notions from affecting the outcome of the study. However, in an emergency this information can be obtained quickly. You may be told once the study is finished.

You will undergo rTMS treatment in this study every weekday for 6 weeks (for a total of 30 sessions). Once your treatment is complete, you will come in for a total of 3 additional visits occurring over 12 weeks for a follow-up of clinical outcomes. In addition to the rTMS component of the study, there are two additional, optional components to the study. First is the option to participate in a brain-based research component of the study, where you will be asked to complete two electrophysiology (EEG) sessions: one before you begin treatment and one after you complete treatment. Second is a blood-based portion of the study where we will draw blood for analysis once prior to the beginning of treatment and once after you complete treatment. This will help us to study biological markers in the blood that are associated with depression.

Should you choose to withdraw from the treatment of the study or are unable to finish all of the scheduled treatment appointments due to unforeseen circumstances, you may still agree to participate in the remaining clinical assessments as scheduled.

What is expected of me?

Screening Session

The first study visit will be a screening visit. This visit will involve an interview to confirm your diagnosis of major depressive disorder and rule out other psychiatric diagnoses that might interfere with treatment. It will also confirm if you can safely undergo rTMS. You will also be asked for information about your substance use (this will include a urine drug screen). Finally, your medical chart will be assessed and you will undergo a blood test to ensure that there is no medical cause for your depression. The results of the tests/questions at the screening visit help the researchers to decide whether you can continue in this study. If you are eligible, your regular physician will be notified of your study participation. If you choose to participate in the optional blood-based component of the study, you will have an additional blood draw during this screening session, to be used to study biological markers that are associated with depression. The results of all tests and interviews are completely confidential. The screening session will take approximately 90 minutes.

Baseline rTMS Session (Calibration)

During your first visit for rTMS, you will be asked to sit in a chair while the study technician takes head measurements to determine where to aim the stimulation. This will be done using a measuring tape and a safe, washable skin pen. Once the best location is determined, the coordinates will be entered into a computer and the rTMS machine will automatically move the stimulation arm over the correct scalp area. Next, they will perform a short stimulation procedure called motor threshold (MT) testing to determine the proper strength of the rTMS, by observing the movements of your hand in response to stimulation. Should you decide to participate in the brain-based (EEG) component of this study, you will complete your first EEG session during this visit, prior to your rTMS treatment. The EEG session will take place on the third floor of the hospital and will last approximately 1.5 hours. During this time period you will undergo a brief hearing test and then you will be brought into a recording chamber where you will be set up in a chair, electrodes will be attached, and recordings will be taken while you are presented with various clicks and tones, as well as at rest with your eyes open or closed.

rTMS Visits

The rTMS treatments will take place over a 6 week time frame, every day from Monday to Friday, for a total of 30 sessions. On each day, you will arrive at the Royal and make your way to the 6th floor where you will be greeted by the study research assistant. You will then enter the rTMS chamber where the rTMS technician will prepare you for stimulation in the same way as the baseline session. The rTMS treatment will last approximately 15 minutes, and your involvement at each session will last approximately 30 minutes in total.

In addition to the rTMS stimulation, you will be required to meet with the study research assistant one time at the end of week 1, week 2, week 4, and week 6 to do a brief interview and series of questionnaires to monitor any changes. This will take approximately an addition 30 minutes at each of the four time points.

If you miss more than 3 consecutive treatment days you will be excluded from the study as that would be clinically significant to your treatment.

Follow-Up Visits

After you have finished your 6 weeks of rTMS treatments, we will ask that you come back in for a total of 3 additional visits occurring 1 week, 4 weeks, and 12 weeks following the completion of treatment. During these sessions you will be asked to complete questionnaires and a short interview to determine if there are any long-lasting effects of your treatment. If you have chosen to take part in the EEG and/or the blood-based component of the study you will complete your second EEG session (which will be identical to the first) and your second blood draw one week following the completion of your rTMS treatment.

Calendar of Visits

Boxes marked with an X show what will happen at each visit:

Visit	Interview and Questionnaires	Motor Threshold Testing	rTMS Treatment
Screening Session	X		
rTMS Calibration	X	X	
rTMS Visits 1-30			X
rTMS weeks 1, 2, 4, and 6 (once at end of week)	X		X
Clinical Assessment Follow-Up (1 week, 4 weeks, 12 weeks post treatment)	X		

How long will I be involved in the study?

The entire study is expected to last approximately 2 years. Your participation in this research study will last approximately 18 weeks (6 weeks of rTMS treatment and 12 weeks of clinical assessment follow-up). Over this time, you will be required to visit the Royal Ottawa Mental Health Centre a total of 36 times.

Your participation in the study may be stopped for any of the following reasons:

- You are not deemed eligible after the screening session
- The study doctor feels it is in your best interest.
- A government agency such as Health Canada cancels the study.
- You need additional health treatment or medication that would interfere with the study.
- If you experience any major side effects to the study treatment during the laboratory sessions.
- You do not follow the study staff's instructions.
- You become pregnant.

What are the potential risks I may experience?

Tens of thousands of people have received rTMS treatment over the last 20 years. rTMS has certain risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in study subjects to date. Some can be managed. Please call the study doctor if you have any side effects (unwanted effects or health problems) even if you do not think it has anything to do with this study.

The risks associated with rTMS that we know of are: (The numbers in brackets show how often the side-effect happened.)

Common: Headache (30%), discomfort or pain at the stimulation site (20%), lightheadedness or dizziness after the treatment (20%), facial muscle twitching (30%). These side effects are usually temporary, and can usually be managed with rest, or with over-the-counter pain medications such as acetaminophen (Tylenol) or ibuprofen (Advil).

Less Common: (1-7%) fatigue, headache persisting after the treatment, dizziness or fainting during the initial sessions of rTMS treatment.

Rare but Serious: Onset of suicidal thinking (less than 1%). There is also a 1% chance that rTMS may lead to a hypomanic episode (the opposite of depression, with symptoms elevated mood and energy, increased activity, impulsiveness, and decreased need for sleep). You will be monitored regularly for these symptoms during treatment and will have immediate access to a study psychiatrist if they appear.

Very Rare but Serious: There are rare cases of an epileptic seizure resulting from rTMS (less than 0.1%). Safety guidelines have been in place since 1997 to minimize the risk of seizures from rTMS, and this study follows those guidelines. Still, worldwide, there have been four reports of a seizure during rTMS even when the guidelines were followed. In many of these cases, patients were taking medications known to increase the chances of a seizure occurring spontaneously. Therefore, be sure to tell the study team about all of the medications you are taking.

Risks of EEG

The risks involved in EEG testing are very minimal. Brain wave activity (EEG) monitoring procedures are similar to those carried out in hospitals. Slight redness may occur where

electrodes are placed on the scalp and skin. You may also experience boredom or restlessness during tasks that are more passive.

Risks of Blood Draw

Obtaining blood samples may cause mild discomfort, pain, bruising and soreness. There may also be slight bleeding at the needle site for a short period of time following the blood draw that will be covered with a bandage.

Risks Related to Pregnancy

There are no known risks of rTMS during pregnancy. However, there is always a possibility that if you are pregnant, rTMS may have risks that we do not know about. For this reason, you should not participate in the study if you may be pregnant. Pregnancy will be assessed with the blood test as part of your screening.

Can I expect to benefit from participating in this research study?

You may or may not receive any direct benefit from being in this study. rTMS may improve your symptoms of depression, or may have no effect. Information learned from this study may help other people undergoing rTMS for major depression in the future.

Do I have to participate? What alternative do I have?

You can choose not to participate in this study. If you choose not to participate, it will not affect your current or future medical care. Your study doctor will discuss your options with you.

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later without affecting the medical care, education, or other services to which you are entitled or are presently receiving at this institution.

Additionally, you do not have to join this study to receive treatment for your condition. rTMS is offered in a non-research setting through some private clinics in Ottawa and elsewhere. There are also many other approved medications/interventions for major depression:

- There are many antidepressant medications that are available alternatives to participation in this study. Your psychiatrist or family doctor can help you decide on the best antidepressant medication for your illness.
- Psychotherapies such as cognitive behavioral therapy (CBT), interpersonal therapy (IPT), or mindfulness-based cognitive therapy (MBCT).
- Brain stimulation therapies such as electroconvulsive therapy, for depression that is severe or unresponsive to other treatments.
- There are also other research studies looking at other treatments for your condition.
- You may also choose not to have any treatment for your condition.

Your doctor will discuss any of these options with you.

If I agree now, can I change my mind and withdraw later?

You may withdraw from the study at any time without any impact on your current or future care at this institution.

- If you decide to stop the study treatment you should contact the study doctor or the study team first. They will discuss the related issues or possible safety concerns for you.
- You may also choose to discontinue your participation in the study. However, a final visit(s) may need to be completed to ensure your safety and well-being.
- If you withdraw your consent, the study team will no longer collect your personal health information for research purposes, unless it is needed for review of safety.

What compensation will I receive if I am injured or become ill in this study?

In the event of a study-related injury or illness, you will be provided with appropriate medical treatment and care. Financial compensation for lost wages, disability or discomfort due to an injury or illness is not generally available. You are not waiving any of your legal rights by agreeing to participate in this study. The study doctor and the Royal Ottawa Mental Health Centre still have their legal and professional responsibilities.

Will I be paid for my participation?

You will be paid \$10 for each rTMS session to compensate for travel expenses for a total of \$300. In addition, you will not have to pay for any of the treatments or other procedures involved with this study. If you choose to participate in the brain-based component of the study, you will be paid an additional \$15 for each of the two EEG sessions (one at baseline and one at 1 week follow-up) in order to compensate for your time.

How is my personal information being protected?

If you agree to participate in the study, you will be assigned a study-specific code for storage of your personal information. A Master List will provide the link between your identifying information and the coded study number. Only the principal investigator, co-investigators, and research assistants will have access to the study information. The coded information will be stored for 25 years in a locked cabinet at the Royal Ottawa Mental Health Centre. The list of participants' names with their matching codes will be stored a secured server in a password-protected file.

The data collected in this study may be used for education and/or scientific purposes. For example, in publications, classroom materials or presentations to conferences. None of these publications, materials or presentations will identify the study's participants. Your research file may also be viewed by the Research Ethics Board and/or Research Quality Associate for quality assurance purposes.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

During the research, if we learn you are having thoughts about suicide or hurting yourself or others, the research staff will ask you more questions about your thoughts. Based on your response, the staff may provide you with help to get treatment. This may include:

- working with you to contact your doctor,
- contact a trusted family member, or a therapist to discuss your thoughts,
- or work with you on a plan that may include getting you to a hospital for safety

Do the investigators have any conflicts of interest?

This study is being funded by NeuroQore, Inc. The researchers in this study have no conflicts of interest to declare.

What are my responsibilities as a study participant?

It is important to remember the following things during this study:

- Ask the study doctor and/or research staff if you have any questions or concerns.
- Tell the study research staff or study doctor if anything about your health has changed.
- Tell study staff if you are considering any changes to your medications or doses.
- Tell study staff if you have changed any of your medications or doses.
- Tell study staff if you become pregnant during the study.
- Tell study staff if your depression becomes worse.
- Tell study staff if you are having thoughts about hurting yourself or anyone else.
- Tell your study team if you change your mind about being in this study.
- Call the study doctor if you experience any side effects, even if you are unsure whether it has anything to do with this study.

Will I be informed about any new information that might affect my decision to continue participating?

You will be told in a timely fashion of any new findings during the study that could affect your willingness to continue in the study. You may be asked to sign a new consent form.

Contact Information

If you have any specific questions about this research, you should contact Dr. Knott, who can be reached 24-hours a day.

If you have any questions about the ethical conduct of this study, please contact the REB of the Royal Ottawa Mental Health Centre at 613-722-6521 ext 6214 during business hours for more information.

NeuroQore Repetitive Transcranial Magnetic Monophasic vs. Biphasic Stimulation for Major Depressive Disorder: A Randomized Trial

Consent to Participate in Research

- I understand that I am being asked to participate in a research study about two different methods of rTMS treatment.
- This study was explained to me by _____.
- I have read, or have had it read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

It is important that your personal doctor be aware you are in a research study, as you may be taking a treatment that could affect your health. With your permission, we will notify him/her that you are taking part in this study.

I consent to my personal doctor being notified that I am taking part in this study.

YES NO Participant's Initials _____

I agree to participate in the rTMS component of this study.

YES NO Participant's Initials _____

I agree to participate in the optional brain-based (EEG) component of this study.

YES NO Participant's Initials _____

I agree to participate in the optional blood-based component of this study.

YES NO Participant's Initials _____

Participant's Printed Name

Participant's Signature

Date

Investigator or Delegate Statement

I have carefully explained the study to the study participant. To the best of my knowledge, the participant understands the nature, demands, risks and benefits involved in taking part in this study.

Investigator/Delegate's Printed Name

Investigator/Delegate's Signature

Date

PARTICIPANT INFORMED CONSENT FORM – Healthy Volunteers

Study Title: **Biomarkers Predictive of and Responsive to Repetitive Transcranial Magnetic Stimulation (rTMS) in Major Depressive Disorder (MDD)**

Principle Investigator: Verner J. Knott, Ph.D., C. Psych.

Co-Investigators: Pierre Blier, M.D., Ph.D., Lisa McMurray, M.D., FRCPC., Ahmed Rostom, M.D., Asif Khan, M.D., FRCPC

Funding Agency: NeuroQore, Inc.

Participation in this study is voluntary. Please read this Information Sheet and Informed Consent Form carefully before you decide if you would like to participate. Ask the study team as many questions as you like. We encourage you to discuss your options with family, friends or your healthcare team.

Why am I being given this form?

You are being asked to take part in a research study to provide brain-based and blood-based biomarker data that will be analyzed in comparison with similar data collected from patients that are diagnosed with treatment-resistant major depressive disorder who will be undergoing repetitive transcranial magnetic stimulation (rTMS) therapy.

Why is this study being done?

- rTMS is a treatment that involves stimulating certain areas of the brain with magnetic field pulses. Over time, the magnetic field pulses can gradually change the activity level of the stimulated brain region. This can be helpful in treating some kinds of psychiatric and neurological disorders.
- The technology used in this study, rTMS, has been approved by Health Canada for investigational research studies like this one. Currently, the standard of care for patients undergoing rTMS involves two-way pulses.
- Biomarkers found in the brain and in the blood that are associated with depression can help us understand the illness and how to better treat it
- 40 healthy volunteer and 40 patient participants will be enrolled in this study
- Healthy volunteers will be asked to complete 2 EEG sessions and 2 blood draws at different time points to serve as a comparison group for patients with major depressive disorder

What is expected of me?

Should you decide to participate in the brain-based (EEG) component of this study, you will complete your first EEG session during your first visit and your second EEG session after 6 weeks. The EEG sessions will take place on the third floor of the hospital and will last approximately 1.5 hours. During this time period you will undergo a brief hearing test, an expired-air carbon monoxide test, and a urine screen. You will then be brought into a recording chamber where you will be set up in a chair, electrodes will be attached, and recordings will be taken while you are presented with various clicks and tones, as well as at rest with your eyes open or closed. You will also be asked to complete several self-report questionnaires.

If you choose to participate in the blood-based component of the study, you will have blood draw during your first visit and another blood draw after 6 weeks; these will be used to study biological markers that are associated with depression. The results of all tests and interviews are completely confidential.

How long will I be involved in the study?

The entire study is expected to last approximately 2 years. Your participation in this research study will occur over the course of 6 weeks (1 baseline visit and 1 visit post-6 weeks). Over this time, you will be required to visit the Royal Ottawa Mental Health Centre a total of 2 times.

Your participation in the study may be stopped for any of the following reasons:

- A government agency such as Health Canada cancels the study.
- You need additional health treatment or medication that would interfere with the study.
- You do not follow the study staff's instructions.

What are the potential risks I may experience?

Risks of EEG

The risks involved in EEG testing are very minimal. Brain wave activity (EEG) monitoring procedures are similar to those carried out in hospitals. Slight redness may occur where electrodes are placed on the scalp and skin. You may also experience boredom or restlessness during tasks that are more passive.

Risks of Blood Draw

Obtaining blood samples may cause mild discomfort, pain, bruising and soreness. There may also be slight bleeding at the needle site for a short period of time following the blood draw that will be covered with a bandage.

Can I expect to benefit from participating in this research study?

You will not receive any direct benefit from being in this study. Information learned from this study may help other people undergoing rTMS for major depression in the future.

Do I have to participate? What alternative do I have?

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now, and then change your mind later.

If I agree now, can I change my mind and withdraw later?

You may withdraw from the study at any time.

- If you withdraw your consent, the study team will no longer collect your personal health information for research purposes

Will I be paid for my participation?

You will be paid \$30 for each session to compensate for your time, for a total of \$60.

How is my personal information being protected?

If you agree to participate in the study, you will be assigned a study-specific code for storage of your personal information. A Master List will provide the link between your identifying information and the coded study number. Only the principal investigator, co-investigators, and research assistants will have access to the study information. The coded information will be stored for 25 years in a locked cabinet at the Royal Ottawa Mental Health Centre. The list of participants' names with their matching codes will be stored a secured server in a password-protected file.

The data collected in this study may be used for education and/or scientific purposes. For example, in publications, classroom materials or presentations to conferences. None of these publications, materials or presentations will identify the study's participants. Your research file may also be viewed by the Research Ethics Board and/or Research Quality Associate for quality assurance purposes.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Do the investigators have any conflicts of interest?

This study is being funded by NeuroQore, Inc. The researchers in this study have no conflicts of interest to declare.

What are my responsibilities as a study participant?

It is important to remember the following things during this study:

- Ask the study doctor and/or research staff if you have any questions or concerns.
- Tell the study research staff or study doctor if anything about your health has changed.

- Tell study staff if you are considering any changes to your medications or doses.
- Tell study staff if you have changed any of your medications or doses.
- Tell your study team if you change your mind about being in this study.

Will I be informed about any new information that might affect my decision to continue participating?

You will be told in a timely fashion of any new findings during the study that could affect your willingness to continue in the study. You may be asked to sign a new consent form.

Contact Information

If you have any specific questions about this research, you should contact Dr. Knott, who can be reached 24-hours a day by telephone.

If you have any questions about the ethical conduct of this study, please contact the REB of the Royal Ottawa Mental Health Centre at 613-722-6521 ext 6214 during business hours for more information.

Biomarkers Predictive of and Responsive to Repetitive Transcranial Magnetic Stimulation (rTMS) in Major Depressive Disorder (MDD)

Consent to Participate in Research – Healthy Volunteers

- This study was explained to me by _____.
- I have read, or have had it read to me, each page of this Participant Informed Consent Form.
- All of my questions have been answered to my satisfaction.
- If I decide later that I would like to withdraw my participation and/or consent from the study, I can do so at any time.
- I voluntarily agree to participate in this study.
- I will be given a copy of this signed Participant Informed Consent Form.

I agree to participate in the optional brain-based (EEG) component of this study.

YES NO Participant's Initials _____

I agree to participate in the optional blood-based component of this study.

YES NO Participant's Initials _____

Participant's Printed Name

Participant's Signature

Date

Witness's Printed Name

Witness's Signature

Date

Appendix B: Adverse Events Questionnaire

Date: _____

ID: _____

Session: _____

Checklist of Symptoms

Please rate how you have felt **since your last treatment** by indicating with a checkmark **one** of the following five options, as they relate to the severity of possible treatment related symptoms you may or may not have experienced.

Symptoms	No symptoms 0	Mild 1	Moderate 2	Moderately Severe 3	Severe 4
Light headedness					
Headache					
Seizure					
Tremors					
Drowsy					
Nausea					
Dizziness					
Spinning sensation					
Lack of coordination					
Jaw/muscle pain					
Disorientation					
Heart palpitations					
Chest pain					
Difficulty breathing					
Agitated					
Irritated					
Fatigue					
Depressed					
Anxious					
Mood swings					
Difficulty concentrating					
Dry mouth					
Blurred vision					
Weakness/lack of energy					
Hallucinations					
High feeling					
Other (please list)					
-					
-					
-					