Markers of Transcranial Magnetic Stimulation for Depression

ELECTROENCEPHELOGRAPHIC BIOMARKERS OF TREATMENT RESPONSE TO TRANSCRANIAL MAGNETIC STIMULATION FOR MAJOR DEPRESSIVE DISORDER

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TITLE: Electroencephalographic Biomarkers of Treatment Response to Transcranial Magnetic Stimulation for Major Depressive Disorder

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Lay Abstract

Clinical depression is difficult to treat, and many patients do not respond adequately to medication alone. Transcranial magnetic stimulation (TMS) offers an alternative by stimulating targeted brain regions, yet its effectiveness varies. Understanding which patients are most likely to benefit requires examining underlying brain activity through tools like electroencephalography (EEG). By reviewing existing research and conducting our own analyses we identified EEG patterns linked to better or worse TMS outcomes. Elevated N100 activity, associated with inhibitory brain processes, before treatment predicted improvement, and decreases in N100 post-TMS were also tied to symptom relief. In contrast, increases in gamma or alpha activity, which relate to perception and attention, were associated with poorer outcomes. Theta activity, tied to working memory, showed a pattern similar to N100; higher levels before TMS and reductions afterward aligned with clinical improvement. These findings are encouraging, though marker-lead clinical trials remain essential before clinical application.

Abstract

Aim: To investigate electroencephalographic (EEG) biomarkers of response to transcranial magnetic stimulation (TMS) in major depressive disorder (MDD), with a focus on predictive (PB) and mechanistic (MB) biomarkers.

Methods: Chapter 1 provided background on the existing literature. Furthermore, Chapter 2 consisted of a systematic review aimed at identifying TMS-EEG and resting-state EEG biomarkers of response to three TMS modalities, across several psychiatric and neurocognitive disorders. For this thesis, only the thirteen clinical trials that examined PB and MB's in MDD were assessed. Lastly, Chapter 3 attempted to identify resting-state EEG biomarkers of response to deep TMS (dTMS) in older adults with treatment-resistant depression (TRD). Twenty-one older adults underwent 20 sessions of either Hesed-coil 4 or 7 of dTMS. EEG recordings and the 24-Item Hamilton Depression Rating Scale (HDRS-24) were conducted at the baseline and posttreatment visits.

Results: Chapter 2 identified one PB indicating that greater baseline N100 amplitude was predictive of response to TMS. Two MBs were also identified, in which a reduction in either N100 amplitude or resting theta connectivity post-TMS were related to a reduction in depressive symptoms. Although none of the effects remained significant after correction, Chapter 3 identified several preliminary biomarkers. Two PBs were identified, revealing that higher baseline relative gamma power predicted a poorer response to dTMS. Furthermore, two MBs indicated that an increase in relative alpha power post-dTMS were associated with a smaller improvement on the HDRS-24. In contrast, four MBs showed that an increase in relative theta power, across three cortical regions and one electrode (F7), were related to a greater improvement on the HDRS-24.

Conclusion: Promising work has been made in identifying potential predictive and mechanistic biomarkers for TMS in MDD, via the utilization of EEG. However, biomarker-informed clinical trials are needed in order to validate these proposed markers, especially in older adults.

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List of Abbreviations

CDC: Centre for Disease Control

DLPFC: Dorsolateral Prefrontal Cortex

DMN: Default Mode Network

DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision

dTMS: Deep Transcranial Magnetic Stimulation

H1: Hesed-coil 1

H4: Hesed-coil 4

H7: Hesed-coil 7

H-coil: Hesed-coil

iTBS: Intermittent Theta Burst Stimulation

ITI: Intertrain Interval

FDA: Food and Drug Administration

MDD: Major Depressive Disorder

MRI: Magnetic Resonance Imaging

PBCAR: Peter Boris Centre for Addictions Research

rTMS: Repetitive Transcranial Magnetic Stimulation

RvACC: Rostral-ventral cingulate cortex

TMS: Transcranial Magnetic Stimulation

TRD: Treatment-Resistant Depression

WHO: World Health Organization

List of Symbols

~	Approximately
%	Percent

Declaration of Academic Achievement

For the two manuscripts apart of the present thesis, I contributed to the conceptualization of the manuscript, methods, the collection of the data, the tables and figures, the writing of the original draft, as well as the review and edits of the final draft. Taking the lead role as first author on both manuscripts. My fellow co-authors also assisted in the collection of data, methods, tables and figures, and the review and edits of the final drafts. Specifically, my supervisor, Dr. Duarte, also assisted in the conceptualization of both manuscripts and their methods, as well as provided reviews and edits to the final drafts.

Chapter 1.

Introduction

1.1. Major Depressive Disorder: Younger-to-Older Adulthood

According to the World Health Organization (WHO), approximately 4% of the global population experiences depression (WHO, 2024).

When examining the prevalence of depressive episodes (a minimum two-weeks in length) experienced by Americans by age group, the Center for Disease Control (CDC) found that 7.7% of those aged between 20 – 39 years old have experienced a depressive episode, 8.4% between the ages of 40 – 59 years and 8.0% for those aged over 60 years (Brody, 2018).

Major depressive disorder (MDD) is a diagnosis of clinical depression, characterized by symptoms of a persistent low mood and/or loss of interest or pleasure, among other symptoms (e.g., feelings of worthlessness, psychomotor agitation), lasting at least two-weeks in length (*Diagnostic and Statistical Manual of Mental Disorders | Psychiatry Online*, 2022). Generally, MDD can lead to serious mental and physical health consequences or risks, including comorbid mental health and substance use disorders, suicide, cardiovascular disease and/or events, dementia, obesity, and autoimmune diseases (Arnaud et al., 2022; Bains & Abdijadid, 2025). Currently, there are no biological measures used in the diagnostic assessment of MDD.

Younger adults have the greatest cumulative risk of developing MDD when compared to other age groups (Kessler et al., 2003; Rohde et al., 2013), with many experiencing their first incidence of depression during this particular stage of life (Kessler et al., 2005; Rohde et al., 2013; Solmi et al., 2022). Younger adults with MDD are also at an increased risk of developing comorbid anxiety and alcohol use disorder, as well as attaining a lower education and employment prospects (Brière et al., 2014; Fergusson et al., 2007; Klein et al., 2013). Women and individuals assigned female at birth are more likely to develop MDD (Baxter et al., 2014; Kessler et al., 2003, 2005; Lopez Molina et al., 2014), with factors such as menses, postpartum, perimenopause, menopause and post-menopause exacerbating depressive symptoms and/or outcomes, affecting younger and/or middle-aged women and females

(Altemus et al., 2014; Bromberger et al., 2015; Haley et al., 2013; Vigod et al., 2025). Middle-aged females with MDD are at a higher risk of experiencing menopause earlier (An et al., 2025), which may increase their risk of developing uterine, cervical and ovarian cancer (Abulajiang et al., 2025). Regardless of sex or gender, Stegenga et al. (2012) discovered that those who experienced their first episode of depression during middle age (41 to 57 years old) were more likely to have had legal issues (e.g., court appearance), have had a significant event affecting their friends or family (e.g., death) or faced personal challenges (e.g., serious illness) (Stegenga et al., 2012).

Depression in older adulthood is associated with an increased risk of disability, suicide, mortality, and morbidity (Benton et al., 2007; Patel et al., 2023; Rodda et al., 2011). As individuals age, the prognosis of MDD tends to worsen, leading to more chronic and severe depressive symptoms, along with an extended period to achieve remission (Schaakxs et al., 2018). Older adults with MDD are also more likely to experience chronic loneliness (Martín-María et al., 2021) and as such, utilize healthcare services more frequently (Gerst-Emerson & Jayawardhana, 2015).

1.2. The Neurophysiological Basis of Major Depression

Evidence suggests that several brain regions, primarily within the prefrontal cortex (PFC), are involved in the pathophysiology of MDD. These regions include the broader PFC, the dorsolateral PFC (DLPFC), the medial PFC (MPFC), the anterior cingulate cortex (ACC) and the insula. Therefore, it is critical to understand these regions and their potential role in depression.

The PFC plays a central role in cognitive control/executive function (Menon & D'Esposito, 2022). Impairments in working memory, a key component of executive function, appear to be associated with MDD (Christopher & MacDonald, 2005; Rose & Ebmeier, 2006), with antidepressants showing limited efficacy in alleviating working memory deficits (Prado et al., 2018). It is believed that the link between MDD and working memory deficits may be related to the emotional salience of the information being processed, otherwise known as "affective" working memory (Songco et al., 2023). Songco et al. (2023) found that both actively depressed and remitted participants (M_{age} = 38.99) showed greater impairment in the presence of negative images compared to neutral images. Furthermore, a meta-analysis of functional magnetic resonance imaging (MRI), by Wang et al. (2015), found that individuals with MDD exhibited

hyperactivation of the left lateral PFC during working memory tasks compared to healthy controls (Wang et al., 2015). In a small study conducted by Dumas and Newhouse (2015), older adults with MDD were also found to have working memory deficits with hypoactivation of the lateral frontal cortex within the toughest section of the n-back (Dumas & Newhouse, 2015). At the network level, the frontoparietal network – a network engaged by the PFC, particularly the DLPFC – has been implicated in geriatric depression as well as working memory in younger adults with MDD (Cao et al., 2021; Menon & D'Esposito, 2021; Zhukovsky et al., 2021).

The DLPFC is crucial for cognitive control and emotion regulation, and abnormalities in this region have been consistently observed in individuals with MDD (Clark & Beck, 2010; Erk et al., 2010; Ochsner & Gross, 2005). Early functional imaging studies identified that reductions in DLPFC activity were indicative of major depression (Biver et al., 1994; Galynker et al., 1998). More recent functional imaging studies, focusing on negative processing bias, found that individuals with MDD exhibited hypoactivation of the DLPFC, when exposed to negative stimuli or related tasks (Fales et al., 2008; Pizzagalli & Roberts, 2022; Zhong et al., 2011). Additionally, an exploratory analysis, utilizing diffusion tensor imaging showed that reduced white matter integrity. between the left DLPFC and the pre-supplementary motor area, may contribute to psychomotor retardation often seen in MDD (Bracht et al., 2012). Furthermore, alterations in the DLPFC have also been observed in older adults with MDD, including reduced gray matter volume (Chang et al., 2011) and decreased functional connectivity (Lin et al., 2023). As noted above, at the network level, the frontoparietal network – which the DLPFC is engaged – has been implicated in geriatric depression as well (Menon & D'Esposito, 2021; Zhukovsky et al., 2021).

The MPFC has been implicated in social cognition and rumination (Cooney et al., 2010; Van Overwalle, 2008) (Van Overwalle, 2009; Cooney et al., 2010; Bzdok et al., 2013). The default mode network (DMN) is similarly believed to potentially play a role in social cognition and rumination, with the MPFC serving as key component of this network (Menon & D'Esposito, 2022; Raichle & Snyder, 2007; Schilbach et al., 2008; Zhou et al., 2020). Social cognitive impairments have been observed in MDD, such as difficulties within tasks related to the theory of mind, which appear to remain even when one is in remission and worsen alongside depression severity (Weightman et al., 2014).While the existing literature has yet to investigate the relationship between the MPFC, MDD and social cognition, a preliminary study

examining social dysfunction (e.g., loneliness) in MDD found reduced functional connectivity between the rostromedial prefrontal cortex and the posterior superior frontal gyrus of the DMN (Saris et al., 2020). Deficits in social cognition have also been observed in community-dwelling older adults exhibiting depressive symptoms, as well as in older adults with MDD who have a history of previous suicide attempts (Ding et al., 2025; Szanto et al., 2012). Regarding rumination, research has implicated this behaviour in depression as well (Nolen-Hoeksema & Aldao, 2011). Specifically, rumination has been associated with an increase in both MPFC and, specifically, dorsal MFPC activity in majorly depressed individuals (Cooney et al., 2010; Zhou et al., 2020).

The ACC is fundamental to emotion regulation (Stevens et al., 2011). In individuals with MDD, increased connectivity has been observed between the subgenual ACC and the medial temporal lobe, with stronger associations to the right amygdala and hippocampus correlating with greater depression severity (De Kwaasteniet et al., 2013). Disruptions in emotion regulation strategies, such as avoidance, have been observed in majorly depressed individuals, including those in remission (Visted et al., 2018). Additionally, hyperactivation of the right dorsal ACC has been observed in individuals with MDD when attempting to self-regulate their emotions (Beauregard et al., 2006). Aside from emotion regulation, older adults with MDD have exhibited reductions in functional connectivity within the ACC, which has been associated with apathy (Alexopoulos et al., 2013). In relation to neural networks, the salience network – which the ACC is engaged – has also been implicated in MDD (Lynch et al., 2024; Menon & D'Esposito, 2021).

The insula has been implicated in socio-emotional processing, including empathy (Uddin et al., 2017). Specifically, the left anterior insula appears to be involved in both affective–perceptual empathy (e.g., observation) and cognitive–evaluative empathy (e.g., imagination), whereas the right anterior insula is only involved in affective–perceptual empathy (Fan et al., 2011). Hypoactivation of the anterior insula has also been observed in healthy participants, during a social pain task designed to measure empathy (Laneri et al., 2017). Individuals with MDD and subclinical depression have been found to exhibit deficits in cognitive empathy and empathetic stress, a form of affective empathy (Schreiter et al., 2013). When examining bipolar depression and MDD, effective connectivity was observed between the anterior insula

and the amygdala, along with a weaker connection between the anterior insula and DLPFC (Kandilarova et al., 2018). In comparison to healthy controls, once again, there was a reduction in functional connectivity in both the left and right anterior insula and the orbital inferior frontal gyrus. Similar to the ACC, functional abnormalities have been reported within the insula of older adults with MDD, with increased insular connectivity being associated with apathy in this population (Alexopoulos et al., 2008, 2013). Once again, in relation to neural networks, the salience network – which the insula is engaged – may play a role in MDD as well (Lynch et al., 2024; Menon & D'Esposito, 2021).

1.3. Treatment-Resistant Depression

Presently, there is no universal definition for treatment-resistant depression (TRD). However, it appears that the most utilized description of TRD in MDD is as follows: the failure to respond to at least two antidepressant trials that were administered at a sufficient duration and dose (Gaynes et al., 2020; Lam et al., 2024). Although this description is widely used, it has notable limitations, as it primarily focuses on antidepressant response and overlooks other treatment modalities such as psychotherapy (Lam et al., 2024). Additionally, it does not account for partial responders, and there is little consistency across studies in how "failure" is defined (Lam et al., 2024). It is also important to recognize that true treatment resistance can be challenging to assess, as it is often difficult to confirm whether a patient received an adequate dose and duration of an antidepressant treatment; this is known as "pseudo-resistance" (Voineskos et al., 2020).

Nevertheless, TRD is not an uncommon challenge among patients with MDD aged 18 – 75 years old, with ~35% – 50% unable to respond to their first and second antidepressant trial (Rush et al., 2006; Trivedi et al., 2006). This issue is particularly pronounced in geriatric depression (aged 60 and above), where about 67% of this population do not respond to their initial antidepressant treatment (Roose & Schatzberg, 2005).

There are a multitude of ways in which TRD can be treated. The most common or "first-line" approaches are to continue medication use by either changing the current dose, augmenting the current treatment or switching the class of antidepressant being utilized (Lam et al., 2024; Voineskos et al., 2020). The "second line" approach involves neural stimulation methods like transcranial magnetic

stimulation (TMS), a central focus of the present thesis (Lam et al., 2024; Voineskos et al., 2020). Unlike other health conditions, there are currently no validated biomarkers that can aid psychiatrists in treatment-decision making for their patients with TRD, which can hamper a timely and effective recovery.

1.4. The Neurophysiological Basis of Treatment-Resistant Depression

In a similar manner to MDD, brain regions such as the broader PFC, DLPFC, MPFC, as well as the ACC and insula have also been implicated in the pathophysiology of TRD, along with the networks each region is engaged in. With respect to the broader PFC, the prefrontal regions of individuals with TRD were found to have extensive reductions in functional connectivity within the PFC (Lui et al., 2011). In relation to the DLPFC and TRD, abnormalities in functional connectivity have also been observed, such as increased connectivity between the left DLPFC and left middle occipital gyrus and decreased connectivity between the right DLPFC and the left middle occipital gyrus as well (Sun et al., 2023).

Furthermore, in a study examining predictive biological measures of rTMS response in TRD found that increased baseline functional connectivity between the rostral ACC and the left parietal cortex, along with a decrease between the subgenual ACC and the right DLPFC, were indicative of a response to rTMS (Ge et al., 2020). Moreover, participants with TRD have also displayed reduced functional connectivity between the left and right anterior insula and the orbital inferior frontal gyrus, relative to participants without TRD (Sun et al., 2023). When looking at older adults with TRD more specifically, reductions in fractional anisotropy were observed, via diffusion tensor imaging, within the DLPFC, dorsal and rostral ACC and white matter within the insula (Alexopoulos et al., 2008).

Interestingly, abnormalities in the connectivity between the frontoparietal network – engaging the DLPFC and, thus, the PFC – and the salience network – engaging both the ACC and insula – have also been linked to TRD (Lees et al., 2025; Machaj et al., 2024; Menon & D'Esposito, 2021).

Lastly, the MPFC has been implicated in a hypothesized hippocampal-originated neural circuit thought to play a role in TRD, potentially regulating stress response (Levinstein & Samuels, 2014) With the default mode network possibly linked to TRD as well (de Kwaasteniet et al., 2015; Li et al., 2013).

1.5. Transcranial Magnetic Stimulation for Depression

As stated above, TMS is a "second line" treatment for TRD (Voineskos et al., 2020). With the use of an electromagnetic coil, TMS delivers a low-intensity, non-invasive electrical current generated by magnetic fields into underlying neurological structures (Roth et al., 2014). Two distinct types of TMS are currently in use: (1) repetitive TMS (rTMS; also known as "traditional TMS") and (2) deep TMS (dTMS). With one commonly used modality called intermittent theta burst stimulation (iTBS). The regions outlined above, implicated in both MDD and TRD, can be targeted by the various TMS types/modalities, which will be explained further.

rTMS became the first TMS treatment to be Food and Drug Administration (FDA) approved for the treatment of TRD in 2008, which was eventually approved by Health Canada as well. Utilizing electromagnetic coils in either a figure-8 (more common) or circular design, rTMS produces repeated pulses of a focal stimulation capable of reaching cortical structures 1 to 4cm below the scalp, with a target preference of the DLPFC (Lam et al., 2024; Milev et al., 2016). However, at 4cm in depth, the commonly used figure-8 coil only sustains an electric field amplitude between of 30 to 40%, with the circular coil between 30 to 52% (Roth & Zangen, 2014). Although, the main target of rTMS is the DLPFC, which is quite superficial at 2 – 3 cm below the scalp (Deng et al., 2014), rTMS is only capable of producing an electric field amplitude between 50 to 80% (Roth & Zangen, 2014).

rTMS treatment for TRD is typically administered daily (5 days per week) over the course of four to six weeks (Lam et al., 2024). Each session is approximately 37 minutes and targets the left DLPFC with 10 Hz stimulation (Bakker et al., 2015; Lam et al., 2024; O'Reardon et al., 2007). The protocol involves 4-second trains, with 3000 pulses per session and a 26-second intertrain-interval (ITI; Bakker et al., 2015; George et al., 2010; O'Reardon et al., 2007; Table 1). It is important to note that rTMS protocols for TRD can vary widely, with sessions ranging from 20 to 40 minutes, stimulation frequencies from 1 to 20 Hz, train lengths between 2 to 10 seconds, and ITI spanning 10 to 60 seconds (Lam et al., 2024; Milev et al., 2016). Research has shown that rTMS is an effective treatment for younger to older-aged adults with MDD (Lam et al., 2024; Valiengo et al., 2022).

Table 1. Types/Modalities of Transcranial Magnetic Stimulation & Standard Major Depression Protocols

Types/Modalities	Coil	Treatment Length	Trains	Pulses Per Session	Inter-Train Interval	Hz	Stimulation Depth	Primary Target	Pros & Cons
rTMS[a]	Figure-8 (more common) or circular	~ 37 mins	4s	3000	26s	10Hz	1 to 4 cm	DLPFC (left sided preference)	**Pro:** focal stimulation **Con:** treatment length
dTMS	H-coil	20 mins	2s	1980	20s	18Hz	2 to 6 cm	**H1:** DLPFC (left sided preference) **H7:** ACC & MPFC **Experimental:** **H4:** PFC & Insula	**Pro:** broader stimulation **Con:** not as widely available
iTBS[bc]	Figure-8, circular or H-coil	~3 mins	2s	600	8s	50Hz	NA	DLPFC (left sided preference)	**Pro:** treatment length **Con:** not enough evidence to back accelerated protocols

Abbreviations: ACC = anterior cingulate cortex; cm = centimetres; DLPFC = dorsolateral prefrontal cortex; dTMS = deep transcranial magnetic stimulation; H-coil = Hesed-coil; Hz = Hertz; mins = minutes; MPFC = medial prefrontal cortex; PFC = prefrontal cortex; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; s = seconds

[a] Protocols for rTMS can vary significantly.

[b] Accelerated protocols slightly differ.

[c] Modality of TMS.

A relatively recent form of TMS is dTMS. Unlike rTMS, dTMS delivers a broader stimulation capable of engaging multiple cortical regions at once, using Hesed-coils (i.e., H-coils) (Deng et al., 2014; Parazzini et al., 2017). These H-coils have also been shown to potentially reach deeper cortical structures, between 2 to 6 cm beneath the scalp (Roth et al., 2007). On average the H-coil achieves an effective stimulation depth of around 3 cm, practically the same depth as rTMS (Deng et al., 2014). However, at this depth, H-coils maintain a stronger electric field amplitude (70–80%) compared to both the figure-8 coil (50%) and the circular coils (50–70%), lending credence to dTMS's name (Roth & Zangen, 2014). dTMS received FDA approval for the treatment of TRD in 2013 and for anxious depression in 2022 (Duarte et al., 2025; Tendler et al., 2017). Research has also demonstrated dTMS's efficacy for treating geriatric TRD (Duarte et al., 2025; Kaster et al., 2018; Roth et al., 2024). With the standard dTMS protocol for MDD involving 20-minute sessions, typically administered daily (5 days per

week) over 4 weeks (Di Passa et al., 2024; Levkovitz et al., 2015). Stimulation is set at 18Hz, with 2-second trains, 1980 pulses and 20-second ITI (Levkovitz et al., 2015).

The H-coil 1 (H1), as mentioned previously, received FDA approval for TRD and has demonstrated efficacy in geriatric TRD (Kaster et al., 2018; Roth et al., 2024; Tendler et al., 2017). Similar to rTMS protocols for MDD, the H1 coil targets the left DLPFC (Levkovitz et al., 2015). Following the H1 coil's approval, the H7 coil was cleared for obsessive-compulsive disorder in 2018 and subsequently anxious depression in 2022 (Duarte et al., 2025; Harmelech et al., 2021). Unlike the H1 coil, the H7 coil primarily stimulates the ACC and the MPFC (Harmelech et al., 2021). Furthermore, the H4 coil received FDA clearance for smoking cessation in 2020 (Duarte et al., 2025). The H4 coil was designed to stimulate both the insula and lateral PFC (Zangen et al., 2021). Moreover, a recent open-label pilot trial by our team at the Peter Boris Centre for Addictions Research (PBCAR), at St. Joeseph's Healthcare Hamilton, found that both the H4 and H7 coils were effective in treating geriatric TRD (Duarte et al., 2025).

Finally, we will now discuss iTBS. A modality utilized within the realm of TMS that consists of a unique stimulation parameter that "mimics endogenous theta rhythms, which can improve induction of synaptic long-term potentiation" (Blumberger et al., 2018). iTBS protocols primarily utilize a figure-8 or circular coil to deliver stimulation (Blumberger et al., 2018; Cole et al., 2020; Milev et al., 2016). However, iTBS can also be administered utilizing H-coils (Tendler et al., 2023). The typical iTBS protocol for TRD is also administered daily (5 days per week) over the course of four to six weeks (Bakker et al., 2015; Blumberger et al., 2018; Lam et al., 2024). Each session is ~ 3 minutes in duration and largely targets the left DLPFC using 50Hz stimulation (Bakker et al., 2015; Milev et al., 2016). The protocol involves 2 second trains, 600 pulses per session, and 8-second ITIs (Bakker et al., 2015; Blumberger et al., 2018; Milev et al., 2016). Promising work has been made in relation to accelerated iTBS, such as the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol in which 10 sessions of iTBS are administered over 5 days, with 1800 pulses per session rather than 600 pulses (Cole et al., 2020; Lam et al., 2024). Other accelerated iTBS protocols are less intense, involving 3 treatments per day over 15 days, with each treatment delivering 1200 pulses (Ramos et al., 2025). The modality of iTBS has also shown efficacy in the treatment of TRD as well, potentially being even more effective than rTMS and

dTMS alone, depending on the protocol (Blumberger et al., 2018; Cole et al., 2020). Although further evidence is needed to back the clinical relevancy of accelerated protocols (Lam et al., 2024). However, as of now, it does appear that the future of TMS treatment is moving towards the utilization of accelerated iTBS, administered via a figure-8 coil.

Although, a significant challenge remains, as not all patients undergoing TMS respond to treatment, irrespective of the protocol, type or modality used (Blumberger et al., 2018; Cole et al., 2020; Duarte et al., 2025; Lam et al., 2024). Therefore, it is increasingly critical to identify treatment biomarkers, such as predictive and mechanistic markers, that not only guide clinicians in making informed decisions about the use of TMS but to also improve our understanding of how TMS acts on the cortex to improve depression symptoms.

1.6. Treatment Biomarkers

According to the FDA and the National Institute of Health (NIH), a biomarker can be defined as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" (FDA-NIH Biomarker Working Group, 2016). Biomarkers have become incredibly relevant within the field of psychiatry, in an attempt to more accurately diagnose and treat mental disorders.

Treatment biomarkers aim to link biological measures of a specific disorder, such as a psychiatric disorder, with treatment outcomes of a particular therapy, to enhance treatment efficacy and patient care. This thesis will focus on two relevant treatment biomarkers: (1) predictive and (2) mechanistic. Predictive biomarkers isolate characteristics defined prior to treatment that can be used to predict treatment response (Cagney et al., 2018). In contrast, mechanistic biomarkers identify aspects of a disorder that change over the course of treatment, which may be influenced by the treatment itself (Robinson et al., 2013; Rush & Ibrahim, 2018).

There are several methods to isolate treatment biomarkers, with neuroimaging techniques (e.g., electroencephalography [EEG]) and phlebotomy (e.g., inflammatory cytokines) being among the most prevalent in psychiatry. A recent review by Klooster et al. (2024) emphasized the significance of

employing neuroimaging techniques to identify neurostimulation treatment biomarkers in depression, particularly highlighting the role of EEG in isolating TMS biomarkers (Klooster et al., 2024). Therefore, EEG may serve as an important tool for identifying predictive and mechanistic biomarkers of treatment response to TMS for MDD.

While EEG has displayed significant promise in potentially isolating biomarkers within TMS, it remains important to understand the nature of neural activity captured by EEG, specifically neural oscillations, and their broader relationship to depression.

1.7. Electroencephalography and Depression

EEG is a relatively cost-effective and non-invasive tool, compared to MRI and phlebotomy, which is currently being used for biomarker discovery in psychiatry. Utilizing electrodes that are placed on the scalp, EEG can record underlying neural activity with high temporal sensitivity (Freeman et al., 2003; Newson & Thiagarajan, 2018). EEG specifically measures macroscopic neural oscillations; synchronized neural activity formed by interacting neurons (Jee, 2021). One method to investigate EEG data is to subdivide the neural oscillations into five distinct frequency bands, each linked to different levels of alertness and cognitive functions. These frequency bands include delta (~0 to 4Hz), theta (~4 to 8Hz), alpha (~8 to 13Hz), beta (~13 to 30Hz), and gamma (~30 to 150Hz; Jee, 2021; Tremblay et al., 2019). Researchers can further examine these frequency bands by using analyses that incorporate power or connectivity.

The present thesis will concentrate specifically on the neural oscillations of theta, alpha, and gamma. Additionally, given the limited literature on TRD, this section will primarily explore the relationship between MDD and the specified frequency bands.

The theta frequency band (~4 to 8Hz) is a neural oscillation suspected to play a role in prefrontal cognition, memory (e.g., working memory; Klimesch, 2018), and sleep (Tremblay et al., 2019) and is believed to be produced within the medial septum (Colgin, 2013). As we age, theta connectivity appears to decline across the cortex (Moezzi et al., 2019). However, a reduction in frontal theta power appears to be associated with better cognitive functioning in older adults, specifically within executive function, verbal

recall and attention (Finnigan & Robertson, 2011). As previously mentioned, working memory deficits appear to be a part of MDD, with theta waves in the frontal cortex also implicated in working memory processes (Riddle et al., 2020). Moreover, working memory deficits in older adults appear to be related to both theta and alpha power between the parietal cortex and parahippocampus (Steiger et al., 2019).

Theta power and connectivity have been identified as potentially influential diagnostic biomarkers for MDD, within the PFC, ACC and parietal cortex. Specifically, individuals with MDD have been shown to have reductions in parietal theta power associated with memory retrieval and impairments in working memory (Kane et al., 2019; Tang et al., 2025). Depressed participants were also found to have reduced connectivity between the DLPFC and rostral-ventral cingulate cortex (rvACC), including reduced theta power in the dorsomedial PFC, rvACC and left DLPFC, during an emotion regulation task (Steinmann et al., 2024). However, one study noted that as anterior theta connectivity increased during a working memory task, so did the severity of symptoms in depressed individuals (Fingelkurts et al., 2006).

In relation to treatment biomarkers in MDD and theta power and connectivity, promising work has been conducted. Increased parietal theta power was mechanistically associated with a reduction in depressive symptoms, after 8 weeks of escitalopram in responders (Schwartzmann et al., 2024). Additionally, there appears to be a subset of depressed individuals with increased frontomidline theta connectivity, who may be more responsive to rTMS. During a working memory task, rTMS responders exhibited an increase in frontomidline theta connectivity both before treatment and during the first week of treatment (N. W. Bailey et al., 2018). Furthermore, an increase in frontomidline theta after completing a rostral anterior cingulate cortex engaging cognitive task (engages working memory and attention) was predictive of a response to rTMS (Li et al., 2016, 2021). Moreover, in another study by Bailey et al. (2019), increased theta connectivity was found across several cortical regions within responders, after one week of rTMS as well (N. Bailey et al., 2019).

Table 2. Neural Oscillations & Major Depression

Neural Oscillation	Frequency Range	Behavioural Function	Features in Depression
Theta	~4 to 8Hz	Memory & prefrontal cognition (e.g., working memory).	**Diagnostic:** Reduced parietal power. **Predictive:** A subset of depressed individuals who have increased

			frontomidline connectivity may respond better to rTMS.
Alpha	~8 to 13Hz	Cognitive inhibition (e.g., memory & attention).	**Diagnostic[b]:** Increased frontal/central connectivity.
Gamma[a]	~30 to 150Hz	Higher-order cognitive functions (e.g., perception)	**Diagnostic:** Increased frontal/central power.

Note Only power and connectivity EEG measures have been accounted for in this table.

Abbreviations: Hz = hertz; rTMS = repetitive transcranial magnetic stimulation

[a] Research is heterogeneous.

[b] One study was recorded at rest and the other during a task

The alpha frequency band (~8 to 13Hz) is a neural oscillation believed to play a role in cognitive inhibition, specifically within memory and attention (Table 2; Klimesch, 2012, 2018; Tremblay et al., 2019), and is typically found in the occipital cortex and when one is either relaxed or has their eyes closed (Klimesch, 2012; Sugimoto et al., 2024; Tremblay et al., 2019). Intriguingly, task-state increases in alpha oscillations are linked to cortical inhibition (Klimesch, 2018). As the brain ages, we begin to see a reduction in alpha power and connectivity across the cortex, with even more pronounced reductions in alpha power, during the 0-Back task, potentially related to pathological aging (Arakaki et al., 2019; Moezzi et al., 2019).

Diagnostic biomarkers have been isolated in MDD with respect to increased alpha power and connectivity. Fingelkurts et al. (2007) found that as alpha connectivity increased across frontal, central and posterior regions of the brain, during a working memory task, depressed individuals' symptoms worsened (Fingelkurts et al., 2006). Additionally, abnormalities in resting-state alpha power and connectivity have also been noted in the PFC of those with MDD. When looking at resting-state alpha power in males with MDD, they were observed to have an increase in upper-alpha (10.5 to 13Hz) power within the frontal and parietal lobes (Jaworska et al., 2012). Depressed males were also found to have reductions in upper-alpha power, within the left midfrontal regions. When looking at resting-state connectivity, Olbirch et al. (2014) identified an increase in alpha connectivity between the left DLPFC, as well as the left MPFC, and the subgenual in individuals with MDD (Olbrich et al., 2014). Additionally, reductions in alpha power or connectivity have been implicated as a possible mechanistic biomarker more generally across treatments for MDD (Hill et al., 2020; Schwartzmann et al., 2023a, 2024).

The gamma frequency band (~30 to 150Hz) is a neural oscillation primarily found within the frontal cortex and is believed to play a role in higher-order cognitive functions, such as perception (Table 2; Jee, 2021; Tremblay et al., 2019). Perception deficits have been observed in MDD, such as within interoception, emotion perception and perceptual filling-in (Bourke et al., 2010; Eggart et al., 2019; Zomet et al., 2008). Much like theta and alpha, gamma connectivity also appears to reduce with age, primarily in the frontal, central and posterior regions (Moezzi et al., 2019). As individuals age, gamma activity seems to shift during cognitive tasks (e.g., global cognition), with gamma power decreasing in the frontal-central regions of the brain and increasing in the parietal-occipital regions (Bakhtiari et al., 2023).

Diagnostic markers have been examined in the gamma frequency band, with some promise. Increased frontocentral gamma power has been observed in depressed participants at rest and during a lexical task across several regions (Strelets et al., 2007; Yamamoto et al., 2018). However, when specifically looking at inattention in MDD, gamma power decreased within frontocentral regions of the brain, along with an increase in inattention (Roh et al., 2016). In relation to connectivity, increases within frontocentral and frontolimibic gamma connectivity have been observed in depression (Jiang et al., 2019). With respect to predictive biomarkers, increased low-gamma (30 – 40 Hz) power, within the medial regions of the brain, may be indicative of a decreased likelihood of response to the H1 coil of dTMS (Zangen et al., 2023). However, Noda et al. (2017) identified a potential mechanistic biomarker to which increased F3 absolute gamma power was associated with an improvement in depression symptoms for left DLPFC rTMS (Noda et al., 2017).

Another form of EEG, which will be briefly touched on, and has shown great promise in biomarker discovery, is TMS-EEG (Farzan, 2024). By combining a single pulse of TMS with EEG, TMS-evoked potentials (TEP), peaks in neural activity occurring within milliseconds (ms) after the single pulse, can be detected, such as N100 (negative deflection at 100 ms) and P200 (positive deflection at 200 ms; Farzan, 2024). For the present thesis, only the TEP N100 will be examined.

The gamma-aminobutyric acid B ($GABA_B$) receptor is believed to be associated with the TEP N100 and, as a result, N100 may play a role in cortical inhibition (Farzan et al., 2013; Premoli et al., 2014; Rogasch et al., 2015). $GABA_B$ is believed to be implicated in MDD (Schür et al., 2016) and potentially

plays a role in behaviours such as anxiety (Luscher et al., 2011) and learned helplessness (Slattery & Cryan, 2006), as evident by studies in animal models.

With regards to diagnostic biomarkers, increased N100, in the left DLPFC, has been observed in majorly depressed individuals with suicidal ideation (Chen et al., 2025). N100 has also been identified as a possible predictive biomarker for neurostimulation therapies and a mechanistic biomarker for TMS in the context of TRD (Farzan, 2024).

Although EEG appears to hold great promise, there are limitations. EEG is not structurally specific and can only detect superficial neural activity. Structural specificity also reduces as fewer channels are utilized, which can make it increasingly difficult to determine the exact brain regions being recorded. Furthermore, regions deep within the cortex also play a role in the pathophysiology of MDD, regions such as the amygdala (Hamilton et a., 2008), which typically cannot be adequately measured via EEG, unlike MRI.

However, given the behavioural functions associated with the frequency bands and N100, and the previous research establishing their relationship to MDD, it can be argued that EEG makes an excellent tool for biomarker discovery in depression. Secondly, a growing body of evidence suggests that EEG shows great promise as a tool to assess treatment response to TMS in MDD. Therefore, the present thesis will utilize EEG to assess biomarkers of treatment response to TMS for MDD, mainly focusing on resting-state EEG biomarkers.

1.8. Isolating Potential Treatment Biomarkers for Depression

To advance the field of precision psychiatry and improve treatment outcomes of individual's struggling with depression, treatment biomarkers identified via EEG hold great promise. As such, the present thesis will look to identify both predictive and mechanistic biomarkers of treatment response to rTMS, dTMS and iTBS, in younger to older aged adults with depression.

Chapter 2 of the present thesis consists of a systematic review, recently published in the Journal of Affective Disorders, identifying resting-state and TMS-EEG predictive and mechanistic biomarkers of treatment response to TMS. This review examined several conditions, including psychiatric and

neurocognitive disorders, isolating three potential biomarkers of rTMS and/or iTBS response for further validation in depression: one predictive biomarker and two mechanistic biomarkers.

Chapters 3 of the present thesis consists of a preliminary study examining predictive and mechanistic biomarkers of treatment response to dTMS in geriatric depression. Utilizing resting-state EEG data, taken from baseline and posttreatment recordings, the study preliminarily identified several biomarkers within the theta, alpha and gamma frequency bands, analyzed using relative spectral power. Markers were observed at both the region level and the electrode level.

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Chapter 2.

Predictive and mechanistic biomarkers of treatment response to Transcranial Magnetic Stimulation (TMS) in Psychiatric and Neurocognitive Disorders, identified via TMS-Electroencephalography (EEG) and Resting-State EEG: A systematic review

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Context: This chapter will attempt to identify TMS-EEG and resting-state EEG biomarkers of treatment response to TMS for Major Depressive Disorders (MDD) via a systematic review. A potential "biomarker" will be defined as a consistent finding within at least two studies. As a result, three potential biomarkers were identified for further validation.

Implications: Predictive biomarkers play a crucial role in helping guide treatment decision-making for clinicians, especially when treatment-resistance is all-too-common among those struggling with MDD. Whereas mechanistic biomarkers play a critical role in identifying how TMS, among other treatments, can act on the cortex to improve the pathophysiology of MDD. Thus, advancing precision medicine in psychiatry.

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ABSTRACT

Electroencephalography (EEG) is a comparatively inexpensive and non-invasive recording technique of neural activity, making it a valuable tool for biomarker discovery in transcranial magnetic stimulation (TMS). This systematic review aimed to examine mechanistic and predictive biomarkers, identified through TMS-EEG or resting-state EEG, of treatment response to TMS in psychiatric and neurocognitive disorders. Nineteen articles were obtained via Embase, APA PsycInfo, MEDLINE, and manual search; conditions included, unipolar depression (*k* = 13), Alzheimer's disease (*k* = 3), bipolar depression (*k* = 2), and schizophrenia (*k* = 2). Two mechanistic biomarkers were identified: one TMS-EEG marker, reductions in N100 post-dorsolateral prefrontal cortex (DLPFC) repetitive TMS or intermittent theta burst stimulation (iTBS) in unipolar depression (*n* = 120; *k* = 2), and one resting-state marker, reductions in theta connectivity post-DLPFC repetitive TMS in unipolar and bipolar depression (*n* = 89; *k* = 2). Whereas one predictive TMS-EEG biomarker was isolated: greater baseline N100 was predictive of unipolar depression improvement in DLPFC repetitive TMS and iTBS (*n* = 113; *k* = 2). Promising markers were briefly discussed for future research in Alzheimer's disease and schizophrenia. In conclusion, across the psychiatric and neurocognitive disorders considered in this study, TMS-EEG and resting-state mechanistic and predictive biomarkers of depression appear to hold the most promise. Further research is needed to validate the biomarkers identified in depression, to help guide treatment plans and advance precision medicine in psychiatry.

KEYWORDS: EEG, TMS, Predictive biomarker, Mechanistic biomarker, Depression, TMS-EEG and Resting-state EEG

INTRODUCTION

As of now, the use of transcranial magnetic stimulation (TMS) – a non-invasive neuromodulation technique that utilizes electromagnetic stimulation to evoke neuronal activity – in psychiatry relies on a patient's treatment resistance to pharmacotherapy to qualify, though not all patients will respond to TMS (Siebner et al., 2022; Ziemann, 2017). Additionally, little is known about how TMS can change the underlying neurophysiology of psychiatric and neurocognitive disorders to improve symptoms. This is further complicated as multiple studies allow for adjunctive therapies alongside TMS, potentially confounding TMS's impact. For example, delta and alpha power early within cognitive behavioural therapy (CBT) for unipolar depression was found to be predictive of treatment response (Schwartzmann et al., 2023b) (Schwartzmann et al., 2023). Biomarkers defined without adjunct therapies could potentially fill these gaps, expanding our understanding of the neurophysiological mechanisms of TMS and helping clinicians to determine ideal candidates for treatment, before TMS even begins. In turn, reducing the global impact of psychiatric and neurocognitive disorders (Arias et al., 2022; GBD 2019 Dementia Forecasting Collaborators, 2022).

Biomarkers have been used across various fields of medicine to better understand diseases and identify indicators of treatment response, with recent research attempting to isolate biomarkers within psychiatric and neurocognitive disorders. According to the Food and Drug Administration (FDA) and the National Institute of Health (NIH), a biomarker can be defined as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" (FDA-NIH Biomarker Working Group, 2016). Isolating biomarkers within the field of psychiatry can play a crucial role in improving the diagnostic process, treatment decision-making, and more (Frey et al., 2013; Abi-Dargham et al., 2023). Specifically, mechanistic biomarkers evaluate potential changes within the pathophysiology of a condition in which the treatment appears to modulate (Table 1; Robinson et al., 2013; Rush & Ibrahim, 2018). Whereas predictive biomarkers examine the likelihood that an individual will respond positively or negatively to a treatment based on underlying characteristics they display before such treatment begins (Table 1; Cagney et al., 2018).

One non-invasive method that has been used to investigate mechanistic and predictive biomarkers is electroencephalography (EEG), a tool used to record neural oscillations across the cerebral

cortex via electrodes placed on the scalp. Specifically, resting-state EEG is recorded while participants are awake but not engaging in a stimulus or a specificized task. Resting-state EEG has shown promise in identifying mechanistic and predictive biomarkers of treatment response to pharmacotherapy in unipolar depression (Freeman et al., 2003; Newson and Thiagarajan, 2018; Strafella et al., 2022; Schwartzmann et al., 2024). Neural oscillations, measured during resting-state recordings, are often processed into frequency bands; delta (~0 – 4 Hz), theta (~4 – 8 Hz), alpha (~8 – 13 Hz), beta (~13 – 30 Hz) and gamma (30 – 70 Hz; Tremblay et al., 2019). These frequency bands can then be used to identify biomarkers within psychiatric and neurocognitive disorders.

In contrast, TMS-EEG is a recording technique that utilizes a single pulse of TMS administered alongside EEG, eliciting a TMS evoked potential (TEP), that provides real-time insight into cortical circuitry (Cao et al., 2021; Farzan, 2024). Encouraging progress has been made in identifying potential predictive TMS-EEG biomarkers in Alzheimer's disease (AD) and unipolar depression (Nardone et al., 2021; Farzan, 2024). There are several TEP's that arise during TMS-EEG recordings, with three of the commonly used TEP's investigated in the field of psychiatry being N45 (inhibitory response, 45 milliseconds post-pulse), N100, and P200 (excitatory response, 200 milliseconds post-pulse; Farzan, (2024)).

Regarding treatment utilizing TMS there are currently three forms of TMS being utilized within psychiatry: (1) repetitive TMS (rTMS), (2) intermittent theta burst stimulation (iTBS), and (3) deep TMS (dTMS). rTMS utilizes either a circular or figure-8 coil, capable of reaching neural structures 1 to 4 cm below the scalp (Milev et al., 2016). rTMS treatment typically lasts 20 to 40 minutes, with a stimulation frequency ranging from 1 to 20 Hz. Repeated pulses of magnetic energy (i.e., trains) are applied within a 2- to 10-second window and followed by a stimulation-free period (i.e., inter-train intervals [ITI]) often lasting 10 to 60 seconds (Milev et al., 2016; Lam et al., 2024). iTBS is a form of rTMS that involves 50 Hz of stimulation for approximately one to three minutes, comprised of a 2-second train and an 8-second ITI (Bakker et al., 2015; Milev et al., 2016). dTMS is another form of rTMS which uses Hesed-coils (i.e., H-coils) of differing configurations to produce a broader stimulation that can target regions 4 cm's beneath the scalp (Deng et al., 2014; Parazzini et al., 2017; Roth et al., 2007; Roth & Zangen, 2014; Tendler et al., 2016). dTMS interventions have an average duration of 20 minutes, wherein 1 to 20 Hz of stimulation is

applied over a 2-3 second train followed by a 15-20 second ITI (Bellini et al., 2024; Carmi et al., 2018; Levkovitz et al., 2015). Various psychiatric conditions, such as unipolar depression, obsessive compulsive disorder and schizophrenia, have been effectively treated using TMS (Di Passa et al., 2024; Tan et al., 2023; Vida et al., 2023). As a whole, TMS is typically utilized in patients experiencing resistance to frontline treatment options, such as psychotropic medications.

Collectively, resting-state EEG and TMS-EEG hold promise as neurophysiological techniques that can be used to effectively detect biomarkers of TMS response across psychiatric and neurocognitive conditions. Therefore, this review aims to synthesize literature investigating the use of resting-state EEG and TMS-EEG in identifying mechanistic and predictive biomarkers of treatment response to TMS, including rTMS, iTBS, and dTMS, in psychiatric and neurocognitive disorders. Of note, this is the first review of its kind to exclude studies that have allowed for concurrent treatments (e.g., psychological therapies or cognitive training) outside of pharmacotherapy. This is a key distinction as the inclusion of these studies can lead to ambiguity about whether biomarkers are related to TMS or the additional therapy use. As it can be difficult to find studies that include a pharmacotherapy washout period, this review only included studies that allowed for concurrent pharmacotherapy.

Table 1. Definitions of Biomarkers Identified

Biomarker Classification	Definition	Example
Mechanistic	A feature of a disorder that changes throughout the course of treatment.	Reduction in N100 posttreatment related to unipolar depression symptom improvement (Voineskos et al., 2021; Strafella et al., 2023).
Predictive	A feature defined prior to treatment that can be used to predict treatment response.	Greater N100 at baseline predicts treatment response to TMS in unipolar depression (Sheen et al., 2024; Strafella et al., 2024).

Abbreviations: TMS = transcranial magnetic stimulation

METHODS

2.1 Literature Search

Before the systematic review was undertaken, the protocol of the review was registered online on PROSPERO (registration number: CRD42024524439). A literature search was conducted via OVID using

the APA PsycINFO, Embase, and MEDLINE databases. The TMS related Boolean searches included "transcranial magnetic stimulation" OR *rTMS* OR *TMS* OR "dTMS TMS" OR "deepTMS" OR "deep transcranial magnetic stimulation". The EEG related Boolean searches included *EEG* OR *electroencephalography* OR *electroencephalogra*. A complete breakdown of the search strategy is available in the Supplementary material (Supplementary 3). The search was conducted on July 3rd, 2025, and was limited to clinical trials utilizing TMS as an intervention and comparing EEG outcomes with changes in clinical symptoms. Author SPM independently ran the search, with both authors SPM and AD partaking in the title-abstract and full-text screening stages. A manual search was also conducted by SPM, to account for eligible articles that may have been unaccounted for in the OVID search.

2.2 Study Selection: Inclusion and Exclusion Criteria

We included clinical trials (e.g., randomized controlled trials, open label, etc.) examining TMS treatments in adults (18 years or older) with a psychiatric or neurocognitive disorder. Patients had to be diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth edition (DSM-IV or DSM-5), the International Classification of Diseases, Eleventh edition (ICD-11), the International Working Group (IWG) or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). We included articles where participants maintained a stable dose of psychotropic medication throughout treatment. Moreover, only studies utilizing rTMS, iTBS or dTMS were included. Furthermore, articles were only selected if they attempted to identify TMS-EEG or resting-state EEG biomarkers of treatment response to TMS. Articles were limited to English only.

Review based studies were excluded, as well as books, annual meetings, letters to the editor, case studies, and case reports. We excluded clinical trials where participants received TMS in conjunction with an add-on treatment, including psychedelic interventions, cognitive training, psychotherapies or other neurostimulation techniques. Lastly, articles that only included healthy participants were excluded.

2.3 Data Extraction

The authors SPM, AD and HY were responsible for data extraction. Specifically, we extracted data and separated them into two distinct categories for the first table, EEG and TMS parameters (Table 2). TMS parameters included TMS modality (e.g., iTBS), study design, TMS trains, intertrain-interval, percentage of motor threshold, frequency (e.g., 10 Hz), pulses per session, frequency of treatment sessions and TMS brain region of target. EEG parameters included EEG modality (e.g., resting state), number of electrodes, electrode placement, electrode reference, eyes open, eyes closed, recording time and recording period (e.g., pre-and-post treatment). Moreover, further data was extracted and placed into a second table, which examined the relationships between EEG and clinical measurement(s) (Table 3). The second table included the sample size for the EEG analysis, EEG measure(s), clinical/cognitive measure(s), period of administration and EEG plus clinical measure(s) identified. Lastly, we extracted demographic and sample characteristics, including clinical diagnosis, intent-to-treat sample size, per-protocol sample size, mean age, percent female and psychotropic medication status, which can be found in the Supplementary material (Supplementary 1). For the purposes of summarizing data, a potential biomarker was defined as a consistent finding within at least two studies.

2.4 Quality Assessment

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) checklist was used to assess the quality of each eligible article, primarily regarding bias (e.g., selection bias) (Meader et al., 2014). The quality assessment was split into six categories based on the GRADE checklist, (1) "was random sequence generation used", (2) "was allocation concealment used", (3) "was there blinding of participants and personnel", (4) "was there blinding of outcome assessment", (5) "was an objective outcome used" and (6) "were more than (80%) a of participants enrolled in trials included in the analysis". From there, the quality of each article was based on the following ratings: low bias risk (0-1), mild bias risk (2-3), moderate bias risk (4-5) and high bias risk (6). If one of the categories was not met, a point would be added against the article, contributing to the article's potential risk of bias.

3. RESULTS

3.1 Eligible Studies

After a subsequent search of Embase, APA PsycInfo and MEDLINE ALL, via OVID, 574 studies were included. Each study was uploaded to Covidence (Covidence., 2024), in which 128 duplicates were automatically removed. On Covidence, a title and abstract screening was performed in which 389 studies were deemed irrelevant and excluded. Furthermore, a full text review was conducted on the remaining 57 studies, in which 29 studies were excluded for various reasons, which can be found in Figure 1. The remaining 28 studies were then thoroughly assessed for eligibility during the extraction process, in which a further 11 articles were excluded (outlined in Figure 1). By means of a manual search, an additional two articles were included. It is unclear as to why these articles did not appear in the OVID search. One reason for the Sheen et al. (2024) article not appearing, is that the keyword "TMS-EEG" was not explicitly used. In total, 19 studies were deemed eligible for inclusion.

3.2 Quality Assessment

Utilizing the GRADE criteria, the following classifications of bias were established based on the number of criteria met, low bias risk (0 – 1), mild bias risk (2 – 3), moderate bias risk (4 – 5) and high bias risk (6). Therefore, five studies were found to have a low risk of bias (Kazemi et al., 2016; Koch et al., 2022, 2025; Pan et al., 2021; Tsai et al., 2022); nine studies were appraised as having a mild risk of bias (Bares et al., 2015; Che et al., 2025; Han et al., 2023; Kamp et al., 2016; Kazemi et al., 2022, 2025; Strafella et al., 2023; Voineskos et al., 2021; Zangen et al., 2023); and five had a moderate risk of bias (Eshel et al., 2020; Godfrey et al., 2024; Guo et al., 2021; Noda et al., 2017; Sheen et al., 2024).

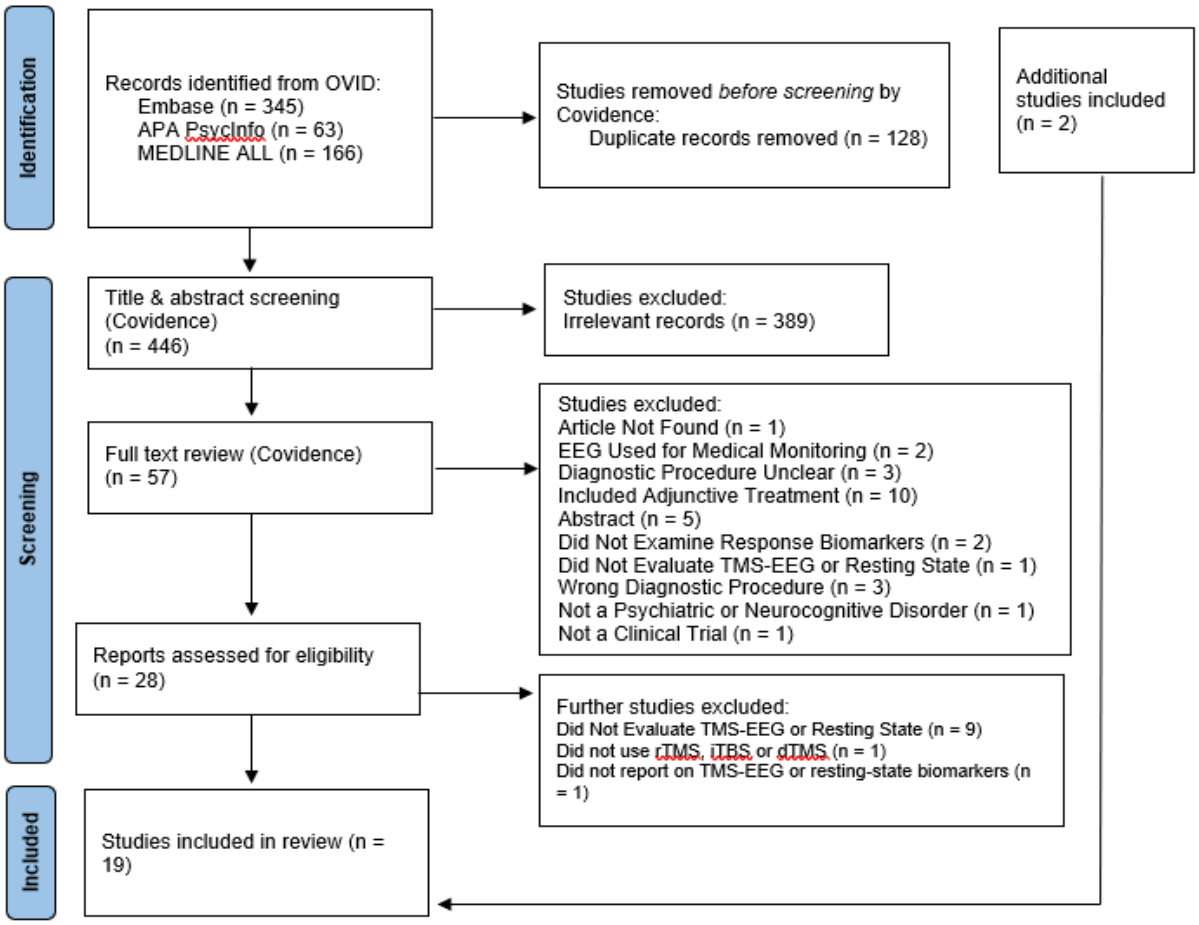

Figure 1. PRIMSA Flowchart. A breakdown of the extraction process, including the reason for exclusions.

Figure 1. Prisma Flowchart. A break down of the extraction process, including the reason for exclusion.

Not one study was found to have a high risk of bias. The majority of the studies reviewed did not report if or how they allocated concealment during the randomization process, or how the participants were randomized into each group, potentially increasing the risk of selection bias. Moreover, the blinding of the outcome assessments was either inconsistent or not reported, making it difficult to determine whether all outcomes examined were adequately blinded. For a comprehensive summary of how we conducted the GRADE quality assessment, please refer to the Supplementary material (Supplementary 2).

Table 2. EEG Parameters & TMS Parameters

Study	EEG Parameters			TMS Parameters				
	Protocol	Recording Protocol	Recording Time & Period	Modality	Treatment Arms	TMS Protocol	Treatment Frequency	Target Brain Region(s)
				TMS-EEG				
Alzheimer's Disease								
Koch et al., 2022	**Electrode #:** 64 **Placement:** NR **Original Reference:** NR	**EC:** NR **EO:** NR	**Time:** NR **Period:** UC	rTMS	PC-rTMS vs Sham-rTMS	**Trains:** 40 **Intertrain-Interval:** 28s **%RMT:** dependent on the PT **Frequency:** 20Hz **Pulses Per Session:** 1600	**Total Sessions:** 32 **Frequency:** 5 days per week for 2 weeks (intensive phase) + once per week for 22 weeks (maintenance phase)	Precuneus
Koch et al., 2025	**Electrode #:** 64 **Placement:** Precuneus **Original Reference:** NR	**EC:** NR **EO:** NR	**Time:** NR **Period:** pre-&-post treatment	rTMS	PC-rTMS vs Sham-rTMS	**Trains:** 2s **Intertrain-Interval:** 28s **%RMT:** UC **Frequency:** 20Hz **Pulses Per Session:** 1600	**Total Sessions:** 60 **Frequency:** intensive course – 2 weeks, 5 days per week; maintenance phase – 50 weeks, once per week	Precuneus
Unipolar Depression								
Eshel et al., 2020	**Electrode #:** NR **Placement:** NR **Original Reference:** NR	**EC:** NR **EO:** NR	**Time:** NR **Period:** baseline & posttreatment	rTMS	Active vs sham	**Trains:** 4s **Intertrain-Interval:** 26s **%RMT:** NR **Frequency:** 10Hz **Pulses Per Session:** 3000	**Total Sessions:** 20 **Frequency:** daily for 4 weeks	Left DLPFC
Voineskos et al., 2021	**Electrode #:** 64 **Placement:** N/A **Original Reference:** electrode posterior to Cz	**EC:** NR **EO:** NR	**Time:** NR **Period:** baseline & after treatment was completed (TMS-EEG)	rTMS	Active (left or bilateral DLPFC) vs sham	**Trains:** 42 (left DLPFC), 30 (bilateral-left DLPFC) & 1 (bilateral-right DLPFC) **Intertrain-Interval:** 25s (left DLPFC) **%MT: 120% Frequency:** 10Hz (left DLPFC & bilateral-left DLPFC) & 1Hz (bilateral-right DLPFC) Pulses Per Session: 600 (bilateral-right DLPFC)	**Total Sessions:** 30 **Frequency:** 5 days a week for 6 weeks	Left or bilateral DLPFC
Han et al., 2023	**Electrode #:** 64 **Placement:** NR **Original Reference:** FCz and AFz	**EC:** No **EO:** Yes	**Time:** NR **Period:** baseline & posttreatment	rTMS	Active vs sham	**Trains:** 180 **Intertrain-Interval:** 8s **%RMT:** 110% **Frequency:** 10Hz	**Total Sessions:** 10 **Frequency:** daily for 10 days	Left DLPFC

Strafella et al., 2023	**Electrode #:** 64 **Placement:** NR **Original Reference:** vertex electrode posterior to Cz	**EC:** NR **EO:** NR	**Time:** NR **Period:** baseline & posttreatment	iTBS	Contiguous schedule (0-minute separation of two treatments) vs separated schedule (54-minute separation of two treatments)	**Pulses Per Session:** 1800 **Trains:** 2s **Intertrain-Interval:** 8s **%RMT:** 120% **Frequency:** 50Hz for 3 pulses then repeated at 5Hz **Pulses Per Session:** 600 (twice per day)	**Total Sessions:** 30 **Frequency:** 6 weeks, 5 days a week (two treatments in one day)	Left DLPFC
TMS-EEG + Resting-State								
Unipolar Depression								
Sheen et al., 2024	**Electrode #:** UC **Placement:** NR **Original Reference:** FCz & AFz	**EC:** NR **EO:** NR	**Time:** 20 min (10 min of pre-post resting + 10 min TMS-EEG) **Period:** baseline & follow-up	rTMS	N/A	**Trains:** 1 **Intertrain-Interval:** N/A **%RMT:** 120% **Frequency:** 1Hz **Pulses Per Session:** 600	**Total Sessions:** 40 **Frequency:** 8 times per day for five days	Right DLPFC
Resting-State								
Alzheimer's Disease								
Guo et al., 2021	**Electrode #:** 64 **Placement:** NR **Original Reference:** FCz	**EC:** Yes **EO:** No	**Time:** 8 min **Period:** baseline & posttreatment	rTMS	N/A	**Trains:** 1s **Intertrain-Interval:** 10s **%RMT:** 100% **Frequency:** 10Hz **Pulses Per Session:** 1600	**Total Sessions:** 20 **Frequency:** 2 treatments per day for 2 weeks	Left DLPFC
Bipolar Depression								
Kazemi et al., 2016	**Electrode #:** 19 **Placement:** 10-20 system **Original Reference:** A1 + A2	**EC:** Yes **EO:** No	**Time:** 10 min **Period:** UC	rTMS	Bilateral vs unilateral	**Trains:** Bilateral right – 150 (10s); bilateral left – 75 (5s); unilateral – 250 (10s) **Intertrain-Interval:** Bilateral right – 2s; bilateral left – 10s; unilateral – 2s **%RMT:** Bilateral right – 120%; bilateral left – 100%; unilateral – 120% **Frequency:** Bilateral right – 1Hz; bilateral left – 10Hz; unilateral – 1Hz **Pulses Per Session:** Bilateral right – 1500; bilateral left – 3750;	**Total Sessions:** 20 **Frequency:** 6 days per week	Left + right DLPFC or only right DLPFC

						unilateral – 2500		
Bipolar + Unipolar Depression								
Godfrey et al., 2024	**Electrode #:** 64 **Placement:** N/A **Original Reference:** POz	**EC:** Yes (4 min) **EO:** Yes (4 min)	**Time:** 8 min **Period:** baseline & after treatment completed	rTMS	N/A	**Trains:** NR **Intertrain-Interval:** NR **%RMT:** 120% **Frequency:** 10Hz **Pulses Per Session:** 4000	**Total Sessions:** 20 **Frequency:** four weeks daily	Left DLPFC
Schizophrenia								
Kamp et al., 2016	**Electrode #:** NR **Placement:** 10-20 system (extended) **Original Placement:** NR	**EC:** NR **EO:** NR	**Time:** NR **Period:** day before treatment & 15 hours after the final treatment.	rTMS	Verum vs Sham	**Trains:** 5s **Intertrain-Interval:** 55s **%RMT:** 110% **Frequency:** 10Hz **Pulses Per Session:** 1000	**Total Sessions:** 10 **Frequency:** 5 days per week for 2 weeks	Left DLPFC
Pan et al., 2021	**Electrode #:** 16 **Placement:** 10-20 system **Original Placement:** Cz	**EC:** Yes **EO:** No	**Time:** 10 min **Period:** baseline & posttreatment	rTMS	Active vs sham	**Trains:** 40 (4s) **Intertrain-Interval:** 26s **%RMT:** 110**%** **Frequency:** 10Hz **Pulses Per Session:** 1600	**Total Sessions:** 20 **Frequency:** 4 weeks, 5 days per week	Left DLPFC
Unipolar Depression								
Bares et al., 2015	**Electrode #:** 32 **Placement:** 10-20 system **Original Reference:** FCz	**EC:** Yes **EO:** No	**Time:** 10 mins **Period:** baseline and a week after treatment	rTMS	rTMS + Placebo vs Venlafaxine + Sham coil	**Trains:** NR **Intertrain-Interval:** NR **%RMT:** 100% **Frequency:** 1Hz **Pulses Per Session:** 600	**Total Sessions:** 20 **Frequency:** 5 days per week for 4 weeks - estimate	Right DLPFC
Noda et al., 2017	**Electrode #:** 19 **Placement:** 10-20 system **Original Reference:** A1 & A2	**EC:** Yes **EO:** No	**Time:** ~10 mins **Period:** baseline & posttreatment	rTMS	N/A	**Trains:** 25 **Intertrain-Interval:** 28s **%RMT:** 82.2 ± 10.6% **Frequency:** 20Hz **Pulses Per Session:** 1000	**Total Sessions:** 10 **Frequency:** 10 sessions over 2 weeks	Left DLPFC
Kazemi et al., 2022	**Electrode #:** 19 **Placement:** 10-20 system **Original Reference:** A1 + A2	**EC:** Yes **EO:** Yes	**Time:** NR **Period:** NR	rTMS	Bilateral vs unilateral vs sham	**Trains:** 150 (right DLPFC) & 75 (left DLPFC) **Intertrain-Interval:** 2s (right DLPFC) & 10s (left DLPFC) **%RMT:** 120% (right DLPFC) & 100% (left DLPFC) **Frequency:** 1Hz (right DLPFC) & 10Hz (left DLPFC) **Pulses Per Session:** 1500 (right DLPFC) &	**Total Sessions:** 20 **Frequency:** UC	Left DLPFC (unilateral group) & left + right DLPFC (bilateral group)

						3750 (left DLPFC)		
Tsai et al., 2022	**Electrode #:** 32 **Placement:** 10-20 system **Original Reference:** A1 & A2	**EC:** Yes **EO:** No	**Time:** 5 min **Period:** baseline & posttreatment	rTMS or iTBS	Prolonged iTBS vs rTMS vs sham	**Trains:** iTBS – 2s; rTMS – 4s **Intertrain-Interval:** iTBS – 10s; rTMS – 30s **%RMT:** iTBS – 80%; rTMS – 100% **Frequency:** iTBS – 50Hz; rTMS – 10Hz **Pulses Per Session:** iTBS – 1800; rTMS – 1600	**Total Sessions:** 10 **Frequency:** 5 sessions per week for two weeks	Left DLPFC
Zangen et al., 2023	**Electrode #:** 32 or 64 **Placement:** N/A **Original Reference:** Cz	**EC:** Yes **EO:** No	**Time:** 300s **Period:** at rest & first treatment	dTMS	H1 coil vs H7 coil	**Trains:** 2s **Intertrain-Interval:** 20s **%RMT:** 120% **Frequency:** 18 Hz **Pulses Per Session:** 1980	**Total Sessions:** 24 **Frequency:** 4 weeks, 5 sessions per week	Lateral or medial PFC
Che et al., 2025	**Electrode #:** 64 **Placement:** extended 10–20 system **Original Reference:** left mastoid	**EC:** Yes **EO:** Yes	**Time:** 10 min **Period:** baseline & posttreatment	rTMS	Active vs sham	**Trains:** NR **Intertrain-Interval:** NR **%RMT:** NR **Frequency:** 10Hz **Pulses Per Session:** 3000	**Total Sessions:** 15 **Frequency:** daily for 15 days	Left DLPFC – area most functionally correlated with NAcc
Kazemi et al., 2025	**Electrode #:** 19 **Placement:** NR **Original Reference:** A1 + A2	**EC:** Yes **EO:** No	**Time:** NR **Period:** baseline & posttreatment	rTMS	Unilateral vs bilateral vs sham	**Trains:** left DLPFC 75 (5s); right DLPFC– 150 (10s) **Intertrain-Interval:** left DLPFC – 10s; right DLPFC - 2s **%RMT:** left DLPFC – 100%; right DLPFC – 120% **Frequency:** left DLPFC – 10Hz; right DLPFC - 1Hz **Pulses Per Session:** left DLPFC – 3750**;** right DLPFC – 1500	**Total Sessions:** unilateral – 20; bilateral – 20; sham – 10; **Frequency:** over 4 weeks	Left DLPFC (unilateral) or left DLPFC + right DLPFC (bilateral)

Abbreviations: DLPFC = dorsolateral prefrontal cortex; dTMS = deep transcranial magnetic stimulation; EC = eyes closed; EEG = electroencephalography; EO = eyes open; H1 = Hesed-coil 1; H7 = Hesed-coil 7; Hz = Hertz; iTBS = intermittent theta burst stimulation; Min = minutes; N/A = not applicable; NR = not reported; NAcc = nucleus accumbens; PFC = prefrontal cortex; PT = participant; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; S = seconds; UC = unclear

Table 3. Relationships Between EEG & Clinical Measurement(s)

Study	EEG Analysis Sample	EEG Measure(s)	Clinical/Cognitive Measure(s) & Period of Administration	EEG + Clinical/Cognitive Measure(s)
			TMS-EEG	
Alzheimer's Disease				
Koch et al., 2022	**PC-rTMS** (n = 22) **Sham-rTMS** (n = 23)	TEP, gamma & beta-gamma range	**Clinical Measure(s):** CDR-SB **Period:** baseline & 24 weeks	In the PC-rTMS condition, a negative correlation was found between ↑ baseline TEP amplitude & a ↓ CDR-SB pre-to-post treatment. In the PC-rTMS condition, a negative correlation was found between ↑ TEP amplitude pre-to-post treatment & a ↓ CDR-SB pre-to-post treatment. From pre-to-post treatment, in participants who experienced CDR-SB improvement had a mean change in TEP of 1.23 μV. **X** b/w gamma & the beta-gamma frequency range and clinical outcomes.
Koch et al., 2025	**PC-rTMS** (n = 18) **Sham-rTMS** (n = 14)	TEP	**Clinical Measure(s):** CDR-SB **Period:** baseline & week 52	↑ in DMN signal propagation at baseline was related to a ↓ in the CDR-SB from baseline to posttreatment.
Unipolar Depression				
Eshel et al., 2020	**Active** (n = 16) **Sham** (n = 12)	P30	**Clinical Measurement:** HDRS **Period:** baseline & posttreatment	The larger the ↓ in prefrontal P30, within the active group, the larger the related change was in depressive symptom improvement.
Voineskos et al., 2021	**N** = 30	GMFAN, TEP, N45, P60 & N100	**Clinical Measurement:** HDRS-17 item **Period:** baseline & posttreatment.	↓ in N100 was positively related to HDRS-17 change in the active group. **X** for P60, GMFAN & N45. TEP amplitude at baseline predictive (87.5% sensitivity, 77.8% specificity, and 82.6% accuracy) of alleviation of suicidality.
Han et al., 2023	**Active** (n = 28) **Sham** (n = 25)	P60/N100 ratio, LMFA-AUC, OFC-SCD, HPC-SCD, OFC-SCS, delta band & gamma band.	**Clinical Measurement:** HDRS-24 item, HARS & PSQI **Period:** baseline & 2 weeks posttreatment	↑ HPC-SCD posttreatment was related to depressive symptom improvements posttreatment, only in the active group. **X** for LMFA-AUC in relation to the HDRS-24, HARS & PSQI. **X** for HPC-SCD in relation to HARS & PSQI. ↑ DLPFC gamma activity posttreatment, in the active group, was related to depressive symptom improvements. ↑ HPC delta activity posttreatment, in the active group, was related to depressive symptom improvements.
Strafella et al., 2023	**Contiguous group** (baseline = 60; posttreatment = 52; paired = 48) **Separated group** (baseline = 54; posttreatment = 46; paired = 42)	GMFA, N45 & N100	**Clinical Measurement:** HDRS-17 item **Period:** baseline & posttreatment	↑ N45 mean amplitude in responders posttreatment. ↓ N100 amplitude posttreatment in responders + positively correlated with ↓ HDRS-17 scores. ↑ N100 amplitude at baseline predictive of ↓ HDRS-17 scores. ↑ GMFA-AUC at baseline negatively correlated with ↓ HDRS-17 scores after treatment + predictive of reductions in the HDRS-17. **Responder = ≥50% reduction in HDRS scores*

TMS-EEG + Resting-State				
Unipolar Depression				
Sheen et al., 2024	n = 23	N100	**Clinical Measurement:** BDI-II **Period:** baseline & follow-up	At channel F4, a positive relationship was found b/w depression improvement & greater N100 amplitude at baseline.
Resting-State				
Alzheimer's Disease				
Guo et al., 2021	n = 23	Beta	**Clinical Measure(s):** MoCA **Period:** baseline & posttreatment	Within the moderate AD group, ↑ power envelope connectivity, from pre-to-post treatment, within an identified network in beta, comprised of the frontal cortex, parietal cortex, primary visual cortex, middle temporal gyrus, insular cortex & limbic lobe, was related to an ↑ in scores on the MoCA posttreatment.
Bipolar Depression				
Kazemi et al., 2016	**Bilateral** (n = 15) **Unilateral** (n = 15)	Alpha, beta & gamma bands	**Clinical Measurement:** BDI-II **Period:** baseline, 10th session & posttreatment	↑ in absolute alpha-2 power, posttreatment, in unilateral stimulation responders at O1. ↓ in absolute alpha-2 power, posttreatment, in unilateral stimulation non-responders at O1. ↓ absolute gamma power, posttreatment, in unilateral stimulation of responders at Fp1, P4, O1, O2, T4, T5, T6 & Cz. ↑ absolute gamma power, posttreatment, in unilateral stimulation of non-responders at Fp1, P4, O1, O2, T4, T5, T6 & Cz. ↓ in absolute alpha-2 power, posttreatment, in bilateral stimulation responders at P3, T5 & O2. ↑ in absolute alpha-2 power, posttreatment, in bilateral stimulation non-responders at P3, T5 & O2. **X** in other frequency bands & absolute power. ↑ in relative gamma power, posttreatment, in unilateral stimulation of non-responders, at P4, T3, T4 & T5. ↓ in relative gamma power, posttreatment, in unilateral stimulation responders, at P4, T4 & T5. ↑ in relative gamma power, posttreatment, in unilateral stimulation of responders at T3. ↓ relative gamma power, posttreatment, in bilateral stimulation non-responders, at F4 & T3. ↑ in relative gamma power, posttreatment, in bilateral stimulation responders, at F4 & T3. **X** in the other frequency bands & relative spectral power. ↓ in beta coherence, posttreatment, in unilateral stimulation responders at pairs P3-O1 & O1-T3. **X** in unilateral stimulation of non-responders and posttreatment beta coherence. ↑ in beta coherence, posttreatment, in bilateral stimulation of non-responders at pairs F7-T3 & F4-T4. ↓ in beta coherence, posttreatment, in bilateral stimulation responders at pairs F7-P3, F7-T3, F4-T4 & T4-O2.

				X in other frequency bands & coherence. ↓ in gamma, alpha-1, alpha-2 & beta-2 current density in bilateral stimulation responders. This was found within the following regions: anterior cingulate, cingulate gyrus, & frontal gyrus (superior, middle, & medial). ↓ in gamma current density in unilateral stimulation responders. This was found within the following regions: precuneus, cuneus, supramarginal gyrus, post-central gyrus, angular gyrus, superior temporal gyrus, superior occipital gyrus, superior parietal lobule, & the inferior parietal lobule. **Response = >50% reduction in mean scores on the BDI-II*
Bipolar + Unipolar Depression				
Godfrey et al., 2024	n = 28	Theta band	**Clinical Measurement:** MADRS **Period:** pre-&-post treatment	A positive correlation was found b/w larger mean ↓ in theta connectivity & a larger percent ↓ in the MADRS, within the eye closed condition. **X** b/w either connectivity or source-level spectral power at baseline & MADRS changes. ↑ in treatment response was related to ↓ baseline theta connectivity
Schizophrenia				
Kamp et al., 2016	**Verum** (n = 15) **Sham** (n = 14)	Delta band	**Clinical Measures:** PANSS & a Facial Affect Recognition Task **Period:** pre-&-post treatment	**X** relationship b/w negative scores on the PANSS & delta power. A negative correlation was discovered between delta power changes & better facial affect recognition.
Pan et al., 2021	**Active** (n = 19) **Sham** (n = 19)	**Microstate D** = attention network	**Clinical Measures:** PANSS **Period:** baseline & posttreatment	**X** found b/w changes in the PANSS & the change in microstate D duration, in either the active or sham group.
Unipolar Depression				
Bares et al., 2015	**rTMS + Placebo** (n = 25)	Theta band	**Clinical Measurement:** MADRS **Period:** before wash-out period, baseline, after week one & week four.	**X** when examining absolute or relative theta power & depressive symptoms. ↓ in cordance after 1 week of treatment was negatively correlated with posttreatment change, by percent, in the MADRS. ↑ in baseline cordance was positively correlated with posttreatment change, by percent, in the MADRS. Responders had a ↓ in prefrontal theta cordance after 1 week of treatment. **X** baseline MADRS scores & baseline prefrontal theta cordance. **X** after one week of treatment in the change in both MADRS scores & prefrontal theta cordance. **Response = ≥50% reduction in MADRS*
Noda et al., 2017	n = 31	Gamma band & theta band	**Clinical Measurement:** HDRS-17, BDI & WCST. **Period:** baseline & posttreatment	↑ in gamma power at F3 overtime was negatively correlated with depression symptom improvement. **X** b/w gamma power at F4 overtime & depression symptom improvement. ↑ in theta-gamma coupling at C3 overtime was positively correlated with an improvement in WCST errors. **X** in theta-gamma coupling at T3 overtime & the WCST.

Kazemi et al., 2022	**Bilateral** (n = 25) **Unilateral** (n = 25) **Sham** (n = 11)	Delta, theta, alpha, beta & gamma bands	**Clinical Measurement:** HDRS-17 & RRS **Period:** pre-&-post treatment	↓ in beta & gamma connectivity was found in bilateral responders. ↓ in alpha connectivity was found in unilateral responders. ↓ beta connectivity b/w unilateral & bilateral responders Positive correlations b/w delta, theta & beta connectivity & the RRS in bilateral responders. Positive + negative correlations found b/w delta, alpha, beta & gamma & the RRS in unilateral responders. ↑ theta connectivity related to ↓ in brooding in bilateral & unilateral responders. ↑ gamma connectivity related to ↓ in brooding in bilateral responders. ↑ delta connectivity related to ↓in brooding in unilateral responders. ↓ alpha, beta, delta, & theta connectivity related to ↓ in reflection in bilateral responders. ↑ theta connectivity related to a ↓in reflection in unilateral responders. ↓ alpha connectivity related to ↓ in reflection in unilateral responders. **Responder = ≥50% reduction in HDRS-17 scores*
Tsai et al., 2022	**Prolong iTBS** (n = 19) **rTMS** (n = 20) **Sham** (n = 22)	Theta & alpha bands.	**Clinical Measurement:** HDRS-17 **Period:** baseline & posttreatment	Prolong iTBS responders showed a ↑ in theta-alpha amplitude modulation frequency (fam 3–11.8 Hz, fc 3–11.8 Hz), especially in frontal regions, which positively correlated with percentage symptom improvement. **X** in the occipital regions. **X** found in rTMS responders. **Response = ≥50% reduction in HDRS-17*
Zangen et al., 2023	**H1 coil** (n = 64) **H7 coil** (n = 79)	Alpha & low-gamma band	**Clinical Measurement:** HDRS-21 item **Period:** baseline, week 3, week 4, week 5 and end of week 6.	↑ medial alpha power (reference: current source density), at baseline, was positively correlated with clinical efficacy in H1. ↑ medial low-gamma power (reference: current source density), at baseline, was negatively correlated with clinical efficacy in H1. ↑ medial low gamma/alpha ratio power (reference: average reference & current source density), at baseline, was negatively correlated with clinical efficacy in H1.
Che et al., 2025	**Active** (n = 26) **Sham** (n = 23)	**GFP Microstates:** **Microstate A** = phonological processing network **Microstate B** = visual network **Microstate C** = DMN **Microstate D** = attentional network **Microstate E** = SN	**Clinical Measurement:** TEPS & HDRS-17 item **Period:** baseline & posttreatment	A positive correlation was found b/w the occurrence in microstate C & anticipatory anhedonia improvements. **X** for microstate E & anhedonia symptoms. ↑ microstate C occurrence was found in responders posttreatment. **X** for microstate A, B, D & E occurrence in relation to response posttreatment. **X** for non-responders. **Response = ≥50% reduction in HDRS-17*

Kazemi et al., 2025	**Unilateral** (n = 24) **Bilateral** (n = 25) **Sham** (n = 11)	Alpha band	**Clinical Measurement:** HDRS & SHAPS **Period:** baseline & posttreatment	↑ trend in parietal alpha asymmetry in bilateral stimulation responders (greater right laterization). ↓ trend in parietal alpha asymmetry in bilateral stimulation non-responders (more left lateralization). ↑ parietal alpha asymmetry at baseline was associated with ↓ in anhedonia post-bilateral stimulation. **X** b/w unilateral responders vs non-responders. ↑ parietal alpha asymmetry at baseline was associated with ↑ anhedonia post-unilateral stimulation. At baseline, bilateral responders' parietal alpha asymmetry was negative (left lateralization). ↑ alpha peak frequency at baseline was associated with ↑ anhedonia post-bilateral stimulation. ↑ parietal alpha asymmetry at baseline was predictive of ↓ anhedonia post-bilateral stimulation. ↑ parietal alpha asymmetry at baseline was predictive of ↑ anhedonia post-unilateral stimulation. **Response = ≥50% reduction in HDRS*

Abbreviations: b/w = between; BDI-II = Beck Depression Inventory; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; fam = amplitude modulation frequency; fc = carrier frequency; GFP = global field potential; GMFA = global mean field amplitude; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; HPC = hippocampus; HPC-SCD = hippocampus significant current density; LMFA-AUC = local mean field amplitude area under the curve; MADRS = Montgomery-Asberg Depression Rating Scale; OFC-SCD = orbitofrontal cortex significant current density; OFC-SCS = orbitofrontal cortex significant current scattering; PANSS = Positive and Negative Syndrome Scale; PSQI = Pittsburgh Sleep Quality Index; PT = participant; RRS = The Ruminative Response Scale; SHAPS = Snaith-Hamilton Pleasure Scale; SN = salience network; TEP = TMS-evoked potentials; TEPS = The Temporal Experience of Pleasure Scale; UC = unclear

Symbols: & = and; ↓ = decrease; ↑ = increase; X = nothing of significance

3.3. TMS-EEG

3.3.1. Unipolar Depression

Five studies examined TMS-EEG biomarkers of TMS response in unipolar depression (Eshel et al., 2020; Voineskos et al., 2021; Han et al., 2023; Strafella et al., 2023; Sheen et al., 2024). The most investigated TMS-EEG measure was the N100 TEP. Two studies applied rTMS to the left dorsolateral prefrontal cortex (DLPFC; Eshel et al., 2020; Han et al., 2023) and one study to the left or bilateral DLPFC (Voineskos et al., 2021). Another study delivered rTMS to the right DLPFC (Sheen et al., 2024)

and one employed iTBS over the left DLPFC (Strafella et al., 2023). All non-significant results are reported in the Supplementary material, in Supplementary 4.

Mechanistic biomarkers were the most examined TMS-EEG markers of treatment response to TMS for unipolar depression. A reduction in N100 was related to depressive symptom improvements after 30 sessions of either iTBS or rTMS (active group) within regions of the DLPFC (Voineskos et al., 2021; Strafella et al., 2023). Furthermore, iTBS responders had reductions in N100 amplitude once treatment had been completed (Strafella et al., 2023). Similarly, when examining the P30 TEP, Eshel et al. (2020) discovered that the change in depressive symptoms was greater when the decrease in P30, from pre-to-post treatment, was more pronounced. However, iTBS responders mean N45 amplitude was greater following treatment, opposite to N100 (Strafella et al., 2023). Likewise, improvements to depressive symptomology, within the active rTMS group, was linked to greater current density posttreatment within the hippocampus (Han et al., 2023). Moreover, greater posttreatment hippocampal delta activity and DLPFC gamma activity was related to an amelioration of depressive symptoms (Han et al., 2023).

In respect to predictive biomarkers, depressive symptom improvements were associated with greater N100 amplitudes at baseline for both rTMS and iTBS (Strafella et al., 2023; Sheen et al., 2024). When utilizing global mean field amplitude (GMFA) to record the area under the curve of TEP's (GMFA-AUC), Strafella et al. found that GMFA-AUC was greater at baseline in iTBS responders and could predict greater improvements in depressive symptoms. An exploratory analysis was conducted by Voineskos et al. (2021), which discovered that suicidal symptom relief could be predicted by TEP amplitude, specifically in the left DLPFC stimulation site, with 82.6% accuracy.

3.3.2. Mild-to-Moderate Alzheimer's Disease

Two studies examined TMS-EEG biomarkers of TMS response in mild-to-moderate Alzheimer's disease (Koch et al., 2022; Koch et al., 2025). The most investigated TMS-EEG measures were TEP's. With both studies applying rTMS to the precuneus. All non-significant results are reported in the Supplementary material, in Supplementary 4.

When examining mechanistic biomarkers, a reduction in the CDR-SB, from baseline to posttreatment, was correlated with an increase in TEP amplitude, from baseline to posttreatment (Koch et al., 2022). The average TEP change, in participants who saw a reduction in their CDR-SB, was 1.23 μV.

Predictive biomarkers were the most examined TMS-EEG markers of treatment response to rTMS for mild-to-moderate Alzheimer's disease. Higher baseline TEP amplitude was negatively correlated with an improvement, from baseline to posttreatment, on the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB; Koch et al., 2022). Additionally, a reduction within the CDR-SB pre-to-post treatment was also negatively correlated with higher default mode network signal propagation (Koch et al., 2025).

3.3.3. Potential Biomarkers Identified: Unipolar Depression

The most consistent result across unipolar depression studies examining TMS-EEG biomarkers showed that N100 was significantly associated with TMS treatment outcomes; identifying a mechanistic and predictive biomarker. One randomized-sham-controlled trial (Voineskos et al., 2021) and one randomized trial (Strafella et al., 2023) identified that reductions within N100 post-rTMS and iTBS were related to depression symptom improvements in a sample of 120 participants; a potential mechanistic biomarker. One open-label trial using rTMS (Sheen et al., 2024) and one randomized-trial utilizing iTBS (Strafella et al., 2023) found that greater baseline N100 amplitude was related to depression symptom improvements in a combined sample of 113 participants; a potential predictive biomarker. Table 4 provides a brief breakdown of the potential function of the TMS-EEG biomarkers identified.

3.4. Resting State EEG

3.4.1. Unipolar and Bipolar Depression

Ten studies investigated resting-state EEG biomarkers of TMS response in unipolar and/or bipolar depression (Bares et al., 2015; Kazemi et al., 2016; Noda et al., 2017; Kazemi et al., 2022; Tsai et al., 2022; Zangen et al., 2023; Godfrey et al., 2024; Sheen et al., 2024; Che et al., 2025; Kazemi et al., 2025). Of these, eight focused exclusively on unipolar depression (Bares et al., 2015; Noda et al., 2017; Kazemi et al., 2022; Tsai et al., 2022; Zangen et al., 2023; Sheen et al., 2024; Che et al., 2025; Kazemi et al., 2025), one on bipolar depression (Kazemi et al., 2016) and one on both unipolar and bipolar

depression (Godfrey et al., 2024). It is important to note that the study including both unipolar and bipolar depression, only had two participants with bipolar depression (Godfrey et al., 2024). The most analyzed resting-state measures were the theta and alpha frequency bands. All non-significant results are reported in the Supplementary material, in Supplementary 4.

EEG Power Analysis

Six studies examined EEG power within participants with unipolar and/or bipolar depression (Bares et al., 2015; Kazemi et al., 2016; Noda et al., 2017; Tsai et al., 2022; Zangen et al., 2023; Godfrey et al., 2024). Four studies applied rTMS to the DLPFC: one targeted the left DLPFC in individuals with unipolar depression (Noda et al., 2017); another stimulated the left DLPFC in a mixed sample of participants with unipolar and bipolar depression (Godfrey et al., 2024); one targeted the right DLPFC for unipolar depression (Bares et al., 2015); and one delivered stimulation either bilaterally or directly to the right DLPFC in individuals with bipolar depression (Kazemi et al., 2016). Lastly, one study administered iTBS to the left DLPFC (Tsai et al., 2022) and another applied dTMS to the lateral or medial prefrontal cortex (Zangen et al., 2023), both in unipolar depressed participants.

Mechanistic biomarkers were the most frequently investigated EEG power marker for unipolar and bipolar depression. When stimulating the left DLPFC via rTMS in unipolar depression, F3 absolute gamma power increased over the course of treatment, negatively correlating with reductions in depression symptoms (Noda et al., 2017). However, when stimulating the right DLPFC via rTMS in bipolar depressed patients, posttreatment increases in absolute gamma power, across frontal to occipital electrode sites (Table 3), was observed in participants who did not respond to treatment (Kazemi et al., 2016). Moreover, participants with bipolar depression, who responded to right DLPFC rTMS showed a decrease in absolute gamma power posttreatment, reported in several electrodes (Table 3). Intriguingly, in alpha frequency between 10 – 12Hz (alpha-2), an increase in absolute power posttreatment at electrode O1 was indictive of bipolar depressed responders to right DLPFC rTMS. However, this flipped in non-responders, resulting in a reduction of posttreatment absolute alpha-2 power at O1. Furthermore, a similar situation occurred in absolute alpha-2 power at electrodes T5, P3 and O2, in bilateral DLPFC rTMS for bipolar depression. Responders displayed a decrease in absolute alpha-2 power posttreatment,

whereas non-responders exhibited an increase. In respect to relative gamma power in participants with bipolar depression, an increase, post-bilateral rTMS, in relative power was observed in responders at electrodes F4 and T3. Once again, non-responders experienced a reduction in relative gamma power at F4 and T3. Interestingly, bipolar depressed right DLPFC rTMS responders had an increase in relative gamma power at T3 or a decrease at P4, T4, and T5. Oddly, non-responders also experienced an increase in relative gamma power at T3, as well as P4, T4, and T5. Rather than examining absolute or relative power, Tsai et al. (2022) utilized a different form of power analysis, called Holo-Hilbert spectral analysis, and investigated amplitude modulation within the theta and alpha frequency bands. When examining unipolar depressed responders to prolonged iTBS (1800 pulses, rather than 600 pulses), Tsai et al. (2022) found that responder's frontal theta-alpha amplitude modulation frequency was increased as compared to sham. As well, a positive correlation was found between the percentage improvement in depression symptoms and the increase in the theta-alpha amplitude modulation frequency.

Concerning predictive biomarkers, Zangen et al. (2023) investigated the efficacy of Hesed-coil 1 (lateral prefrontal cortex stimulation) to treat individuals with unipolar depression. Baseline resting-state EEG, using a current source density (CSD) reference, revealed a significant positive correlation between medial alpha power and improvement in depression symptoms. In contrast, significant negative correlations were found between depression symptom improvement and medial low-gamma power (CSD reference) and medial low gamma/alpha power ratio (CSD and average reference). Furthermore, Kazemi et al. (2025) identified that greater baseline alpha peak frequency was linked to an increase in posttreatment anhedonia.

EEG Connectivity

Two studies examined EEG connectivity; one in unipolar depression (Kazemi et al., 2022) and one in both unipolar and bipolar depression (Godfrey et al., 2024). Kazemi et al. (2022) utilized sensor-level connectivity, whereas Godfrey et al. (2024) used functional connectivity. Both studies applied rTMS over the left DLPFC, with Kazemi et al. (2022) additionally including a bilateral stimulation group.

Mechanistic biomarkers were the most frequently investigated EEG connectivity marker in unipolar and bipolar depression. In individuals with unipolar depression who responded to left DLPFC

stimulation, Kazemi et al. (2022) observed a reduction in sensor-level alpha connectivity within three frontal electrode pairs. Additionally, improvements in brooding were associated with increased theta and delta connectivity across frontal, temporal and parietal cortical pairs, in left DLPFC responders. Improvements in reflection symptoms of depression were linked to increased theta connectivity across frontal and temporal electrode pairs, including decreased alpha connectivity in pairs within frontal, temporal and parietal regions. Furthermore, both positive and negative correlations were identified between connectivity in the delta, alpha, beta and gamma bands and ruminative symptoms more generally, within pairs spanning the frontal, temporal and parietal cortices. Responders to bilateral stimulation exhibited reductions in beta and gamma connectivity across pairs in the frontal, temporal and parietal regions. Improvements in brooding were also related to increased theta connectivity, as well as gamma connectivity, in pairs in the parietal and frontal cortices. In contrast, improvements in reflection were associated with a decrease in theta connectivity, as well as in delta, alpha and beta, in pairs in the frontal, temporal and parietal areas. Markedly, in participants with unipolar or bipolar depression who received left DLPFC stimulation, greater mean reductions in functional theta connectivity were positively correlated to larger percentage reductions in depression symptoms (Godfrey et al., 2024). These effects were exclusively found in the eyes-closed condition, within a network consisting of 25 nodes and 34 edges. Returning to bilateral stimulation in unipolar depression, positive correlations were again found between sensor-level delta, theta and beta connectivity and ruminative symptoms, more broadly, with these associations presented across frontal, temporal and parietal pairs (Kazemi et al., 2022).

In relation to predictive biomarkers, when stimulating the left DLPFC in both unipolar and bipolar depressed individuals, Godfrey et al. (2024) found that greater improvements in depressive symptoms were associated with lower baseline theta connectivity.

Other Analyses

Several studies have examined mechanistic and predictive biomarkers in response to rTMS, targeting various regions of the DLPFC within unipolar and bipolar depression. Kazemi et al. (2025) investigated EEG asymmetry following left or bilateral DLPFC stimulation in unipolar depression. As well, Kazemi et al. (2016) previously also assessed EEG coherence and current density after right or bilateral

DLPFC stimulation in bipolar depression. On the other hand, Bares et al. (2015) focused on EEG cordance following right DLPFC stimulation in unipolar depression. Furthermore, Noda et al. (2017) chose to analyze EEG coupling in unipolar participants treated with left DLPFC stimulation. Lastly, Che et al. (2025) examined EEG microstates in unipolar depression after left DLPFC stimulation as well.

Mechanistic biomarkers were the most frequently investigated markers across the various EEG analyses discussed above. When bilaterally stimulating the DLPFC in participants with unipolar depression, Kazemi et al. (2025) found that treatment responders had an increase in trend alpha asymmetry within the parietal cortex. Nevertheless, non-responders exhibited a decrease in trend alpha asymmetry within the parietal cortex. In bipolar depressed participants, those who did not respond to bilateral DLPFC stimulation were found to have an increase in posttreatment beta coherence at pairs F4-T4 and F7-T3 (Kazemi et al., 2016). However, individuals who responded to treatment had a reduction in beta coherence at pairs F4-T4 and F7-T3, as well as F7-P3 and T4-O2. Responders also had reductions in current density within gamma, alpha and high beta (15-18 Hz) frequency bands, found across several regions of the cortex (Table 3). Much like those who had bilateral stimulation, responders to right DLPFC stimulation had a reduction in posttreatment beta coherence at pairs P3-O1 and O1-T3. Gamma current density also decreased in individuals who responded to right DLPFC stimulation, throughout various regions of the cortex (Table 3) as well. When applying stimulation over the left DLPFC, Noda et al. (2017) found that an improvement in errors on the Wisconsin Card Sorting Task that was associated with an increase in theta-gamma coupling at electrode C3 in unipolar depressed participants. While also examining left DLPFC stimulation for unipolar depression, Che et al. (2025) discovered that improvements in participants anticipatory anhedonia was positively correlated with an increase in the occurrence of microstate C (global field potential within the default mode network). Posttreatment responders also had an increase in the occurrence of microstate C.

In respect to predictive biomarkers, when stimulating the DLPFC bilaterally in unipolar depressed participants, Kazemi et al. (2025) found that higher baseline alpha asymmetry, within the parietal cortex, was not only related to but also predictive of a reduction in anhedonia posttreatment. Responders to bilateral stimulation also had left lateralized alpha asymmetry at baseline within the prefrontal cortex.

Interestingly, higher baseline alpha asymmetry, within the parietal cortex, was both associated and predictive of worsened anhedonia in participants who had left DLPFC stimulation. In unipolar depressed individuals who had right DLPFC stimulation, an increase in the percentage change of the MADRS posttreatment was related to higher baseline cordance (Bares et al., 2015). Similarly, reductions in cordance after only one week of treatment was also related to greater percent improvements in the MADRS. With responders demonstrating a distinct decrease in prefrontal theta cordance one week into treatment.

3.4.3. Schizophrenia

Two studies examined resting-state EEG biomarkers of TMS response in schizophrenia. Both studies applied rTMS to the left DLPFC (Kamp et al., 2016; Pan et al., 2021). Due to the heterogeneity across the study measures, there was no common resting-state measures isolated.

One mechanistic biomarker was identified, and no predictive biomarkers were examined. Kamp et al. (2016) found a negative correlation between changes in delta power and better recognition in facial affect. Pan et al. (2022) did not identify any biomarkers – their non-significant finding, along with Kamp et al.'s (2016), can be found in the Supplementary material (Supplementary 4).

3.4.4. Mild-to-Moderate Alzheimer's Disease

One study examined resting-state EEG biomarkers of TMS response in mild-to-moderate Alzheimer's disease; severity was assessed via the Montreal Cognitive Assessment (Guo et al., 2021). The study by Guo et al. (2021) applied rTMS to the left DLPFC. Resting-state EEG biomarker measures were assessed in the delta, theta and beta frequency bands.

One mechanistic biomarker was identified, and no predictive biomarkers were examined. Within an isolated network (defined in Table 3) in the beta frequency band, Guo et al. (2021) found that an improvement in the Montreal Cognitive Assessment was associated with an increase in power envelope connectivity.

3.4.5. *Potential Biomarker Identified: Unipolar and Bipolar Depression*

The most consistent findings across unipolar and bipolar depression studies examining resting-state EEG biomarkers showed that reductions in theta connectivity were related to depression symptom improvements in a combined sample of 89 participants, thereby representing a potential mechanistic biomarker. In a randomized controlled trial by Kazemi et al. (2022) it was discovered that reductions in theta connectivity were related to a decrease in reflection within rumination, specifically among treatment responders (≥50% reduction in HDRS-17 scores) who received bilateral DLPFC rTMS. Moreover, in another randomized controlled trial, utilizing rTMS over the left DLPFC, by Godfrey et al. (2024) it was found that greater mean reductions in theta connectivity were related to depressive symptom improvements. Potentially, identifying a mechanistic resting-state EEG biomarker for further investigation in unipolar and bipolar depression. Table 4 provides a brief breakdown of the potential function of the resting-state biomarker identified.

Table 4. Summary of Potential Biomarkers Identified

Biomarker Classification	Biomarker	Function
Unipolar Depression		
Mechanistic Biomarker	Reductions in N100 post-DLPFC rTMS & iTBS.	An excitatory & inhibitory imbalance within the PFC, characteristic of unipolar depression, may be modulated by TMS to the PFC, as N100 is an inhibitory neural response (Ghosal et al., 2017; Farzan, 2024).
Predictive Biomarker	Greater baseline N100, in DLPFC rTMS & iTBS, predictive of depression symptom improvement.	
Unipolar & Bipolar Depression*		
Mechanistic Biomarker	Decreased theta connectivity post-DLPFC rTMS.	Greater connectivity within the theta frequency band may play a role in aspects of unipolar and bipolar depression (Fingelkurts & Fingelkurts, 2015; Wang et al., 2021). TMS to the DLPFC may have an inhibitory effect on theta rhythms, resulting in a reduction in connectivity.

Abbreviations: BD = bipolar depression; DLPFC = dorsolateral prefrontal cortex; iTBS = intermittent theta burst stimulation; PFC = prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation

*There were only two participants with bipolar disorder enrolled in one of the studies utilized to identify this biomarker.

DISCUSSION

Clinical trials over the past decade have been incorporating TMS-EEG and resting-state measures to identify biomarkers of treatment response to TMS. This systematic review is the first to

evaluate TMS-EEG and resting-state biomarkers of treatment response to TMS in both psychiatric and neurocognitive disorders, exclusively examining clinical trials involving TMS interventions that allowed for psychotropic medication augmentation only. After a comprehensive review of the current literature, we identified three potential biomarkers of TMS response. Two mechanistic biomarkers were identified: (1) reductions in N100 post-DLPFC rTMS and iTBS in unipolar depression (n = 120; k = 2) and (2) reductions in theta connectivity post-DLPFC rTMS in unipolar and bipolar depression (n = 89; k = 2). With one predictive biomarker isolated: greater N100 at baseline was predictive of unipolar depression improvement, in rTMS and iTBS (n = 113; k = 2).

Mechanistic biomarkers play a crucial role in helping researchers to better understand the underlying mechanisms of how TMS modulates the brain to alleviate psychiatric and cognitive symptoms. As identified in this review, reductions in N100 and theta connectivity, as potential mechanistic biomarkers, could help provide insights into how the neurophysiology of unipolar and/or bipolar depression may be modulated by TMS and, thus, lead to depression symptom improvement. On the other hand, predictive biomarkers play a critical role in identifying underlying baseline neurophysiological characteristics that increase or decrease a patient's chances of responding to TMS treatment. Greater N100 at baseline, as a potential predictive biomarker, can help improve treatment outcomes in unipolar depressed patients by predicting their response to TMS before treatment even begins.

Previous reviews have identified the importance of the TEP N100 and the theta frequency band as essential features across biomarkers in unipolar depression. In a review of TMS-EEG biomarkers by Farzan (2024), it was identified that the TEP N100 played a critical role across several biomarkers associated with unipolar depression. Specifically, Farzan (2024) also determined that greater baseline N100 could potentially assist as a predictive biomarker in neurostimulation treatments. As well as N100 reductions as a mechanistic biomarker in TMS. In a separate review by Strafella et al. (2022), the theta frequency band appeared to play a significant role as a predictive biomarker across treatments for unipolar depression, notably within theta cordance and current density. Regarding theta connectivity more specifically, a study by Steinmann et al. (2024) identified a potential diagnostic biomarker of unipolar depression, via a decrease in theta connectivity between the DLPFC and the rostral -ventral cingulate cortices, during an appraisal task in individuals with unipolar depression (Steinmann et al., 2024). In

relation to bipolar depression and the theta frequency band, Wang et al. (2021) identified a potential diagnostic biomarker of bipolar depression examining reward processing in BD relative to healthy controls and found that bipolar depression patients experiencing loss had greater theta activity as opposed to when they experienced a gain in a gambling paradigm (Wang et al., 2021).

Though biomarkers were identified, a common theme across this review is the limitation of heterogeneity across treatment protocols, TMS-EEG and resting-state biomarker measures/methods and, as a result, findings. Subsequently, leading to the inability for a meta-analysis to be run. Due to the heterogeneity of treatment protocols and findings within the studies reviewed in schizophrenia and mild-to-moderate Alzheimer's disease, no mechanistic or predictive biomarkers could be isolated. The issue of heterogeneity also impacted unipolar and bipolar depression findings. First, due to the heterogeneity across the depression literature reviewed, strong conclusions could not be made regarding the relevancy of the biomarkers identified, as the results from only two studies per biomarker could be utilized. As such, the findings should be taken with caution. Secondly, heterogeneity also impacted the ability for this review to isolate further depression biomarkers. Several different measures were used to assess biomarkers in depression, from cordance to coupling to asymmetry. Moreover, Strafella et al. (2022) identified an increase in mean N45 amplitude in participants who responded to iTBS treatment over the left DLPFC, whereas Voineskos et al. (2021) found no relationship between N45 and treatment outcomes of rTMS over either the left or bilateral DLPFC. Though this begs the question if N45 is a better marker for iTBS response, we could not identify N45 as a biomarker because of the different TMS methods and their separate outcomes. Highlighting the need for standardization of measures/methods. Thirdly, the mechanistic biomarker of decreased theta connectivity identified within this review came from two studies that utilized different connectivity measures; sensor-level versus functional connectivity. Once again, emphasizing the necessity for standardized measures. Lastly, Kazemi et al. (2022) also found that *increased* theta connectivity was associated with a reduction in brooding, in unipolar depressed responders, when stimulating both the left and bilateral DLPFC, as well as a decrease in the reflection when stimulating the left DLPFC only. Aligning with this, previous research found that unipolar depressed treatment responders to rTMS had greater theta connectivity at baseline, during a working memory task (Bailey et al., 2018). Taken together, the current literature, in general, remains heterogenous in terms of

the relationship between theta connectivity and rTMS response in depression. Overall, the heterogeneity across EEG studies in general, particularly due to varying methodologies, has been discussed previously by Perotteli et al. (2021) and Miljevic et al. (2023) in the context of schizophrenia and unipolar depression. This variability has significantly hindered efforts to draw definitive conclusions regarding potential biomarkers. Therefore, it is vital for researchers to develop standardized analytical protocols when assessing TMS-EEG and resting-state biomarkers of TMS response, to lessen the burden of heterogeneity.

Although heterogeneity across studies in mild-to-moderate Alzheimer's disease and schizophrenia limited the identification of mechanistic and predictive biomarkers in this review, promising findings emerged that could help guide future research. In respect to Alzheimer's disease, TEP's may play an important role in biomarker discovery more generally. As, a study by Tăuţan et al. (2023) discovered a distinctive TEP feature of Alzheimer's disease between the 45 – 80 milliseconds timeframe following pulse administration. Although delta power was not associated with negative scores on the Positive and Negative Syndrome Scale, possibly due to the small sample size of the study, a negative correlation was found between changes in delta power and improvement in facial affect recognition. Aligning with previous research, which has emphasized the compelling association between schizophrenia and the delta frequency band (Lisman, 2016).

A second limitation of this review was that we did not examine TMS response between psychiatric disorders, other than unipolar and bipolar depression, and their symptom similarities that may have similar pathophysiology. For example, anhedonia is a symptom that is found in both schizophrenia and unipolar depression. Could stimulating the left DLPFC via TMS in both conditions improve symptoms of anhedonia? This limitation, though, was also impacted by heterogeneity.

A third limitation of this study is the limited number of participants with bipolar depression in the study by Godfrey et al. (2024), that helped in identifying theta connectivity as a mechanistic biomarker. Only two participants had a diagnosis of bipolar disorder, limiting theta connectivity as a possible mechanistic biomarker in TMS for individuals with bipolar depression.

Moving forward, continued and standardized research protocols are warranted in investigating the use of theta connectivity and N100 as mechanistic and predictive biomarkers of TMS response in unipolar and/or bipolar depression. Specifically, protocols that prioritize the use of dTMS or iTBS and that limit treatment augmentation, including pharmacotherapy. Further biomarker research is also heavily needed within schizophrenia and mild-to-moderate Alzheimer's disease and TMS response, to identify mechanistic and predictive biomarkers. Identifying TMS-EEG and resting-state biomarkers of treatment response to TMS are of great importance to expand the field of precision psychiatry. TMS-EEG and resting-state EEG are comparatively inexpensive, making them optimal methods for identifying predictive biomarkers in the healthcare setting. Thus, future clinicians could incorporate TMS-EEG or resting-state EEG into their clinical toolbox as an effective method at determining the appropriateness of a given patient for TMS treatment.

CONCLUSION

The present systematic review analyzed TMS-EEG and resting-state biomarkers of treatment response to TMS across psychiatric and neurocognitive disorders. Three potential biomarkers were identified in patients with unipolar and/or bipolar depression: (1) a mechanistic biomarker of decreased theta connectivity post-DLPFC rTMS for unipolar and bipolar depression, (2) a mechanistic biomarker of N100 reductions post-DLPFC rTMS and iTBS for unipolar depression. and (3) a predictive biomarker of greater baseline N100, in DLPFC rTMS and iTBS, predicting for unipolar depression improvement. Further research should aim to explore mechanistic and predictive biomarkers of TMS response in patients with Alzheimer's disease and schizophrenia.

DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.120194

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Chapter 3.

Electroencephalographic Biomarkers of Deep Transcranial Magnetic Stimulation Treatment Response for Major Depressive Disorder in Older Adults: A Preliminary Study

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Context: This chapter will attempt to identify resting-state electroencephalographic (EEG) biomarkers of treatment response to deep transcranial magnetic stimulation (TMS) for major depressive disorder (MDD) in older adults. Several preliminary biomarkers were identified.

Implication: The current research on EEG biomarkers within TMS and MDD is greatly lacking among older adults, with this manuscript being the first. Hopefully our study will inspire hypothesis-driven research to be undertaken, advancing precision medicine in geriatric psychiatry.

ABSTRACT

Major depressive disorder (MDD) in older adults can result in detrimental health consequences and often presents with resistance to antidepressant treatment. While Hesed-coil 4 (H4) and 7 have shown great promise in the treatment of MDD in older adults, not all participants will respond. Establishing biomarkers to predict individual treatment responses and to better understand how these coils work to treat MDD in older adults is essential. Resting-state electroencephalography (rsEEG), a cost-effective technique, has been previously used to identify response biomarkers to psychiatric treatments. This study therefore aims to identify rsEEG biomarkers of response to the H4 and H7 coils in older adults with MDD.Twenty-one older adults with treatment-resistant MDD were randomly assigned to undergo 20 sessions of either H4 or H7 coils. rsEEG recordings were ascertained at baseline and posttreatment, along with the 24-item Hamilton Depression Scale (HDRS-24). Although none of the effects remained significant after correction, several preliminary biomarker patterns emerged. Higher baseline gamma power at Fp1 and F4 predicted a lower likelihood of treatment response. Similarly, an increase in F4 and P3 alpha power was associated with smaller improvements in the HDRS-24. However, increased theta power at F7 and across multiple cortical regions were associated with greater reductions in the HDRS-24.This study identified preliminary rsEEG biomarkers of H4 and H7 coil response in older adults with MDD, providing initial proof-of-concept. Therefore, these findings can help guide hypothesis generation in future research. With larger sham-controlled trials needed for definitive characterization and validation.

INTRODUCTION

Depression is a substantial contributor to poorer health outcomes among older adults who experience higher mortality rates and a greater risk of disability and suicide (Patel et al., 2023; Rodda et al., 2011). Antidepressant medication is a frontline treatment for older adults with major depressive disorder (MDD), but only approximately one third of seniors reach remission when prescribed such medications (Kok & Reynolds, 2017; Roose & Schatzberg, 2005). With a greater risk for falls with antidepressant augmentation and transient cognitive side effects of electroconvulsive therapy in elderly patients, it is important to investigate alternative treatment options for depression in older adults (Meyer et al., 2018; Lenze et al., 2023).

Non-invasive neurostimulation techniques have become popular over the past decade for the treatment of MDD, with such techniques including repetitive transcranial magnetic stimulation (rTMS) (Lam et al., 2024). Through the use of a figure-8 coil, rTMS is able to emit focalized repeated pulses of magnetic energy up to 4 cm's below the scalp (Milev et al., 2016; Lam et al., 2024). rTMS has been proven to not only be an effective treatment for MDD in younger adults, but it has also been shown to be an effective treatment for MDD in older adults (Valiengo et al., 2022; Lam et al., 2024). Deep transcranial magnetic stimulation (dTMS) is a novel Food and Drug Administration (FDA) and Health Canada approved treatment for major depressive disorder (MDD), that evolved from rTMS (Filipčić et al., 2019). Utilizing electromagnetic coils, dTMS can emit a broad current capable of stimulating numerous regions of the brain at a depth of ~6 cm's below the scalp, dependent on the Hesed-coil (H-coil) being used, unlike rTMS (Deng et al., 2014; Parazzini et al., 2017; Roth et al., 2002, 2007; Roth & Zangen, 2014; Tendler et al., 2016).

Initially, research focused on evaluating the efficacy of H-coil 1 (H1) for treating MDD in older adults (Kaster et al., 2018; Roth et al., 2024). Recently, our team conducted a novel pilot trial assessing the tolerability and feasibility of the H4 and H7 coils, with a secondary focus on their efficacy within this population (Duarte et al., 2025). Notably, these coils were originally FDA and Health Canada approved for smoking cessation (H4 coil) and obsessive-compulsive disorder (H7 coil) (Harmelech et al., 2021; Zangen et al., 2021). In the pilot trial, both coils resulted in significant reductions in depressive symptoms, with

posttreatment response rates of 66.7% for the H4 coil and 50% for the H7 coil (Duarte et al., 2025). The H4 coil targets the lateral insula and prefrontal cortex (PFC), while the H7 coil stimulates the bilateral anterior cingulate cortex (ACC) and medial PFC (Harmelech et al., 2021; Zangen et al., 2021). Symptoms of apathy in older adults with MDD have been linked to decreased functional connectivity in the dorsal ACC and increased connectivity within the insula (Alexopoulos et al., 2013). Additionally, older adults with treatment-resistant MDD have exhibited reduced fractional anisotropy in both the dorsal and rostral ACC, as well as within the white matter of the insula (Alexopoulos et al., 2008). Moreover, age-related brain atrophy may also necessitate deeper stimulation to reach critical structures (Fregni et al., 2006; Manes et al., 2001). These findings suggest that the H4 and H7 coils could be ideal for treating treatment-resistant MDD in older adults. However, not all geriatric patients respond, underscoring the importance of identifying biomarkers of treatment response (Duarte et al., 2025). While H4 and H7 coils hold great promise for older adults with MDD, understanding the mechanisms underlying treatment success and variability is crucial for advancing this therapy.

Electroencephalogram (EEG) is a relatively cost-effective and non-invasive recording technique with high temporal sensitivity, used to examine neural activity via electrodes placed on the scalp (Freeman et al., 2003; Newson and Thiagarajan, 2019). EEG has been found to be a promising technique for use in rTMS biomarker discovery in MDD (Klooster et al., 2024; Strafella et al., 2022). Literature within the younger population suggests that task-state frontal-midline theta power, as a predictive biomarker (PB), and resting-state theta connectivity, as a mechanistic biomarker (MB), hold promise as biomarkers of treatment response to rTMS for MDD (Godfrey et al., 2024; Klooster et al., 2024; Strafella et al., 2022). Among older adults generally, neural oscillations (e.g., alpha) appear to change with aging in cognitively healthy and declined older adults (Hogan et al., 2011; Moezzi et al., 2019).

One of the most preferred recordings techniques of EEG is resting-state EEG (rsEEG), where participants are instructed to have their eyes closed or open, but to "not think of anything in particular". To our knowledge, no known studies have explored the use of rsEEG in older adults with MDD undergoing TMS treatment. EEG biomarkers of great interest pertain to predictive and mechanistic biomarkers — markers that directly examine underlying biological features of treatment response. While MBs can

identify pathophysiological changes modulated by a given treatment, PBs assess the likelihood of a patient responding to a given treatment based on pre-interventional, baseline characteristics (Cagney et al., 2018; Robinson et al., 2013; Rush & Ibrahim, 2018). Only one dTMS (H1 and H7) study, using the H1 and H7 coils, has examined EEG biomarkers in younger adult MDD (Zangen et al., 2023). In this study, potential PBs were established for the H1 coil via greater baseline medial alpha and medial low-gamma waves recorded at rest.

The current literature suggests that the H4 and H7 coils are promising candidates for the treatment of MDD in older adults, but not all patients will respond. Furthermore, EEG has played a pivotal role in identifying potential predictive and mechanistic biomarkers of rTMS response in younger adults with MDD, yet only one other study has examined such markers in dTMS (Zangen et al., 2023). To address these gaps, this study aims to examine the potential of rsEEG to identify predictive and mechanistic biomarkers of treatment response to the H4 and H7 dTMS coils in older adults with MDD.

METHODS

2.1. Study Design and Participants

This study was a part of a randomized, phase I open-label, pilot trial (registered on clinicaltrials.gov (NCT05855850)) conducted at the Peter Boris Centre for Addictions Research, at St. Joseph's Healthcare Hamilton, located in Hamilton, Ontario (Duarte et al., 2025). Eligible participants were between the ages of 60 to 85; had a primary diagnosis of MDD, in agreement with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); scored ≥ 20 on the Hamilton Depression Rating Scale 24-Item (HDRS-24); had a history of antidepressant treatment resistance indicated by either one failed adequate trial or two inadequate trials; and had a stable dose of a psychotropic medication for minimum four weeks. Individuals were excluded if they scored < 24 on the Mini Mental State Examination (MMSE); had a pacemaker and/or implantable cardioverter-defibrillator; a history of epilepsy or seizures; and hearing and visual impairments that could affect their ability to fully participate in the study. For a complete list of inclusion and exclusion criteria, please refer to the Supplementary Material (Table S1).

In total, 21 participants comprised the intent-to-treat (ITT) sample and were randomized to undergo a total of 20 sessions (per session: 55 trains, 2 second train, 20 second inter-train interval and 1980 pulses), lasting 20 minutes each, of either H4 (n = 11) or H7 (n = 10) of the dTMS BrainsWay device (BrainsWay™ Ltd. Jerusalem, Israel), over the course of four weeks. A follow-up session was completed two weeks after the end of treatment. Participants received 18Hz stimulation, in which their resting motor threshold progressively increased to 120% throughout the duration of the trial. Over the course of the treatment, two individuals from the H7 condition discontinued treatment due to a feeling of exacerbated dizziness and subjective increase in MDD symptoms, resulting in a sample of 19 older adults.

2.2. EEG Recording and Processing

rsEEG recordings were collected at baseline and at the end of each treatment week for four weeks (including post-treatment), yielding a total of five sessions. Data were acquired with the 20-channel Quick 20r V2 system (CGX, San Diego, California) which employs an international 10-20 system. Data was recorded using BrainVision software, and each session consisted of five-minute recordings under both eyes-open and eyes-closed conditions. Participants were instructed to think of nothing in particular and to let their mind wander while avoiding any kind of cognitive functions. Recordings were sampled at 500 Hz with the left earlobe (A1) serving as the reference electrode. The current analysis is limited to the eyes-closed recordings, due to the decreased likelihood of noise in specific frequency bands (e.g., theta; Hagemann & Naumann, 2001). The EEG data were preprocessed using NEAT, an automated pipeline built on EEGLAB functions (Schwartzmann et al., 2025). More information regarding the cleaning process can be found in the Supplementary Material (Data S1).

2.3. EEG Analysis

Power spectral density (PSD) between 1 to 50 Hz, selected in accordance with Schwartzmann et al. (2025) who recently established standards for EEG biomarker-informed trials for MDD across multiple sites, was estimated using Welch's method with a frequency resolution of 0.5 Hz and periodograms computed from overlapping 2-second windows. Relative power (RP) for each channel was then derived

by dividing the absolute PSD within each frequency band by the total absolute PSD across all frequency bands; delta (1–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta (12.5–30 Hz) and gamma (30.5–50 Hz).

2.4. Brain Region Segmentation

Electrodes were grouped into six regions based on the International 10–20 system: prefrontal (Fp1, Fp2), dorsolateral prefrontal (DLPFC; F3, F4), ventrolateral prefrontal (VLPFC; F7, F8), midline frontal (Fz, Cz), temporal (TC; T3, T4, P7, P8), and parietal (PC; C3, C4, P3, P4, Pz; Li et al., 2024).

2.5. Clinical Outcome Measures

Depression severity was assessed using the HDRS-24, administered at baseline, weekly during the four-week treatment period (including post-treatment), and at follow-up. For this analysis, only baseline and post-treatment HDRS-24 scores were considered. Predictive and mechanistic biomarkers were evaluated using baseline and post-treatment HDRS-24 scores, defining treatment response as ≥50% symptom reduction for predictive outcomes, and change in HDRS-24 scores from pre-to post-treatment for MBs.

2.6. Statistical Analyses

Statistical analyses were conducted using R version 4.4.1., SPSS and Microsoft Excel. Normality was addressed using logarithmic transformations where necessary (Data S2). Independent-samples t-tests and Chi-squared tests were conducted to compare demographic and clinical characteristics of participants between treatment coils.

To evaluate potential PBs, one analysis was conducted. A logistic regression was used to test whether baseline RP predicted posttreatment responder status, with H-coil included as a fixed effect. To evaluate potential MBs two analyses were conducted. First, a linear mixed-effects model was used to examine whether RP changed over time with treatment and whether this differed by H-coil (H4 vs. H7), with fixed effects for time, H-coil, and their interaction (Time × H-Coil), and a random intercept for participant. Second, Pearson correlations were performed to assess whether changes in RP (ΔRP) were associated with reductions in depression severity. Statistical significance was defined as $p < .05$, with $p \leq .075$ considered a trend. To reduce the number of comparisons, analyses were conducted primarily at

the region level, with results corrected for multiple testing using a False Discovery Rate (FDR) procedure; electrode-level correlations were examined as well, with their corresponding tables found in the Supplementary Material.

RESULTS

3.1 Demographics & Clinical Characteristics

Twenty-one participants (ITT sample) were originally enrolled in the trial, with 2 participants dropping out and an additional 2 participants removed due to poor quality EEG data, leading to a per-protocol (PP) sample of 17 participants evaluated in total. All 17 participants (H4, n = 8; H7, n = 9) completed the baseline and posttreatment EEG recordings.

There were no statistically significant differences by age (p = .932), sex (p = 1.00) or ethnicity (all participants were Caucasian) between H-coils at baseline (Table 1). However, H7 participants appeared to have a higher education and income level, as well as all being retirees, when compared to H4 participants, though these observations were not statically significant (p = .303 - .475). In respect to clinical characteristics, there were no significant differences between H-coils except in respect to the MMSE (t = 3.83, p = .003). With H7 participants on average performing two points lower on the MMSE when compared to H4 participants (H4: 29.56 ± 0.73; H7: 27.33 ± 1.58). Among PP responders, it appeared that H4 had a greater percentage of participants who responded to treatment (62.5%) as compared to H7 (55.6%; Table S2). Once again, this observation was not statistically significant (p = .772). Lastly, there were no significant differences across medication use in the PP sample (Table S2). Although a greater number of H7 participants took antidepressants, this was not statistically significant ($p_{Posttreatment}$ = .110).

Table 1. Participant Demographics and Clinical Characteristics

Variables	Sample			t/X^2	p
	Whole Sample (n = 18)	H4 (n = 9)	H7 (n = 9)		
		Demographics			
Age, M ± SD	70.22 ± 5.26	70.11 ± 6.17	70.33 ± 4.56	-0.09	.932
Sex, % Female	66.7	66.7	66.7	0.00	1.00

Ethnicity, % Caucasian	100	100	100	-	-
Education Level, Median	Associate's Degree	Some College/University	Bachelor's Degree	4.53	.475
Employment Status, % Retired	94.4	88.9	100	1.60	.303
Income (CAD), Median	$60K – $75K	$45K – $60K	$75K – $90K	8.33	.304
Clinical Characteristics					
Baseline HDRS-24, M ± SD	29.78 ± 4.75	29.33 ± 6.00	30.22 ± 3.38	-0.39	.705
Baseline MMSE, M ± SD	28.44 ± 1.65	29.56 ± 0.73	27.33 ± 1.58	3.83	.003
Responders, % [N]	58.8 [10]	62.5 [5]	55.6 [5]	.084	.772

Abbreviations: CAD = Canadian Dollar; HDRS-24 = 24-Item Hamilton Depression Rating Scale; MMSE = Mini Mental State Examination

3.2 Predictive Biomarker Analysis

At the region level, no significant associations were observed between baseline RP and responder status (Tables S7). At the electrode level, logistic regression analyses identified significant effects for Fp1 (*Stdz. β* = -1.854, *p* = .042) and F4 gamma (*Stdz. β* = -1.503, *p* = .043), but neither remained significant after correction for multiple comparisons (adjusted *p* = .294 and .151, respectively; Table S8).

3.3 Mechanistic Biomarker Analysis

A linear mixed-effects model showed no main effects of time, H-coil or either interaction (Time x H-Coil) on RP at the region level (Table S3). Electrode-level analyses revealed an effect of time at F8 alpha (*p* = .045, η_p^2 = 0.242) and a time x H-coil interaction at Fp2 beta (*p* = .030, η_p^2 = 0.276), P3 beta (*p* = .022, η_p^2 = 0.305), and P7 gamma (*p* = .047, η_p^2 = 0.238; Figure S1; Table S4). Results were not significant following FDR correction (adjusted *p* > .15). At the region level, Pearson correlations revealed significant positive associations between changes in RP and reductions in depression severity in the VLPFC (*r* = 0.488, *p* = .047), temporal cortex (*r* = 0.483, *p* = .049), and parietal cortex (*r* = 0.498, *p* = .042) theta bands (Table S5; Figure 1). At the electrode level, significant negative correlations were observed at F4 (*r* = -0.571, *p* = .017) and P3 (*r* = -0.551; *p* = .022) alpha, and a positive correlation at F7

(*r* = 0.49, *p* = .046) theta (Table S6; Figure 1). Visualizations of the Pearson correlations across the cortex can be seen in Figure 2. However, none of these associations remained significant after correction for multiple comparisons (all adjusted p > .09).

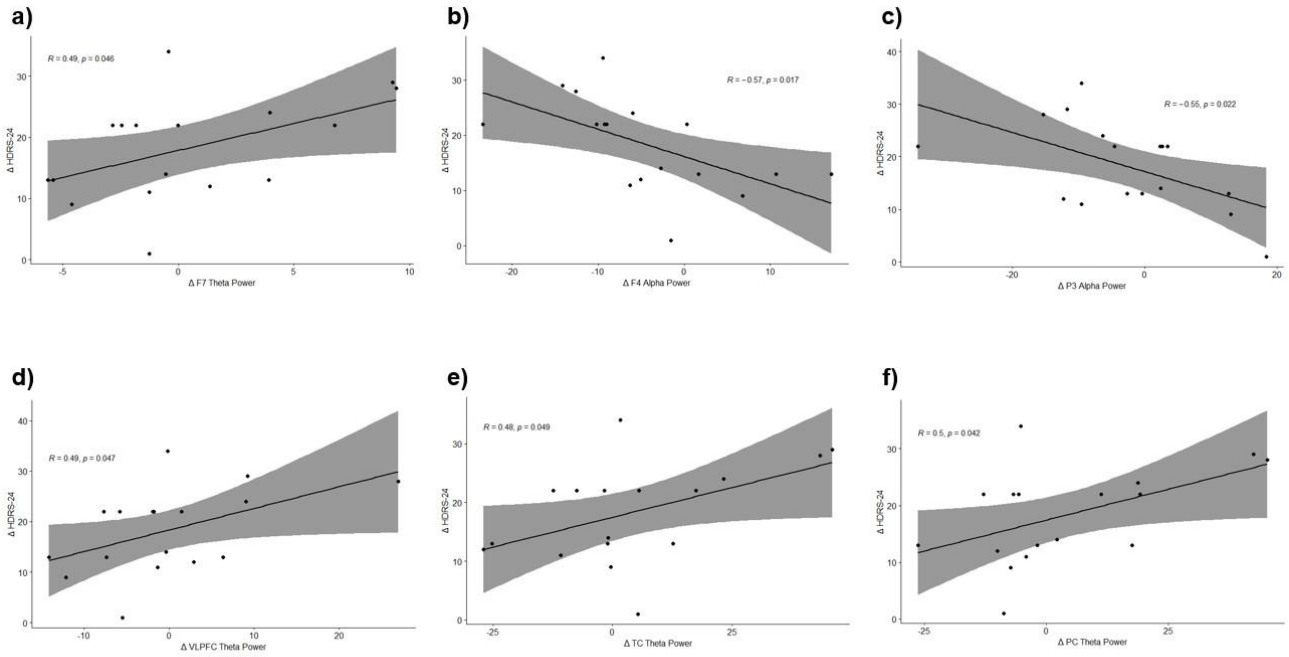

Figure 1. Scatter plot of significant Pearson correlations. a) Positive correlation between the reduction in the HDRS-24 and the change in F7 theta power. b) Negative correlation between the reduction in the HDRS-24 and the change in F4 alpha power. c) Negative correlation between the reduction in the HDRS-24 and the change in P3 alpha power. d) Positive correlation between the reduction in the HDRS-24 and the change in VLPFC theta power. e) Positive correlation between the reduction in the HDRS-24 and the change in TC theta power. f) Positive correlation between the reduction in the HDRS-24 and the change in F7 theta power.

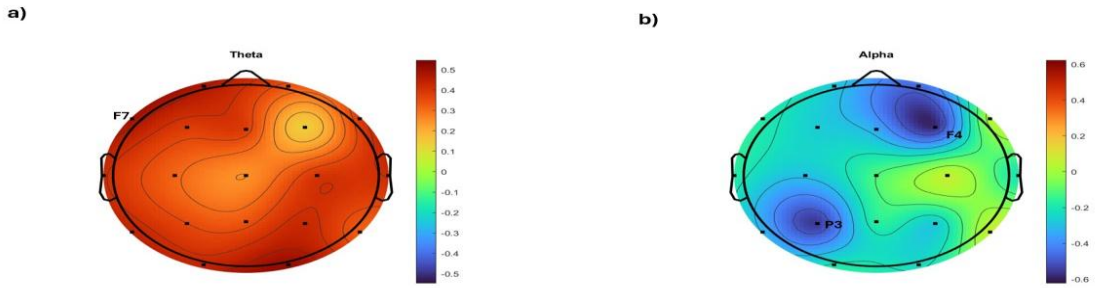

Figure 2. Topographic plots of significant Pearson correlations. a) Significant theta correlations. b) Significant alpha correlations.

DISCUSSION

This exploratory investigation examined both predictive and mechanistic rsEEG biomarkers of treatment response to H4 and H7 dTMS H-coils in older adults with MDD. Due to the studies' limited statistical power, no potential biomarkers could be identified, though promising preliminary markers were observed for future investigation.

Two promising preliminary biomarkers were identified within the gamma band. Two PBs were observed at electrodes Fp1 and F4, in which greater baseline gamma RP at Fp1 and F4 were predictive of a lower likelihood of one responding to dTMS regardless of H-coil. One mechanistic finding was also identified at electrode P7 in the gamma band, with reductions in RP for participants randomized to H7 and increases for those who received H4. Though limited statistical power prevented us from conducting this analysis based on responder status. However, considering these preliminary findings, depressed older adults with greater baseline gamma power, at electrodes Fp1 and F4, may be less likely to respond to dTMS. Intriguingly, these results align with previous research identifying rsEEG biomarkers of dTMS response, in a 143-participant sample. In a study by Zangen et al. (2023) it was found that depressed younger adults who had greater baseline medial low-gamma power were also less likely to respond to H1 dTMS; though, current source density referencing was utilized. This may suggest that regardless of age depressed patients who present with greater baseline gamma power are less likely to respond to dTMS.

Although no significant findings were found in relation to H7, depression severity and resting-state gamma in Zangen et al.'s analysis. This underscores the potential of baseline gamma power as a screening tool for dTMS treatment in MDD, advancing the goal of precision medicine in psychiatry. Alternatively, when applying left DLPFC rTMS in younger and middel-aged adults with MDD, an increase in F3 absolute gamma power over the course of treatment was correlated with an improvement in depression symptoms in a 31-participant sample (Noda et al., 2017). Suggesting that in prefrontal cortex TMS an increase in gamma power throughout treatment, as opposed to an initial presentation of greater baseline gamma power, may be indicative of a better treatment outcome regardless of age.

In respect to older adults, gamma oscillations have been previously implicated in the aging brain. Gamma functional activity was observed to possibly reduce age, as a study by Moezzi et al. (2019) found that older adults had decreased gamma connectivity when compared to younger adults. However, artifacts may have disrupted reliable interpretation of the gamma results. Moreover, when completing a visual paired-associates task, younger adults had increased gamma coherence within frontal–parietal networks when compared to healthy older adults and cognitively declined older adults (Hogan et al., 2011). Interestingly, regardless of age, low gamma power may contribute to the pathophysiology of MDD as a whole. Roh et al. (2016), found that fronto-central low-gamma power was linked to attention deficits in individuals with MDD. In a mouse model, Yin et al. (2024) observed that reductions in medial prefrontal gamma corresponded with depressive behaviours. Based on our findings, along with the existing evidence that gamma activity tends to reduce with age and that MDD appears to be associated with reductions in gamma activity, older adults with lower baseline gamma power may have a greater likelihood of responding to TMS treatment more broadly.

For the alpha band, two preliminary biomarkers were identified. Two MBs were observed at electrodes F4 and P3, where an increase in F4 and P3 alpha RP was associated with a smaller improvement in HDRS-24 scores. Another mechanistic finding was observed at electrode F8 in the alpha band, where reductions in RP were seen in both H-coils. Once again, limited statistical power prevented us from conducting this analysis based on responder status. Nonetheless, an increase in RP at electrodes F4 and P3 alpha may be indicative of smaller improvements in depressive symptoms in older

adults undergoing dTMS. Conversely, in the same study by Zangen et al. (2023) it was observed that greater baseline medial alpha power was associated with increased clinical efficacy in H1. Once again, nothing of significance was found in the H7 rsEEG. These inconsistencies could reflect the influence of age and or the H-coil on alpha oscillations and dTMS response, or the limited power of the current study.

In older adults, alpha oscillations have been shown to potentially play a significant role in brain aging. Reductions in alpha coherence and connectivity may contribute to both healthy and pathological age-related changes, particularly within frontal, parietal and temporal regions (Fischer et al., 2023; Meghdadi et al., 2021; Moezzi et al., 2019; Vysata et al., 2014). Higher alpha coherence has been associated with better executive functioning, and when comparing depressed older adults to non-depressed younger and older groups, those with depression exhibited poorer executive function (Wang et al., 2017; Basharpoor et al., 2019). Notably, in studies of younger adult MDD, decreases in alpha activity over the course of either escitalopram, cognitive behavioral therapy or electroconvulsive therapy were primarily indicative of a positive treatment outcome (Hill et al., 2020; Schwartzmann et al., 2023, 2024). Such findings discussed suggest that in younger adult MDD, decreases in alpha activity may indicate positive treatment outcomes across varying treatment modalities. Conversely, in older adults, where alpha activity naturally diminishes with age and is associated with declines in executive function particularly in depressed older adults, an increase in alpha activity might represent a favorable response to treatments such as dTMS.

For theta oscillations, several preliminary MBs were isolated: increased theta RP at electrode site F7 and regions VLPFC, PC and TC, were associated with a more pronounced improvement in HDRS-24 scores. Theta connectivity and coherence have been found to potentially decline with age (Moezzi et al., 2019; Vysata et al., 2014), with reductions in theta coherence also observed in Alzheimer's disease (Fischer et al., 2023). Interestingly, greater frontal theta RP has been associated with healthier cognitive function in older adults (Finnigan & Robertson, 2011). However, greater frontal-posterior theta connectivity has been associated with poorer working memory performance in older adults as well (Fleck et al., 2016). Although the research is heterogeneous, much like alpha activity, increases in theta activity may also represent a greater likelihood of a favorable response to dTMS in older adults.

No preliminary biomarkers were identified in beta or delta oscillations. However, at Fp2 and P3 beta, pre-to-posttreatment reductions in RP were observed in participants randomized to the H4-coil, whereas increases in RP were found in the H7-coil condition.

The current analysis has several limitations. Due to the exploratory nature of the study, a hypothesis-driven analysis was not conducted, thus limiting the ability to rigorously cross-examine and confirm findings within the current literature. To mitigate potential spurious associations resulting from the exploratory approach, FDR corrections were applied. As mentioned, significant results were obtained but did not survive after FDR corrections for multiple comparisons. This is likely attributable to the inflation of type II error, particularly given the small sample size (N =17) and the relatively high number of comparisons corrected for. As a result of the low statistical power, the analysis of differences in potential biomarker expression between H-coils could not be conducted as well. Moreover, due to the absence of a sham control group, direct comparisons between neurophysiological findings in active dTMS versus sham conditions could not be performed. It is also important to note that since the current study used a 20-electrode system, the relatively low spatial resolution may have reduced the sensitivity to detect effects at the brain region level. Partly explaining the lack of robust regional findings. Nevertheless, this study will serve as a foundation for hypothesis generation in future research investigating predictive and mechanistic biomarkers of dTMS treatment response in MDD in older adults, as well as MDD as a whole.

Future research should consider further analyzing the treatment efficacy of H4 and H7 coils for MDD in older adults through larger, blinded, sham-controlled trials. Furthermore, additional research is warranted to identify rsEEG biomarkers for dTMS overall. Currently, this study represents one of the few papers contributing to the preliminary investigation of EEG biomarkers of dTMS treatment response in psychiatric conditions. Collectively, additional research is needed to isolate reliable rsEEG biomarkers, particularly focusing on alpha and gamma oscillations, that can predict dTMS response and help us deepen our understanding of the neural mechanisms through which dTMS acts on older adult MDD. Such biomarkers could significantly improve treatment outcomes for older adults with treatment-resistant depression and in turn elevate burden on the healthcare system.

CONCLUSION

The present study investigated potential predictive and mechanistic rsEEG biomarkers of treatment response to dTMS (H4 and H7 coils) in older adult MDD. While the findings did not withstand FDR correction, region- and electrode-level MBs emerged, alongside two electrode-level patterns with predictive potential. Alpha and gamma bands showed the greatest promise as future targets for dTMS response, particularly within the frontal and parietal lobes, with theta also demonstrating some potential. Continued research is necessary to validate these preliminary predictive and mechanistic biomarkers in larger, sham-controlled trials for their potential applications in clinical practice.

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Chapter 4. Discussion

Major depressive disorder (MDD) is a debilitating condition with a substantial global burden. As outlined earlier, treatment-resistant depression (TRD) is a significant challenge for both clinicians and patients, often resulting in unsuccessful outcomes or prolonged, complex treatment plans. Neurostimulation through transcranial magnetic stimulation (TMS) has emerged as a promising treatment option for individuals with MDD; however, this treatment can be further refined by establishing neural signatures that can predict TMS response, as well as mechanistic biomarkers that can clarify the mechanisms of TRD. This need is further highlighted in older adults, as geriatric patients are at an elevated risk of experiencing TRD. Electroencephalography (EEG) is an inexpensive and non-invasive tool that can be employed to assess both predictive and mechanistic biomarkers and address these critical gaps, leading to an enhanced understanding of MDD and the factors underlying treatment success.

To address these issues, the present thesis aimed to identify potential predictive and mechanistic EEG biomarkers of treatment response to TMS in MDD. In Chapter 2, predictive and mechanistic TMS-EEG and resting-state biomarkers were investigated across several conditions, including MDD and across three modalities of TMS, within younger-to-middle aged adults. In Chapter 3, resting-state EEG was used to assess for predictive and mechanistic biomarkers of treatment response to deep TMS (dTMS) in a geriatric depression.

Due to the limited literature on TRD and/or older adults, this section primarily draws from studies focusing on either MDD and/or younger-to-middle aged adults, while integrating findings related to TRD and/or older adults were available. As well, the discussion section will primarily focus on the results pertaining to the resting-state findings and will briefly cover the findings related to TMS-EEG.

4.1. Mechanistic Biomarkers

4.1.1. Theta Oscillations

In Chapter 2, significant reductions in theta connectivity, at rest, particularly within the frontal, temporal and parietal regions, were found to be a mechanistic biomarker for rTMS treatment success for

MDD, primarily among younger to middle-aged adults (18 – 70 years old; Godfrey et al., 2024; Kazemi et al., 2022). In the study by Kazemi et al. (2022), the unilateral rTMS group had a mean age of 34.0 whereas the bilateral group had a mean age of 32.0. With Grodfrey et al.'s study, mean age being higher at 42.8 years old.

However, in chapter 3 a significant increase in theta power, at both the region level (ventrolateral prefrontal cortex [VLPFC], as well as the parietal and temporal cortices) and electrode level (F7 [left VLPFC]), following dTMS was observed to be a potential preliminary mechanistic biomarker related to a greater reduction in depressive symptoms among older adults (M_{age} = 70.22).

4.1.1.1. Assumptions: Theta Connectivity

In this section assumptions will be made utilizing the current literature, to better understand the results of chapter 2 by examining research related to the frontal, parietal and temporal cortices and these regions relationship to both MDD and the behaviours associated with the condition. Furthermore, the brain region targeted by rTMS (i.e., DLPFC) will be examined along with the cognitive functions associated with the theta frequency band. Though not directly assessed in chapter 2, behaviours such as rumination and emotion regulation as well as cognitive processes such as working memory will be examined, given the current literature implicating such behaviours in the structures listed above, the theta frequency band and/or MDD. Although, rumination was directly explored in Kazemi et al.'s (2022) paper, it was not examined in Godfrey et al.'s (2024).

Considering all the findings, theta connectivity appears to play a role in DLPFC rTMS response in individuals with TRD and MDD in general. Specifically, in chapter 2, a reduction in theta connectivity among younger-to-middle-aged adults is associated with a decrease in depression severity after DLPFC rTMS treatment. When considering the location of these findings, the effects were largely concentrated in the frontal, parietal and temporal regions of the brain, also referred to as the "frontomidline regions".

The frontal, parietal and temporal cortices are all interconnected through the default mode network (DMN; Raichle & Snyder, 2007) in which the DMN has been implicated in recurrent MDD and TRD (Sun et al., 2023; Yan et al., 2019) and more specifically the symptom of rumination (Zhou et al.,

2020). Similar to the findings in Chapter 2, greater baseline frontomidline theta connectivity, during a working memory (WM) task, has been found to be a potential predictive biomarker of treatment response to DLPFC rTMS (Bailey et al., 2018; Li et al., 2016; Li et al., 2021). With it being suggested that the DMN may play a role in WM, with symptoms like rumination contributing to WM deficits as well (Bruning et al., 2023; Sambataro et al., 2010; Vatansever et al., 2017; Yuan et al., 2021).

Theta oscillations are believed to play a role in WM (Klimesch, 2018), including affective WM which appears to be a key cognitive deficit in MDD (Christopher & MacDonald, 2005; Rose & Ebmeier, 2006; Songco et al., 2023). Notably, increased frontal theta connectivity during WM tasks have been associated with worsening MDD symptoms (Fingelkurts et al., 2007; Steinmann et al., 2024). Additionally, individuals with TRD also exhibit WM deficits (Vancappel et al., 2021). MRI research has shown similar findings, identifying increased lateral PFC activation, during WM tasks, could be a possible diagnostic feature of MDD (Wang et al., 2015). As previously mentioned, a subset of depressed patients exhibiting increased frontomidline theta connectivity, during WM tasks, have been observed to respond well to DLPFC rTMS (Bailey et al., 2015; Li et al., 2016, 2021).

As identified in Chapter 2, reductions in theta connectivity were related to an improvement in depressive symptoms (Kazemi et al., 2022; Godfrey et al., 2024). This observation may be reflective of the subset of depressed younger-to-middle aged patients who display an increase in frontomidline theta connectivity. Consequently, as theta connectivity diminishes within frontomidline areas of the brain during DLPFC rTMS treatment, improvements in depressive symptoms may occur, potentially facilitated by enhancements in WM. Moreover, functions such as emotion regulation, which is processed within the DLPFC and often impaired in MDD, have been associated with WM (Xiu et al., 2018). Additionally, it is important to note that both the temporal and parietal cortex have been implicated in MDD (Aston et al., 2005; Cheng et al., 2018; Kane et al., 2019; Shen et al., 2015), as well as WM (Tang et al., 2025; Woloszyn & Sheinberg, 2009).

Though, the relationship between rumination and rTMS response is not completely clear. In the study by Kazemi et al. (2022), it was discovered that responders in both unilateral and bilateral conditions had shown reductions in both reflective rumination (i.e., attempting to rationalize distress and emotions;

Wei et al., 2024), brooding rumination, and total score in Rumative Response Scale. Notably, in the theta band of the bilateral condition, a significant positive correlation between frontotemporal theta connectivity and reflective rumination, and a significant negative correlation between frontoparietal theta connectivity and brooding rumination was seen in responders. On the other hand, in the unilateral condition, increased theta connectivity between temporal and frontal electrodes was associated with decreased reflective and brooding rumination.

Research suggests that increased frontal, including frontomidline, theta activity may be related to greater WM load but not necessarily improved WM performance (Jensen & Tesche, 2002; Maurer et al., 2015). It is plausible that an increase in WM load could be reflective of the increased effort required to cope effectively with symptoms of rumination, via reflection rather than brooding. A study by Poormohammad et al. (2025) found that an increase in frontotemporal theta coherence in depressed participants may be associated with improved cognitive control and emotion regulation, in which WM may play a role in. Given that elevated theta activity does not necessarily indicate greater WM, this may explain why some participants demonstrated a decrease in both healthy (reflective) and unhealthy (brooding) ruminative coping strategies.

As previously discussed, some majorly depressed individuals have decreased parietal theta (Kane et al., 2019; Tang et al., 2025) as well as reduced frontal theta connectivity (Steinmann et al., 2024). While under acute stress, a study by Gärtner et al. (2014) also found that healthy males exhibited greater deficits on a challenging section of the n-back task, which was associated with a decrease in frontal theta activity. These subsets of depressed patients, decreased theta versus increased theta activity, could potentially represent subtypes of MDD, that could be differentiated via WM tasks.

4.1.1.2. Assumptions: Theta Power

In this section assumptions will be made utilizing the current literature, to better understand the results of chapter 3 by examining research related to the ventrolateral PFC (VLPFC), parietal and temporal cortices and these regions relationship to both MDD and the behaviours/cognitive functions associated with the condition. Furthermore, regions also targeted by the H4 and H7 coils will be examined along with behaviours associated with the theta frequency band. Though not directly assessed in chapter

3, behaviours such as emotion regulation and working memory will be examined, given the current literature implicating such behaviours in the structures listed above, the theta frequency band and/or MDD.

In chapter 3, though none of the results survived correction (i.e., $p > .09$), several preliminary mechanistic biomarkers were identified, reflecting increases in relative theta power in the ventrolateral PFC (VLPFC), temporal and parietal cortex, as well as the electrode site F7; it is important to note that effect sizes were moderate (i.e., 0.483 – 0.498). These increases were associated with a greater reduction in HDRS-24 scores following H4 and H7 dTMS in geriatric depressed participants.

Though emotion regulation was not assessed in chapter 3, the literature suggests that the VLPFC is believed to play an indirect role in emotion regulation (Kohn et al., 2014), with the left VLPFC, the site of electrode F7, believed to potentially be involved in cognitive reappraisal in depressed individuals (Keller et al., 2021). Regardless of age, younger-to-older adults with greater depressive symptoms were more likely to engage in maladaptive emotion regulation strategies (Nolen-Hoeksema & Aldao, 2011). As previously mentioned, the theta frequency band is thought to contribute to working memory (though, not assessed in chapter 3; Klimesch, 2018; Tremblay et al., 2019), which has been associated with emotion regulation and, more specifically, cognitive reappraisal (Andreotti et al., 2013; Xiu et al., 2018). Reductions in the left VLPFC, identified via near-infrared spectroscopy, have been associated with MDD in younger adults (Lee et al., 2021). Additionally, the VLPFC has also been suggested to potentially mediate the relationship between the severity of both suicidal ideation and depression (Lee et al., 2021). More generally speaking, the insula (H4 coil target), modulated by the VLPFC, has been shown to play a role in emotional regulation (Fig. 1a; Veit et al., 2012). More specifically, increased functional connectivity between the right VLPFC and right insula have been implicated in cognitive reappraisal as well (Fig 1a; Yang et al., 2021), with gray matter reductions in right VLPFC being associated with suicidal ideation in patients with MDD (Zhang et al., 2020). Preliminary research also suggests that the VLPFC may be involved in the salience network, in which the ACC (H7 coil target) and insula are both a part of (Trambaiolli et al., 2022), with the salience network being involved in MDD as well (Lynch et al., 2024).

It is possible, a subset of patients with MDD may experience an increase in theta power within the VLPFC and/or left VLPFC (F7) when treated with the H4 or H7 dTMS coils. This increase in theta power could improve emotion regulation capabilities, such as cognitive reappraisal, in depressed individuals. With this potential improvement in symptoms of emotional regulation possibly facilitated by the theta frequency band's role in working memory. This could be especially true in the older adult population, to which stable executive functioning is related to an increase in frontal theta power (Finnigan & Robertson, 2011).

Ultimately, the increase in theta power within the VLPFC is likely predominantly driven by the H4 coil due to the VLPFC's connection to the insula in cognitive reappraisal (Fig. 1a); however, this effect was not detected as H-coil was not controlled for. While there is currently limited evidence indicating a clear relationship between the VLPFC and ACC.

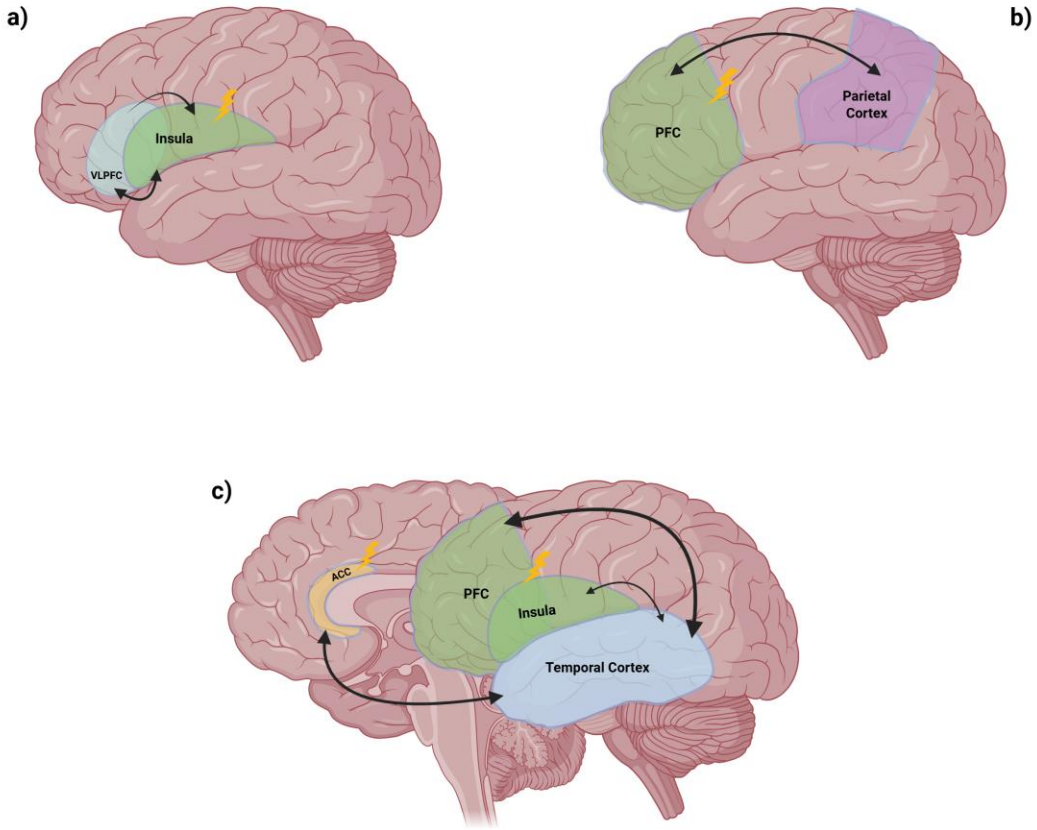

Figure 1. Preliminary Theta Biomarker Regions & Stimulation Sites via BioRender

A superficial visualization of the potential relationships between the identified preliminary biomarker regions, of the theta frequency band, and stimulation sites. a) Increased functional connectivity between the right VLPFC & right insula (H4 target) related to cognitive reappraisal. The VLPFC is believed to modulate the insula (H4 target) during emotion regulation. b) The PFC (H4 target), most likely the DLPFC, and the parietal cortex are interconnected through the frontoparietal network, which has been implicated in geriatric depression. c) Increased connectivity between the ACC (H7 target) & temporal cortex, regions both implicated in emotion regulation, in MDD. The PFC (H4 target), insula (H4 target) & temporal cortex are interconnected through the ventral attention network, which has been implicated in emotion regulation & MDD.

Note For consistency, the brain is shown from the left side which may not be anatomically representative of the position of the biomarkers themselves. It is also important to note that EEG is temporally sensitive and not structurally sensitive, and that this must be considered while interpreting the findings. Lastly, the green shading represents the region targeted by the H4 coil, the yellow shading represents the regions targeted by H7 and the blue and purple shading represents the preliminary biomarker regions.

The current literature suggests that reductions in parietal theta power may play a role as a diagnostic biomarker in MDD (Kane et al., 2019; Tang et al., 2025). More specifically, reductions in parietal theta power have been associated with working memory in MDD (Tang et al., 2025). Aside from theta, changes in white matter tracts associated with the parietal cortex have been observed in TRD (Klok et al., 2019). When looking at working memory, the ACC (H7 coil target) has been found to potentially

modulate working memory processes within the parietal lobe (Di et al., 2020). With the parietal cortex intricately linked to the PFC (H4 coil target) through the frontoparietal network (Fig. 1b; Menon & D'Esposito, 2021), or the central executive network, which has been implicated in older adult MDD (Zhukovsky et al., 2021). This network is believed to play a role in working memory as well (Yang et al., 2025), with noticeable deficits in individuals with less severe depressive symptoms (Tan et al., 2021). More specifically, working memory deficits in depressed older adults has been linked to possible reductions in both the lateral frontal regions and the parietal cortex (Dumas & Newhouse, 2015).

Given that reduced parietal theta power has been implicated in MDD, it is possible that stimulation from either the H4 or H7 coil may increase theta power within the parietal cortex. This increase in theta power could lead to an improvement in depressive symptoms possibly regardless of age and potentially driven by an improvement in working memory, a key role of theta. Nonetheless, this effect is likely more influenced by the H4 coil, as there is a stronger body of evidence linking the parietal cortex to the regions targeted by the H4 coil (Fig. 1b). But, since coil type was not controlled for, this could not be determined. As well, due to the limited sample size of the study a main effect of the H4 coil may not have been detected even if coil type was controlled for.

The temporal cortex is thought to potentially play a role in emotion regulation (Kohn et al., 2014; Wang et al., 2024), a function that may be influenced by working memory, in which theta oscillations are involved (Andreotti et al., 2013; Klimesch, 2018). As previously discussed, individuals with MDD experience impairments in emotion regulation (Visted et al., 2018). With the temporal cortex being implicated in both TRD (Sun et al., 2023) as well as depression severity in community dwelling older adults (Szymkowicz et al., 2016). As mentioned prior, increased connectivity between the ACC, a region also implicated in emotion regulation, and the temporal cortex has been observed in depressed individuals (Fig. 1c; De Kwaasteniet et al., 2013). The temporal cortex is also believed to be interconnected to the PFC and insula through the ventral attention network (Fig 1c; Menon & D'Esposito, 2021), which has been implicated in both emotion regulation and in majorly depressed individuals (Cui et al., 2024; Viviani, 2013; Z. Zhang et al., 2025).

As a result, it is likely that an increase in theta power within the temporal cortex, following H4 and H7 dTMS, may lead to a greater improvement in depressive symptoms (Fig. 1c). This larger reduction in the HDRS-24 may be attributed to an improvement in working memory, consistent with the known influence of theta on this cognitive function.

In the end, emotion regulation assessments and work memory tasks should be implemented in future research, whether at baseline and post-treatment or during EEG sessions themselves, to examine the relationships between the biomarker regions and the theta frequency band more affectively. Working memory tasks could even be implemented before EEG sessions, to "engage" theta activity within the brain. Tasks that also may be able to engage behaviours such as emotion regulation well as working memory may also be completed before or during the EEG sessions.

4.1.2. Alpha Oscillations

Even though none of the effects remained significant after correction (i.e., > .09), two preliminary mechanistic biomarkers were observed, reflecting increases in relative alpha power in the electrode sites F4 and P3 in depressed older adults, in chapter 3; it is important to note that effect sizes were moderate (i.e., 0.551 – 0.571). These increases corresponded with a smaller reduction in the HDRS-24 scores following H4 and H7 dTMS. The electrode site F4 is likely spatially indicative of the right DLPFC (Li et al., 2024). Whereas the electrode site P3 likely corresponds to a region of the left posterior parietal cortex, adjacent to the occipital cortex (Li et al., 2024).

4.1.2.1. Assumptions: Alpha Power

In this section assumptions will be made utilizing the current literature, to better understand the results of chapter 3 by examining research related to the right DLPFC and left parietal cortex and these regions relationship to both MDD and the behaviours associated with the condition. Furthermore, regions also targeted by the H4 and H7 coils will be examined along with behaviours associated with the alpha frequency band. Though not directly assessed in chapter 3, behaviours and cognitive processes such as emotion regulation, rumination, working memory and attention will be examined, given the current

literature implicating such behaviours and cognitive processes in the structures listed above, the theta frequency band and/or MDD.

Increased upper-alpha (10.5 to 13Hz) power has been previously identified in males with MDD, within both the frontal and parietal regions of the brain (Jaworska et al., 2012). During a working memory task, increased left parietal-occipital upper-alpha power was also noted within females with MDD (Segrave et al., 2010). Potentially, more generally identifying increased alpha power as a diagnostic feature of MDD. Possibly explaining why, a potential further increase in alpha power could be associated with a relatively limited decrease in depressive symptoms.

Alpha has been found to play a role in cognitive inhibition, particularly in attention (Klimesch, 2012; Klimesch, 2018; Tremblay et al., 2019). It has been hypothesized that attention, specifically "affect-biased attention", is a component of emotional regulation (Todd et al., 2012). The DLPFC has been recognized to potentially play a role in emotion regulation (Golkar et al., 2012). In general, the posterior parietal cortex is thought to be involved in attention processes (Behrmann et al., 2004). Both deficits in emotion regulation (Visted et al., 2018) and attention have been observed in MDD (Eizenman et al., 2003; Wang et al., 2020). With attention deficits corresponding with depressive symptoms in community-dwelling older adults (McBride & Abeles, 2000). Both the parietal cortex (Kane et al., 2019; Tang et al., 2025) and the DLPFC (Fales et al., 2008; Fitzgerald et al., 2008; Pizzagalli & Roberts, 2022; Zhong et al., 2011) have been implicated in MDD, as well as geriatric depression (Chang et al., 2011; Dumas & Newhouse 2015; Lin et al., 2023).

The DLPFC is a region within the PFC and is, thus, likely targeted by the H4 coil (Fig. 2a; Fiocchi et al., 2018; Zangen et al., 2021). As noted earlier, the parietal cortex is interconnected to the PFC (H4 target) via the frontoparietal network (Fig. 2a; Menon & D'Esposito, 2021) which has been implicated in older adult MDD (Zhukovsky et al., 2021) and may play a role in attention as well (Scolari et al., 2015). With greater frontoparietal interconnections observed in majorly depressed younger adults as well, during a working memory task (Cao et al., 2021).

Increased effective connectivity, measured via TMS-EEG, between the DLPFC and the ACC (targeted by H7; Fig. 2b; a region also implicated in emotion regulation) has been found in depressed

individuals with suicidal ideation (Chen et al., 2025). Interestingly, in older adults, it appears that they rely more heavily on the DLPFC in the context of emotion regulation than younger adults (Allard & Kensigner, 2014). Increased functional connectivity between the right DLPFC and the left dorsal ACC has also been observed as well in majorly depressed individuals (Fig. 2b; Ye et al., 2012). On the other hand, the MPFC (targeted by H7) is interconnected to the parietal cortex through the DMN (Fig. 2b), which is believed to play a role in rumination (Menon & D'Esposito, 2022; Raichle & Snyder, 2007; Zhou et al., 2020). Moreover, in individuals with MDD, trait rumination has been observed to potentially be related to greater "attentional bias towards negative information" (Donaldson et al., 2007, p. 2664).

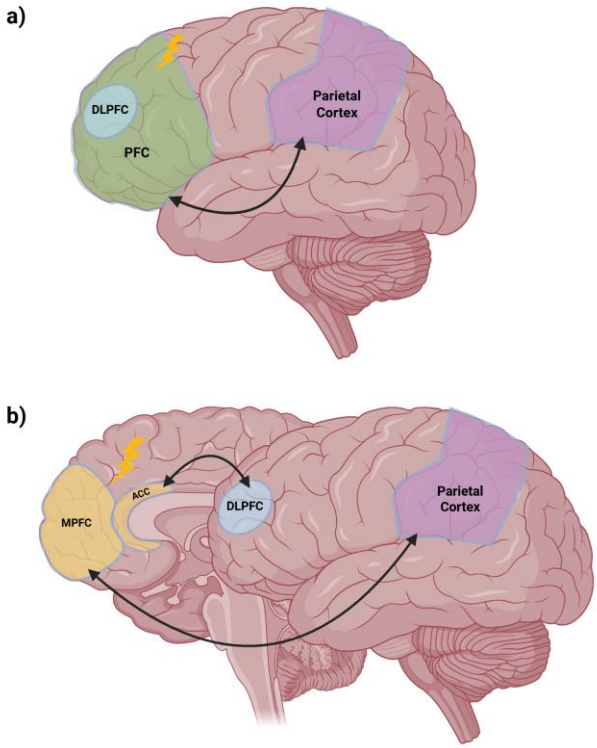

Figure 2. Preliminary Alpha Biomarkers & Stimulation Sites via BioRender

A superficial visualization of the potential relationships between the identified preliminary biomarker regions, of the alpha frequency band, and stimulation sites. a) The DLPFC, believed to play a role in geriatric depression, is a region within the PFC (H4 target). The parietal cortex, potentially involved in attentional deficits in MDD, and the PFC (H4 target) are interconnected to one another through the frontoparietal network, which is implicated in geriatric depression. b) Increased connectivity between the DLPFC & ACC (H7 target) in MDD. The parietal cortex & the MPFC (H7 target) are interconnected through the default mode network, which is believed to play a role in rumination.

Note For consistency, the brain is shown from the left side which may not be anatomically representative of the position of the biomarkers themselves. It is also important to note that EEG is temporally sensitive and not structurally sensitive, and that this must be considered while interpreting the findings. Lastly, the

green shading represents the region targeted by the H4 coil, the yellow shading represents the regions targeted by H7 and the blue and purple shading represents the preliminary biomarker regions.

Considering the current literature, it is possible that an increase in alpha power at F4 and P3 may be associated with a modest reduction in depressive symptoms following either H4 or H7 dTMS, irrespective of age (Fig. 2). This observation is particularly noteworthy given that elevated global alpha power could serve as a potential diagnostic feature of MDD. This effect could have been influenced by the alpha frequency band's role in attention. Interestingly, based on Jaworska et al.'s (2012) findings, the significant increase in alpha at F4 could potentially be driven by the male participants, but since sex was not accounted for, a significant effect of sex was not identified.

In the end, emotion regulation and rumination assessments as well as work memory and attention tasks should be implemented in future research, whether at baseline and post-treatment or during EEG sessions themselves, to examine the relationships between the biomarker regions and the alpha frequency band more affectively. Attention tasks, specifically, could even be implemented before EEG sessions, to "engage" alpha activity within the brain. Tasks that also may be able to engage behaviours such as emotion regulation and/or rumination as well as attention, may also be completed before or during the EEG sessions.

4.1.3. TMS-Evoked Potential N100

In chapter 2, a decrease in N100 amplitude over the course of DLPFC rTMS or iTBS was related to an improvement in MDD in younger-to-middle aged adults (Voineskos et al. [2021]: 45.95 ± 14.01 [active group]; Strafella et al. [2023]: 41.26 ± 10.28 [separated schedule] and 40.92 ± 12.14 [contiguous schedule]), suggesting a possible mechanistic biomarker. The N100 TMS-evoked potential (TEP) is likely related to the gamma-aminobutyric acid B ($GABA_B$) receptor (Schür et al., 2016), which has been potentially implicated in MDD as well as behaviours related to depression, such as anxiety and learned helplessness (Luscher et al, 2011; Slattery & Cryan, 2006). Additionally, the DLPFC may play a role in these behaviours as well, an area targeted by rTMS and iTBS (Balderston et al., 2017, 2020; Tafet & Ortiz Alonso, 2025).

In animal models where $GABA_B$ has been deleted, anti-depressant-like effects have been observed (Mombereau et al., 2004; Slattery & Cryan, 2006). This could help explain the antidepressant effects of DLPFC rTMS or iTBS, especially when there is a reduction in N100 amplitude among patients with MDD.

4.2. Predictive Biomarkers

4.2.1. Gamma Oscillations

Though none of the effects remained significant after adjustment (i.e., .294 and .151), two preliminary predictive biomarkers were observed at electrode sites Fp1 and F4, in which greater gamma power was predictive of a lesser likelihood of responding to either H4 or H7 dTMS; it is important to note that effect size was large (i.e., -1.854 and -1.503). The electrode site Fp1 is spatially indicative of the left PFC, whereas the electrode site F4 is more precise, spatially representing the right DLPFC (Li et al., 2024).

4.2.1.1. Assumptions: Gamma Power

In this section assumptions will be made utilizing the current literature, to better understand the results of chapter 3 by examining research related to the PFC and the DLPFC and these regions relationship to both MDD and the behaviours associated with the condition. Furthermore, regions also targeted by the H4 and H7 coils will be examined along with behaviours associated with the gamma frequency band. Though not directly assessed in chapter 3, the cognitive process perception will be examined, given that the current literature has implicated perceptual processes in the structures listed above, the gamma frequency band and/or MDD.

Increased global gamma power has been observed as a potential diagnostic feature of MDD, specifically within the frontocentral region of the brain (Strelets et al., 2007; Yamamoto et al., 2018). When utilizing the H1 dTMS coil, Zangen et al. (2023) found that greater baseline medial low-gamma power could be predictive of a lesser response to treatment in younger-to-middle aged adults with TRD. Although, no significant findings were reported for the H7 coil (Zangen et al., 2023). This may suggest

that an additional increase in gamma power, especially in the central regions of the brain, may lead to less of a response to dTMS.

Gamma has been found to play a role in higher-order cognition, such as perception, and is typically found within the frontal cortex (Tremblay et al., 2019; Jee, 2021). As previously stated, impairments in perception have been noted in MDD (Bourke et al., 2010; Eggart et al., 2019; Zomet et al., 2008). High-gamma activity (70 – 150 Hz) within the PFC is believed to possibly play a key role in the process of moving "perception into action" (Haller et al., 2018, p. 2). Furthermore, Philiastides et al. (2011) found that when low frequency rTMS was administered to the DLPFC, to inhibit the region, perceptual deficits were observed that were related to decision-making. With the right DLPFC potentially implicated in emotion perception, specifically when observing positive faces (Yang et al., 2018). As previously suggested, both the PFC and the DLPFC have been implicated in MDD (Fales et al., 2008; Fitzgerald et al., 2008; Pizzagalli & Roberts, 2022; Wang et al., 2015; Zhong et al., 2011) and in geriatric depression more specifically (Chang et al., 2011; Dumas & Newhouse 2015; Lin et al., 2023).

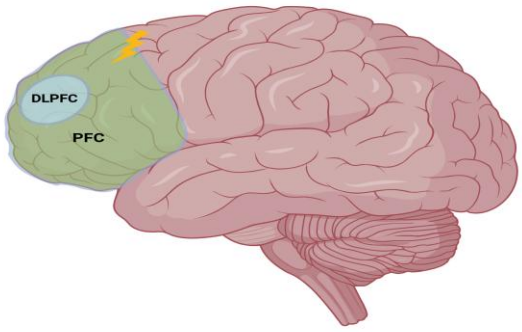

Figure 3. Preliminary Gamma Biomarkers & Stimulation Sites via BioRender

A superficial visualization of the potential relationships between the identified preliminary biomarker regions, of the gamma frequency band, and stimulation sites. The PFC is a target of the H4 coil and, by association, likely the DLPFC as well. Both regions have been implicated in geriatric depression.

Note For consistency, the brain is shown from the left side which may not be anatomically representative of the position of the biomarkers themselves. It is also important to note that EEG is temporally sensitive and not structurally sensitive, and that this must be considered while interpreting the findings. Lastly, the green shading represents the region targeted by the H4 coil, and the blue shading represents the preliminary biomarker region.

The PFC is a region targeted by the H4 coil, which likely also targets the DLPFC as a result (Fig 3; Fiocchi et al., 2018; Zangen et al., 2021). As stated in the previous section on alpha, a connection between the DLPFC and the ACC (related to perception through its role in emotion regulation; Lemay et al., 2025) has been established, especially in individuals with MDD; including the PFC as a result (Chen et al., 2025; Ye et al., 2012).

Given the existing evidence, greater baseline gamma power in the left PFC (Fp1) and the right DLPFC (F4) may predict a reduced response to either H4 or H7 dTMS, possibly regardless of age and potentially due to gamma's involvement in perceptual processes. It is important to note that increased frontocentral gamma power has been associated with MDD; however, the literature is conflicting. Specifically, while frontocentral reductions in gamma power have been proposed as a possible diagnostic feature of MDD (Roh et al., 2016), greater F3 gamma power has been identified as a predictive feature of response to rTMS (Noda et al., 2017).

This suggests, that much like theta oscillations, MDD may have subtypes that can be identified via gamma power, where some patients display increased frontocentral gamma power and while others have reductions. Given this, dTMS may be more beneficial for patients with decreased gamma power, whereas rTMS may cater better to patients with increased gamma power. However, the current evidence is insufficient to support this hypothesis. Lastly, considering the lack of significant results for the H7 coil in Zangen et al's study, it is plausible that the effects observed may be influenced primarily by the H4 coil (Fig. 3), as it likely targets the DLPFC similarly to the H1 coil.

In the end, perception-based tasks should be implemented in future research, whether at baseline and post-treatment or during EEG sessions themselves, to examine the relationships between the biomarker regions and the gamma frequency band more affectively. Perception-based tasks could even be implemented before EEG sessions, to "engage" gamma activity within the brain, or during EEG sessions.

4.2.2. TMS-Evoked Potential N100

Greater baseline N100 amplitude was found to be predictive of a response to DLPFC rTMS and iTBS for MDD in youger-to-middle aged adults (Sheen et al., 2024; Strafella et al., 2023), highlighting a potential predictive biomarker. As stated previously, the TEP N100 is believed to be related to the $GABA_B$ receptor (Schür et al., 2016), which has been linked to symptoms of MDD (Slattery & Cryan, 2006; Luscher et al, 2011), and is suspected to play a role in cortical inhibition (Farzan et al., 2013; Premoli et al., 2014; Rogasch et al., 2015).

As mentioned above, the removal of the $GABA_B$ receptor in animal models has been associated with an anti-depressant-like effect (Mombereau et al., 2004; Slattery & Cryan, 2006). This leads to the plausible suggestion that increased N100 amplitude may reflect greater depression severity, particularly since elevated N100 amplitude has been observed in majorly depressed patients with suicidal ideation (Chen et al., 2025) and has shown promise as a potential diagnostic biomarker for TRD (Farzan, 2024). On the other hand, the DLFPC, a target of rTMS and iTBS, has also been implicated in symptoms of anxiety and learned helplessness (Balderston et al., 2017; Balderston et al., 2020; Tafet & Alonso, 2025), behaviours also related to the $GABA_B$ receptor (Slattery & Cryan, 2006; Luscher et al, 2011). Thus, younger-to-middle aged adults with greater N100 amplitude may display more severe symptoms of MDD and may be more likely to respond to rTMS or iTBS, with a reduction in N100 amplitude associated with a greater response to treatment.

4.3. Age and EEG Biomarkers in TMS for Depression

As compared to younger-to-middle aged adults, limited research has been conducted to establish EEG biomarkers among depressed older adults. With chapter 3 being the first study to attempt to identify preliminary EEG biomarkers of TMS response in geriatric depression. As of now, promising work has been established in isolating potential diagnostic EEG biomarkers (e.g., reduced parietal theta power), mechanistic EEG biomarkers (e.g., reductions in theta connectivity), and especially predictive EEG biomarkers (e.g., greater frontomidline theta connectivity) for rTMS, in younger-to-middle aged adults with MDD. However, this is not the case for geriatric depression.

When comparing the results from chapter 3 with the existing EEG literature on aging it appears that depressed older adults exhibit electrophysiological activity that may be more akin to that of depressed younger-to-middle aged adults, especially in relation to the gamma and alpha bands. For example, in chapter 3 an increase in gamma power post-dTMS (H4 and H7) was representative of a smaller reduction in depressive symptoms in older adults, which was similar to findings of a study previously conducted by Zangen et al (2023) in younger-to-middle aged adults. This study found that greater gamma power was associated with a decreased likelihood of response to the H1 coil of dTMS as well. However, this may also be influenced by stimulation region as well. As it was previously discussed that the preliminary predictive gamma biomarkers identified in chapter 3 may predominately influenced by the H4 coil. Especially, when considering that both the H4 and H1 coils target the DLPFC (the H4 targets the PFC more broadly).

The current literature on healthy and pathological aging suggests that older adults appear to experience reductions in overall gamma and alpha activity (Arakaki et al., 2019; Hogan et al., 2011; Moezzi et al., 2019), which contrasts with the findings discussed above. As it may be assumed that increased electrophysiological activity would be associated with an improvement in depressive symptoms among older adults, especially given the decrease in electrophysiological activity across the frequency bands gamma and alpha during both the natural and pathological aging (Arakaki et al., 2019; Hogan et al., 2011; Moezzi et al., 2019).

Interestingly, in chapter 3 theta power was found to increase post-dTMS, within several regions of the cortex, and was associated with greater reductions in depressive symptoms. As previously mentioned, reductions in frontal theta power have been associated with improved cognitive functioning in older adults, such as executive functioning (Finnigan & Robertson, 2011). In respect to connectivity, the current literature on ageing suggests that as one age's theta connectivity decreases as well (Moezzi et al., 2019). The pathophysiology of MDD, particularly in relation to the frequency band theta, appears to potentially remain uninfluenced by age. Considering the relationship between cognition, primarily working memory, and depressive symptomology, it would be assumed that an increase in theta power would be

representative of both healthier cognitive aging and improved depressive symptomology. However, this does not appear to be the case.

Nevertheless, in chapter 2 depressed younger-to-middle aged adults who responded well to rTMS were found to have a reduction in theta connectivity within frontal, parietal, and temporal regions of the brain. Which further complicates the influence of age within the theta frequency band. Though, these studies utilized DLPFC rTMS and not the dTMS coils H4 (target: PFC and insula) and H7 (target: MPFC and ACC), which may influence the discrepancies noted. As of now, the literature remains heterogeneous regarding the influence of the pathophysiology of MDD and age on the theta frequency band in respect to TMS treatment biomarkers.

Due to the heterogeneity of the current literature and lack of research in geriatric depression in relation to TMS markers, it is difficult to conclude whether age influences biomarker discovery in TMS. Especially, when chapter 3's results did not survive correction; the first study to examine TMS biomarkers in geriatric depression. Though the results from chapter 3 may appear to align with the broader literature, as per the assumption sections, and suggest that age may not play a significant role in EEG treatment biomarkers for TMS, there is currently no concrete evidence (e.g., multiple randomized controlled trials) to say with confidence that age has no impact. Future research must continue to examine EEG biomarkers of TMS response in geriatric depression, especially across TMS modalities (rTMS vs dTMS vs iTBS) to adequately determine the influence of age on TMS biomarker discovery, particularly EEG biomarkers.

4.4. Main Limitations of the Present Thesis

Two of the main limitations of the current thesis is (1) the heterogeneity of the literature and (2) the lack of research examining geriatric depression and or the influence of age on TMS markers. Especially in respect to chapter 2, the heterogeneity of current literature, primarily in respect to the methodology (e.g., TMS method, stimulation region) and analyses (e.g., relative power, connectivity) utilized, only three biomarkers could be identified out of the 19 studies included. This also was a challenge for chapter 3, where it was increasingly difficult to compare the findings from other EEG and TMS studies when the methodologies and analyses were also different across the literature.

On the other hand, chapter 3 was greatly impacted by both the limited research examining depression in older adults and the complete lack of research examining EEG biomarkers of TMS response in geriatric depression; not to mention, the inability to control for age as a covariate. As a result, it was virtually impossible to draw any solid conclusions regarding the influence of age on EEG biomarkers of TMS response for MDD. Even when examining differences in EEG activity by age, very little research has been conducted in respect to depression. Making it difficult to tie the results of chapter 3 to findings related to geriatric depression more specifically.

Beyond age, no firm conclusions could be drawn regarding the effects of sex or H-coil type in chapter 3. Although the existing literature offers ground for speculation, the limited sample size and lack of control over these variables prevented any definitive interpretation.

It is also important to recognize that EEG is not structurally sensitive, but rather temporally sensitive. While the current thesis explores brain regions in the context of biomarker discovery, it is imperative to approach this topic with careful consideration due to the limitations of EEG and structural specificity. The assumptions sections related to chapter 3, along with the corresponding figures, aim to enhance our understanding of the results without drawing definitive conclusions, given EEG's limitations. To potentially improve the structural specificity of EEG results, the technique of low-resolution brain electromagnetic tomography (LORETA) can be employed to more precisely estimate the brain regions associated with biomarker sites by generating "three-dimensional images of cortical current density" (Pascual-Marqui et al., 1999, p. 169). This is particularly advantageous when utilizing a 20-channel EEG device, like in chapter 3, where the low spatial resolution limits the sensitivity to detect effects at the region level.

4.5. Conclusion

In conclusion, several resting-state EEG and TMS-EEG biomarkers of treatment response to TMS for MDD have been identified. With mechanistic biomarkers being the most common biomarkers observed, particularly within the theta frequency band. In general, the theta frequency band, regardless of age, may hold the most promise, of all the neural oscillations, when it comes to isolating treatment biomarker in TMS for MDD. Especially in rTMS and dTMS. Regarding TMS-EEG biomarkers, N100

amplitude appears to hold the greatest promise and is best suited for iTBS in younger-to-middle aged adults with MDD. However, further research is needed to validate these biomarkers. Particularly, the biomarkers observed in dTMS, which can only be referred to as "preliminary markers" as they did not survive correction. Lastly, continued research is highly recommended for geriatric populations where TRD is high and where little research has been conducted. Such research could continue examining EEG biomarkers of H4 response or could examine diagnostic EEG markers for geriatric depression.

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