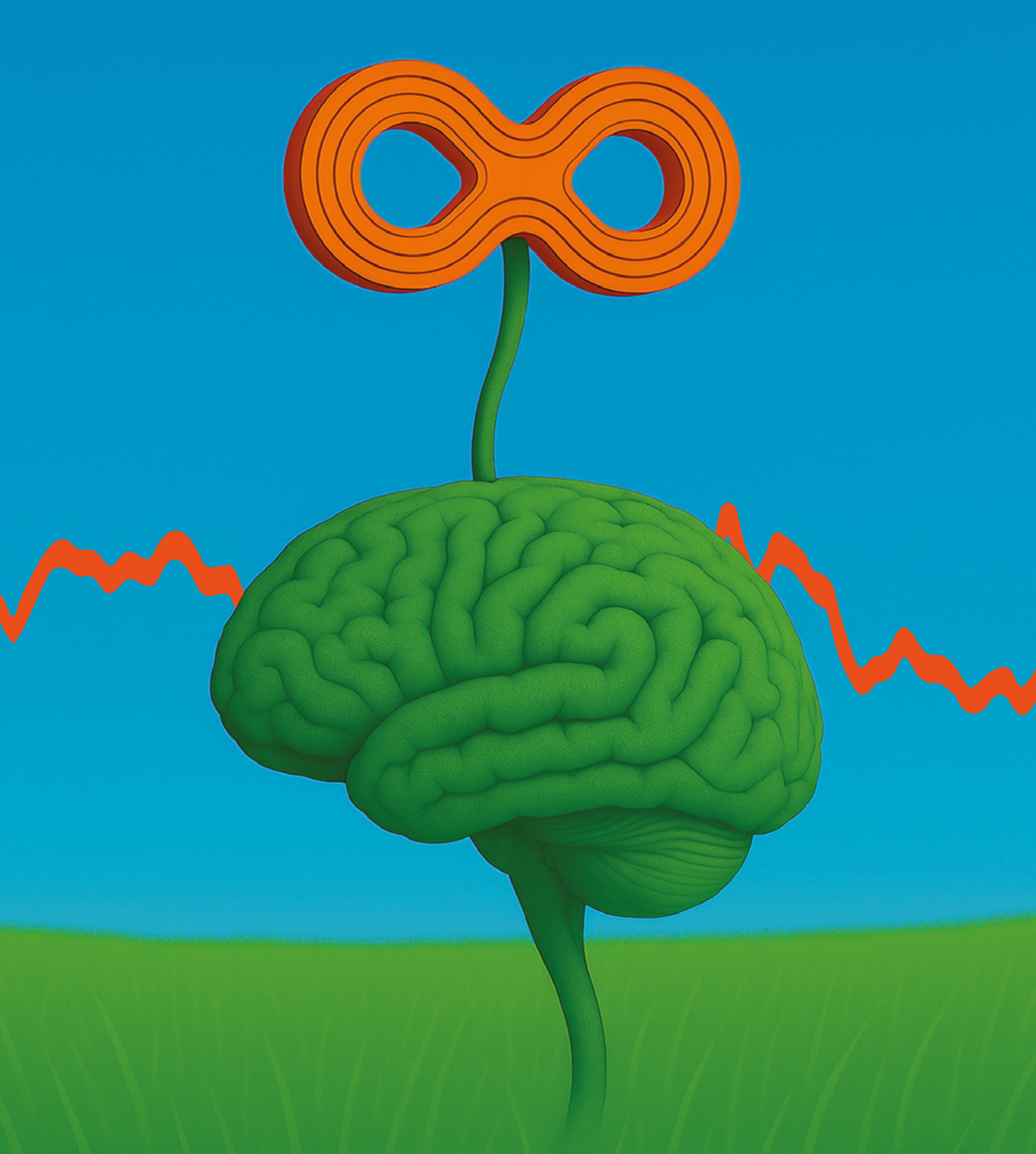

# Novel interventions and treatment selection predictors for treatment-resistant depression

Amourie Prentice

# NOVEL INTERVENTIONS AND TREATMENT SELECTION PREDICTORS FOR TREATMENT-RESISTANT DEPRESSION

Amourie Prentice

The work described in this doctoral dissertation was carried out at Stichting Brainclinics Foundation and Synaeda Psycho Medisch Centrum, in collaboration with Maastricht University.

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# NOVEL INTERVENTIONS AND TREATMENT SELECTION PREDICTORS FOR TREATMENT-RESISTANT DEPRESSION

DISSERTATION

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the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus,
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in accordance with the decision of the Board of Deans,
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# 1

# INTRODUCTION

## BACKGROUND AND CONTEXT

### DEFINITION OF DEPRESSION

Depression, also known as major depressive disorder (MDD), is a complex mental health disorder characterized by persistent feelings of sadness and a loss of interest or pleasure, accompanied by a broad range of cognitive and physical symptoms that severely hinder daily life (Reiff & Feldman, 2014). Common symptoms include low mood, anhedonia (loss of interest or pleasure), reduced energy and concentration, alterations in appetite, dysregulated sleep patterns, and feelings of guilt (Reiff & Feldman, 2014). In more severe cases, individuals may experience suicidal ideation and engage in self-harming behaviors (Kendler & Gardner, 2016). The World Health Organization (WHO) has recognized MDD as a leading cause of global disease burden, and as the primary cause of disability among people aged 15-44 (World Health Organization, 2017). The chronic and recurring nature of MDD drastically diminishes the quality of life, underscoring the urgent need for effective management and intervention strategies to mitigate its impact and improve the well-being of those affected.

## EPIDEMIOLOGY AND PUBLIC HEALTH IMPACT

With over 280 million people affected globally, depression has been recognized by the WHO as the leading cause of disability due to its widespread prevalence and severe impact on quality of life (Friedrich, 2017; World Health Organization, 2023). This mental health condition is pervasive across all age groups and demographic characteristics, making it a critical concern for public health systems (World Health Organization, 2023).

Epidemiological studies have indicated that global prevalence of MDD is approximately 5% of the population at any given time, with lifetime prevalence rates ranging from 13 to 16% (Baxter et al., 2014; Hasin et al., 2005; Kessler et al., 2003). The prevalence of MDD is similar in high-income (5.5%) and low-to-middle-income countries (5.9%) (Vos et al., 2015), though some studies suggest higher rates in high-income countries, with lifetime and 12-month prevalence at 14.6% and 5.5% compared to 11.1% and 5.9% in lower-income countries (L. Andrade et al., 2003; Kessler, 2012). Risk factors for depression include genetic vulnerability, chronic illness, socioeconomic status, and exposure to stressful life events (De Aquino et al., 2018; World Health Organization, 2017). MDD typically occurs between mid-adolescence and mid-forties, with about 40% of individuals experiencing their first episode before the age of twenty (Moffitt et al., 2010; Nihalani et al., 2009). Women are twice as likely to develop MDD as men, a disparity linked to biological, psychological, and environmental factors (Kuehner, 2017; World Health Organization, 2017).

The economic impact of MDD is substantial, costing the USA over $326 billion annually, with work-related costs (e.g. absenteeism and reduced work performance) alone accounting for $199 billion (Greenberg et al., 2021). This economic burden includes healthcare expenses, lost productivity, and significant effects on families and communities (Greenberg et al., 2015). In 2015, the total cost of mental disorders in Europe was estimated to be more than €600 billion, which included direct costs to the healthcare system, spending on social security programs, and the indirect costs to the labor market (Johnston et al., 2019). These figures highlight the critical need for effective interventions to reduce the profound public health impact of MDD.

## DIAGNOSTIC CRITERIA OF DEPRESSION

The diagnostic criteria for MDD are outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which provides a framework for accurate diagnosis and effective treatment (Psychiatric Association, 2000). MDD is characterized by a combination of symptoms that significantly impairs daily functioning (social, occupational, or other important areas). According to the DSM-5, for a clinical diagnosis of MDD, the presence of at least five of the following nine symptoms over a two-week period is required, with at least one of these symptoms being either a depressed mood or loss of interest or pleasure in nearly all activities (Psychiatric Association, 2000). The symptoms are depressed mood (persistent sadness or emptiness), loss of interest or pleasure, changes in appetite or weight, sleep disturbances (insomnia or hypersomnia), fatigue (loss of energy or chronic fatigue), feelings of worthlessness or guilt, difficulty concentrating, psychomotor agitation or retardation (restlessness or being slowed down), and recurrent thoughts of death or suicidal ideation (Psychiatric Association, 2000). Furthermore, these symptoms should not be attributable to the physiological effects of a substance or another medical condition and should not be better explained by another mental health disorder, such as bipolar disorder (Fried et al., 2014).

The eleventh revision of the International Classification of Diseases (ICD-11) provides similar diagnostic criteria for depressive disorders but with slight variations in terminology and diagnostic thresholds (White & Hudson, 2023). Both systems emphasize the importance of a comprehensive clinical assessment to ensure accurate diagnosis and differentiation from other mood disorders.

Understanding the course and prognosis of depression is crucial, as it varies significantly among patients. Some individuals experience gradual onset while others have an abrupt start to their depressive episodes. MDD is considered a lifelong recurrent illness, with periods of wellness interspersed with acute depressive episodes (Malhi & Mann, 2018). The duration of these episodes typically ranges from 3-6 months, with recovery usually occurring within 12 months (Verduijn et al., 2017). However, the risk of recurrence increases with each depressive episode, leading some patients to develop chronic depressive

illness (Malhi & Mann, 2018; Verduijn et al., 2017).

Recognizing the complexity of MDD, it is often beneficial to supplement the DSM-5 criteria with additional scales and tools to capture the diverse symptom presentations, including symptoms not fully covered by the DSM-5, such as anxiety (Drysdale et al., 2017; Kendler & Gardner, 2016; Schneibel et al., 2012).

### ASSESSMENT OF DEPRESSION SEVERITY

The Beck Depression Inventory-II (BDI-II) is a widely used self-report questionnaire designed to assess the severity of depression in adolescents and adults, and serves as a tool to support the diagnosis of depression (Beck et al., 1996). Developed by Aaron T. Beck and colleagues, the BDI-II is an updated version of the original 1961 Beck Depression Inventory, revised to align with the DSM-IV diagnostic criteria for depression (Beck et al., 1961, 1996; Guze, 1995). The BDI-II consists of 21 items, each corresponding to a symptom of depression, rated on a 4-point scale ranging from 0 (absence of symptoms) to 3 (severe symptoms), regarding the past two weeks. The total score, ranging from 0 to 63, is calculated by summing the ratings for all items. Based on the total score, depression severity can be categorized as minimal (0-13), mild (14-19), moderate (20-28), or severe (29-63) (Dozois et al., 1998). The BDI-II has demonstrated high reliability and validity in both clinical and non-clinical populations. Studies have indicated that the BDI-II has strong internal consistency, with Cronbach's alpha values typically exceeding 0.90 (Storch et al., 2004). Test-retest reliability is also robust, ensuring consistency over time (Y.-P. Wang & Gorenstein, 2013). Strengths of the BDI-II include its ease of use, comprehensiveness, and ability to capture a broad range of depressive symptoms. However, as a self-report measure, it is subject to potential biases, such as social desirability and the accurate self-assessment of symptoms (Beck et al., 1996). Moreover, although the BDI-II correlates well with other established depression measures, it tends to categorize a higher proportion of individuals as having severe depression compared to the Patient Health Questionnaire-9 (PHQ-9) (Titov et al., 2011). Despite these limitations, the BDI-II remains a reliable tool for both clinical and research purposes in the field of depression (Beck et al., 1996).

The Hamilton Rating Scale for Depression ($HRSD_{17}$), also known as the Hamilton Depression Rating Scale (HAM-D or HDRS), is a widely used clinician-administered questionnaire designed to assess the severity of depression in patients already diagnosed with the disorder (M. Hamilton, 1960). Developed by Max Hamilton in 1960, the $HRSD_{17}$ is considered one of the gold standards for evaluating depressive symptoms. The scale includes 17 items that cover a range of symptoms associated with depression, such as mood, feelings of guilt, insomnia, agitation, anxiety, weight loss, and somatic symptoms (M. Hamilton, 1960). Each item on the $HRSD_{17}$ is rated on a scale of 0 to 2 or 0 to 4, with higher scores indicating greater symptom severity. The total score ranges from 0 to 52, with scores over 23 suggesting very severe depression, 19-22 severe depression, 14-18 moderate depression, 8-13 mild depression, and 0-7 no depression or normal (Zimmerman et al., 2013). The $HRSD_{17}$ is known for its strong psychometric properties, including high inter-rater reliability and internal consistency. It has been extensively validated across diverse clinical populations and remains one of the most frequently used instruments in both clinical and research settings for assessing the efficacy of depression treatments (Faries et al., 2000; J. B. Williams, 1988). However, the scale has been criticized for its focus on somatic symptoms, which may overlook important cognitive and affective dimensions of depression (Bagby et al., 2004).

The PHQ-9 is a widely used self-report for assessing the presence and severity of depression. Developed by Dr. Robert L. Spitzer and colleagues in the late 1990s, the nine-items of the PHQ-9 correspond to diagnostic criteria for MDD outlined in the DSM-IV (Guze, 1995; Kroenke et al., 2001). For the PHQ-9, individuals rate the frequency of each symptom over the past two weeks on a scale from 0 (“not at all") to 3 ("nearly every day"), resulting in a total score that ranges from 0 to 27. Scores on the PHQ-9 will categorize individuals into different severity levels of depression: 0-4 (none), 5-9 (mild), 10-14 (moderate), 15-19 (moderately severe), and 20-27 (severe) (Kroenke et al., 2001). The PHQ-9 is renowned for its simplicity and brevity, and dual utility in screening for depression and monitoring treatment progress. Its psychometric properties are robust, with high internal consistency (Cronbach’s alpha typically above 0.80) and strong

test-retest reliability (Gilbody et al., 2007; Manea et al., 2012). The PHQ-9's validity is well-established, showing high correlations with other depression scales such as the BDI-II and the $HRSD_{17}$ (Beck et al., 1996; M. Hamilton, 1960). The PHQ-9 is widely used in research due to its reliability and validity across diverse populations and settings, despite potential self-report biases that require clinical judgment when interpreting scores.

## CURRENT TREATMENTS AND THEIR LIMITATIONS

### CONVENTIONAL TREATMENTS

Depression is a multifaceted and pervasive mental health disorder affecting millions worldwide. Conventional therapies, primarily psychotherapy and pharmacotherapy (antidepressants), are the primary treatment used to manage depressive symptoms. Each therapy has its strengths and limitations concerning efficacy, response rates, side effects, and patient compliance.

*Psychotherapy*
Psychotherapy is an effective treatment for depression, involving structured interactions between a therapist and a client to address psychological and emotional issues (Cuijpers, van Straten, et al., 2008). It includes various approaches such as cognitive-behavioral therapy (CBT), behavioral activation therapy, interpersonal psychotherapy (IPT), and psychodynamic therapy (Cuijpers, Karyotaki, et al., 2014). Each method aims to alleviate symptoms and promote emotional well-being (American Psychological Association, 2024).

CBT, widely regarded as the gold standard for psychotherapy in treating depression worldwide, focuses on identifying and altering maladaptive thought patterns and behaviors to improve emotional regulation and provide long-term coping strategies (David et al., 2018; Hofmann et al., 2012). Numerous RCTs have demonstrated CBT's efficacy in reducing depressive symptoms, with response and remission rates of 40-50% in patients with mild to moderate depression, comparable to pharmacotherapy (Figure 1) (Cuijpers, Karyotaki,

et al., 2014; Cuijpers, Van Straten, et al., 2008; DeRubeis et al., 2008).

One of psychotherapy's key advantages is its enduring effects; studies suggest that the benefits of CBT may persist longer than those of antidepressants, with a lower relapse rate post-treatment (Cuijpers et al., 2013). Furthermore, psychotherapy lacks the pharmacological side effects associated with antidepressants, making it a suitable option for patients sensitive to medications or with contraindications to pharmacotherapy (Cuijpers, Straten, Andersson, et al., 2008). CBT can also be delivered in various formats, including individual sessions, group therapy, and online therapy, enhancing its accessibility to a broad patient population (Andersson, 2016).

However, 1 in 5 patients still drop out from psychotherapy, especially younger clients and those with personality or eating disorders (Swift & Greenberg, 2012). Limited access to qualified therapists, geographical and financial constraints can also affect compliance (P. S. Wang et al., 2000). Furthermore, in cases of severe depression or complex comorbid psychiatric conditions, CBT alone may be less effective and might need to be combined with other treatments, such as antidepressants (Cuijpers, Sijbrandij, et al., 2014).

*Antidepressants*

Antidepressants, the cornerstone of pharmacological treatment for depression, are categorized into several classes, each with distinct mechanisms of action, efficacy rates, and side effect profiles.

Selective serotonin reuptake inhibitors (SSRIs), such as escitalopram, sertraline, fluoxetine and paroxetine, are often the first line treatment due to their favorable side effect profile and safety in overdose (Cipriani et al., 2018). They function by selectively inhibiting the reuptake of serotonin—a neurotransmitter involved in mood regulation—thereby increasing serotonin levels in the brain and improving mood (Ferguson, 2001). SSRIs are generally effective, with response and remission rates of 35-50% (Figure 1) (Rush et al., 2006). Common side-effects, like gastrointestinal disturbances, sexual dysfunction, weight gain, and sleep disturbances, are usually manageable but can lead to non-adherence in some patients (Ferguson, 2001; Garland et al., 2016).

Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, are effective alternatives for patients who do not respond to SSRIs, with no clinically significant difference in efficacy for treating MDD (Machado & Einarson, 2010). SNRIs have a dual mechanism, inhibiting the reuptake of both serotonin and norepinephrine, which can provide additional benefits for treating symptoms like chronic pain, often co-occurring with depression (C. Andrade, 2010). Like SSRIs, they are generally well-tolerated with similar side effects but potentially more side effects, such as elevated blood pressure and withdrawal symptoms, which can lead to treatment discontinuation (Stahl et al., 2005).

Atypical antidepressants, such as bupropion and mirtazapine, provide alternatives for patients who cannot tolerate SSRIs or SNRIs. Bupropion affects dopamine and norepinephrine reuptake and is less likely to cause sexual dysfunction or weight gain compared to SSRIs (C. Andrade, 2010). Mirtazapine, known for its sedative effects, can be beneficial for patients with insomnia or anxiety but may cause significant weight gain (Watanabe et al., 2010). Atypical antidepressants are often used as adjunctive treatments or in cases of treatment-resistant depression (TRD).

Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, and monoamine oxidase inhibitors (MAOIs), such as phenelzine and tranylcypromine, are older classes of antidepressants, and remain viable treatment options for depression, particularly for patients who have not responded to SSRIs or SNRIs, despite their higher side effect burden (Anderson, 2000). Response rates for TCAs and MAOIs are comparable to SSRIs and SNRIs (McGrath et al., 2006; Rosenbaum et al., 1998). However, side effects are more severe, with TCA side effects including anticholinergic effects (e.g., dry mouth, constipation), weight gain, drowsiness, and cardiotoxicity, making them an option for TRD patients (Stahl, 2000). The major limitation of MAOIs is their interaction with tyramine-containing foods and other medications, which can lead to hypertensive crises, necessitating strict dietary and medication adherence (Krishnan, 2017; McGrath et al., 2006).

Conventional therapies for depression, including psychotherapy and antidepressants, offer significant benefits but also present challenges. While efficacy and response rates are generally favorable, side effects and compliance issues remain critical barriers to successful treatment. Personalized treatment plans that consider the individual patient's needs, preferences, and tolerability can optimize outcomes and improve overall adherence.

## TRD OR DIFFICULT-TO-TREAT DEPRESSION (DTD)

### DIAGNOSTIC CRITERIA FOR TRD

MDD presents a significant global health challenge, with millions of individuals affected worldwide. For approximately 30% of these patients, response is not achieved after two or more adequate trials of antidepressants, leading to a classification of TRD (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is the most extensive investigation into depression treatment effectiveness to date, focusing on real-world applications for patients with MDD. The study found that only about a third of patients achieved remission with their first antidepressant treatment, typically with the SSRI citalopram. For those who did not remit, the likelihood of remission diminished with each successive treatment step (Figure 1). Around 50% achieved remission after two steps, but these patients had higher relapse rates compared to those who remitted after the first step. By the third step, remission rates dropped to approximately 13% and by the fourth step, about one-third of patients still did not achieve remission, indicating TRD. The STAR*D study reported a cumulative remission rate of 67% after four steps, although a critical reanalysis suggested the actual remission rates may be lower (35%–41%) and TRD prevalence higher than initially indicated (Gaynes et al., 2020; Pigott et al., 2023; Rush et al., 2006). These findings underscore the challenges of treating TRD and highlight the need for alternative therapeutic approaches, such as earlier integration of non-pharmacological treatments like brain stimula-

tion therapies, to improve outcome and prevent the chronicity of depression (Rush et al., 2006; Trivedi et al., 2006).

While the definition of TRD is clinically useful, it has several limitations. It tends to overlook the heterogeneity of depression, including the impact of comorbid conditions, the variability in patient response to different therapeutic modalities, and the influence of psychosocial factors. Moreover, the label "treatment-resistant" can be stigmatizing, implying a sense of hopelessness for patients who do not respond to standard treatments. In response, the more recent conceptualization of DTD has emerged, offering a broader, less stigmatizing framework that better encompasses the complex and multifaceted nature of depression by acknowledging that depression may be difficult to treat due to a variety of factors beyond pharmacological resistance, and encourages more tailored interventions (McAllister-Williams et al., 2021; Wilhelm, 2019). Unfortunately, the term "TRD" remains the most commonly used in both clinical practice and research (McIntyre et al., 2023).

#### EXISTING TRD THERAPEUTIC STRATEGIES AND THEIR LIMITATIONS

TRD (or DTD) poses a substantial clinical challenge, requiring more than standard pharmacological interventions due to its complex nature. Various non-pharmacological therapeutic strategies have been developed to address TRD. Each offers unique benefits but also comes with significant limitations that must be considered.

Electroconvulsive therapy (ECT) remains one of the most effective non-pharmacological treatments for TRD, particularly in severe or psychotic depression (Sackeim, 2017). ECT is an invasive brain stimulation technique that involves inducing controlled seizures under general anesthesia, leading to neurochemical changes that alleviate depressive symptoms (UK ECT Review Group, 2003). Response rates for ECT are notably high, ranging from 60% to 80% in patients with TRD (Espinoza & Kellner, 2022). ECT has a rapid onset of action, making it a favorable option for patients at high risk of suicide or those with severe functional impairment (Kellner et al., 2006). However, ECT's limitations are significant and have contributed to its somewhat limited use. One

of the primary concerns is the potential for cognitive side effects, particularly memory loss, which can be both anterograde (affecting new memory formation) and retrograde (affecting past memories) (Sackeim et al., 2007). Although most cognitive side effects are transient, they can be distressing for patients and may impact their willingness to undergo treatment. Additionally, the requirement for general anesthesia and the stigma associated with ECT further limit its widespread acceptance and availability (Lisanby, 2007). Despite these drawbacks, ECT remains a valuable option for patients unresponsive to other forms of treatment, and ongoing research aims to optimize its safety and efficacy.

Repetitive transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that uses magnetic fields to stimulate specific brain regions involved in mood regulation (Janicak & Dokucu, 2015). Multiple studies have shown TMS to be effective in treating TRD, with response rates around 30-50% (Carpenter et al., 2012; Gaynes et al., 2014). Its non-invasive nature and minimal side effects make TMS a safer alternative to ECT for TRD patients, though conventional TMS regimens typically require multiple sessions per week over the course of several weeks, posing challenges in terms of time and cost (Perera et al., 2016). Another limitation is the variability in individual response to TMS, with some patients showing significant improvement while others experience little to no benefit. This variability highlights the need for further research to identify predictors of response and to optimize treatment protocols (Lefaucheur et al., 2014). Additionally, newer targets for stimulation, such as the orbitofrontal cortex (OFC), are being explored to enhance the efficacy of TMS (Fettes et al., 2017).

Deep brain stimulation (DBS) is an invasive neurosurgical procedure involving electrode implantation into specific brain regions, such as the subcallosal cingulate (SCC), associated with mood regulation (Mayberg et al., 2005). DBS has shown promise in treating severe TRD with initial studies reporting significant improvements and around 55% achieving response (Holtzheimer & Mayberg, 2011). However, the limitations of DBS are considerable. As an invasive procedure, DBS carries risks such as infection, bleeding, and potential brain tissue damage (Grill, 2005). High costs, procedural complexity, and ethical considerations regard-

ing patient consent and potential personality changes further complicate its clinical use (Fins, 2009).

Vagus nerve stimulation (VNS) is a treatment option for TRD, where electrical pulses are delivered to the left vagus nerve, indirectly affecting brain regions implicated in mood regulation (Howland, 2014). The most common form of VNS involves the surgical implantation of a pulse generator device (similar to a pacemaker) under the skin in the chest (Howland, 2014). The response to VNS is often delayed, with significant improvement typically taking months to manifest. Its effectiveness is considered moderate, with around 32% of patients showing improvement after prolonged use (96 weeks) (Berry et al., 2013). Risks include infection, voice changes, and difficulty swallowing, which can impact the patient's quality of life (Aaronson et al., 2017). Additionally, the high cost of the device and surgery, along with the need for regular follow-up and device adjustments, further limits its accessibility (Berry et al., 2013).

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a novel treatment for TRD. Administered intravenously, ketamine acts quickly, often within hours, making it valuable for acute depressive episodes (Berman et al., 2000). Esketamine, a nasal spray formulation of ketamine, offers the convenience of easier administration for the treatment of TRD (Daly et al., 2018). While ketamine's rapid antidepressant action effects are a significant advantage, several limitations must be considered. Its effects are short-lived, requiring repeated administration to maintain benefits, which raises concerns about long-term safety and the potential for abuse. Additionally, ketamine can cause dissociative symptoms, dizziness, and elevated blood pressure, further complicating its use. The high cost of treatment and the need for specialized medical supervision also restricts access, limiting its widespread adoption as a treatment option for depression (Jelen et al., 2021; Zarate et al., 2006).

As the limitations of current treatments become more apparent, research into novel therapeutic strategies for TRD continues to expand. One area of focus is the development of personalized treatment approaches that take into account individual differences in genetics,

neurobiology, and treatment history. For example, neuroimaging techniques are being used to identify biomarkers that can predict treatment response, potentially allowing for more targeted interventions (Drysdale et al., 2017). Additionally, research into new neuromodulation techniques, such as transcranial direct current stimulation (tDCS) and magnetic seizure therapy (MST), is ongoing, with the goal of improving efficacy and reducing side effects (Lisanby et al., 2003; Shiozawa et al., 2014).

## ADVANCES IN UNDERSTANDING AND TREATING DEPRESSION

Over the past few decades, numerous non-anatomical theories of depression have emerged, offering valuable insights into the psychological and social dimensions of the condition. However, with the advent of anatomically based treatments and a deeper understanding of the brain's role in depression, it has become increasingly important to integrate these approaches with neurobiological and anatomical theories. The following sections will explore the key psychosocial factors, neurobiological mechanisms, brain network dysregulation underlying depression, providing a comprehensive and holistic understanding of the disorder. Following this, the role of TMS in treating depression will be examined, discussing both conventional protocols and emerging alternative approaches, as well as the evolving targets within the brain for optimizing therapeutic outcomes.

### PSYCHOSOCIAL AND ENVIRONMENTAL FACTORS IN DEPRESSION

The social-psychological hypothesis of depression suggests that social and psychological factors, such as interpersonal relationships, social support, and cognitive patterns, play a significant role in the onset and development of MDD. Interpersonal theories of depression suggest that negative social interactions and relationships play a role in the development of depressive symptoms (Coyne, 1976; Joiner, 2000). According to Coyne's interpersonal theory, individuals exhibiting depressive behaviors, such as excessive reassurance-seeking or negative affect, will create interpersonal conflict and rejection, which in turn

will exacerbate their depressive symptoms and lead to further social rejection (Coyne, 1976). Joiner's interpersonal-psychological theory expands on this by suggesting that feelings of social rejection and perceived burdensomeness are critical in the development of depression and increase the risk of suicidal ideation (Joiner, 2005). Social support is another critical factor in the social psychological hypothesis of depression. Research shows that low social support and perceived isolation increase the risk of depression, as social support buffers against stress and reduces vulnerability to depressive symptoms (Cohen & Wills, 1985). Studies have demonstrated that individuals with strong social networks are less likely to experience severe depressive episodes compared to those with limited social connections (Berkman et al., 2000). Cognitive theories, such as Beck's cognitive theory of depression, suggest that negative cognitive styles and maladaptive thought patterns contribute significantly to depression. Beck proposed that individuals with depression frequently experience a cognitive triad of negative thoughts about themselves, their environment, and their future. These cognitive distortions, when triggered by social stressors, perpetuate and intensify depressive symptoms, creating a self-reinforcing cycle of negative thinking (Beck, 1967).

## NEUROBIOLOGICAL AND MOLECULAR MECHANISMS OF DEPRESSION

### GENETIC AND EPIGENETIC ANOMALY HYPOTHESIS

The genetic and epigenetic anomaly hypothesis suggests that depression arises from a complex interplay between genetic predispositions and epigenetic modifications, which collectively influence brain function and vulnerability to the disorder (Malhi & Mann, 2018).

Genetically, early studies identified several candidate genes to be linked to depression, particularly those involved in neurotransmitter systems (e.g., serotonin transporter (5-HTT) gene) and the hypothalamic-pituitary-adrenal (HPA) axis (e.g., glucocorticoid receptor gene, FKBP5) (Binder et al., 2004; Caspi et al., 2003). Variations in these genes may affect neurotransmission and neuroplasticity, contributing to depressive symptoms. However, recent genome-wide associa-

tion studies (GWAS) with large sample sizes (N>50K) have suggested that the contribution of individual genetic variants to depression is small (Hek et al., 2013; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium et al., 2013). Many earlier findings from smaller single nucleotide polymorphism (SNP) studies have not been replicated, leading researchers to shift focus toward more complex genetic and environmental interactions, rather than relying on individual SNP findings alone.

Epigenetic modifications, such as DNA methylation, can also alter gene expression without changing DNA sequence. For example, increased methylation of the SLC6A4 gene has been associated with reduced serotonin transporter expression and heightened depression risk (Olsson et al., 2010; Philibert et al., 2007). These genetic and epigenetic factors interact with environmental influences, such as early-life stress, which can induce lasting changes in genes like the glucocorticoid receptor gene (Nr3c1), leading to HPA axis dysregulation and increased depression risk (Turecki & Meaney, 2016). While these mechanisms are still being explored, treatments targeting epigenetic modifications, such as histone deacetylase inhibitors, are being investigated to reverse abnormal gene expression and restore neuroplasticity in depression (Nestler et al., 2016).

#### HPA AXIS DYSFUNCTION HYPOTHESIS

The HPA axis dysfunction hypothesis suggests that abnormalities in this stress-response system play a key role in depression. The HPA axis, which regulates cortisol production through interactions between the hypothalamus, pituitary gland, and adrenal glands, is a significant component of the body's stress response (Pariante & Lightman, 2008). In depression, hyperactivity of the HPA axis often results in elevated cortisol levels, contributing to mood disturbances and cognitive impairment (Stetler & Miller, 2011). Prolonged high cortisol exposure can lead to brain changes, such as reduced hippocampal volume and impaired neurogenesis, which are commonly observed in depression (McEwen, 2007; Sapolsky, 2000). Additionally, impaired feedback mechanisms that normally regulate cortisol levels lead to impaired HPA axis hyperactivity in depression, further exacerbating

symptoms and increasing risk of comorbid conditions, including anxiety and cardiovascular diseases (Grippo et al., 2003; Pariante & Miller, 2001). Although the involvement of the HPA axis in depression is well-documented, no targeted therapies for its components have been approved, and routine clinical tests to identify suitable patients are lacking (Menke, 2019). However, ongoing research aims to develop precision treatments by stratifying patient groups and matching them with specific agents targeting the HPA axis (Block et al., 2018; Leistner & Menke, 2018; Menke, 2019).

#### MONOAMINE HYPOTHESIS OF DEPRESSION

The monoamine hypothesis of depression proposes that a deficiency in certain neurotransmitters—serotonin, norepinephrine, and/or dopamine—is central to the pathophysiology of MDD (Ruhé et al., 2007; Stahl, 1998). This hypothesis originated from observations that medications enhancing monoamine activity, such as tricyclic antidepressants and monoamine oxidase inhibitors, can alleviate depressive symptoms (Hirschfeld, 2000; Schildkraut, 1965). Serotonin and norepinephrine are key regulators of mood, sleep and memory, with norepinephrine also influencing alertness and arousal, while dopamine is critical in reward processing and motivation (Ikemoto & Panksepp, 1999; Ressler & Nemeroff, 2000). Support for the monoamine hypothesis grew with the success of SSRIs, like escitalopram and sertraline, and SNRIs, like venlafaxine, which increase serotonin and norepinephrine levels by blocking their reuptake in the brain (Ferguson, 2001; Stahl et al., 2005). However, despite the success of these medications in treating many MDD patients, a substantial proportion do not respond to them (Nestler et al., 2002). More recently, an umbrella review questioned the validity of the monoamine hypothesis of depression, finding no consistent evidence that MDD is caused by reduced monoamine levels or activity. This review advocated for moving beyond the "chemical imbalance" narrative and embracing more comprehensive models of depression (Moncrieff et al., 2023). Integrating the monoamine hypothesis with other factors, such as neuroplasticity, inflammation, and genetics, would provide a more nuanced understanding of depression's complexity (Harmer et al., 2017; Malhi & Mann, 2018).

### INFLAMMATORY HYPOTHESIS OF DEPRESSION

The inflammatory hypothesis of depression suggests that chronic inflammation is a significant contributor to the pathophysiology of MDD. This hypothesis is supported by numerous studies reporting that individuals with depression frequently exhibit elevated levels of inflammatory markers, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), indicating an ongoing inflammatory response (Leighton et al., 2018; Maes et al., 2009; Miller et al., 2009). This inflammatory state is believed to impact neurotransmitter systems in the brain, leading to alterations in neural circuits that regulate motivation, motor activity, anxiety, arousal and alarm responses (Miller et al., 2009; Miller & Raison, 2016). Moreover, inflammation can disrupt the function of the HPA axis, leading to dysregulated cortisol production and further exacerbating depressive symptoms (Pariante, 2017; Troubat et al., 2021). Chronic stress, a known risk factor for depression, can also activate the immune system, creating a vicious cycle where stress-induced inflammation perpetuates depressive states (Slavich & Irwin, 2014). Interventional studies support the inflammatory hypothesis by showing that anti-inflammatory treatments can alleviate depressive symptoms. Randomized controlled trials (RCTs) have found that nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors help alleviate depressive symptoms in some patients, opening new possibilities for treatment (Köhler et al., 2014). Neuroinflammation imaging is still in its developmental stages but holds promise for identifying specific brain targets, which could aid in the testing of anti-inflammatory treatments for depression (Drevets et al., 2022).

## BRAIN CIRCUITRY AND NETWORK DYSREGULATION IN DEPRESSION

### BRAIN REMODELING HYPOTHESIS OF DEPRESSION

The brain remodeling hypothesis of depression proposes that the structural and functional changes in key brain regions contribute to the onset and development of MDD (Drevets et al., 2008). Structural brain changes in depression often present as reductions in gray matter volume. Magnetic resonance imaging (MRI) studies have shown that

individuals with MDD often exhibit atrophy in the hippocampus, prefrontal cortex, and amygdala—regions critical for memory, emotional regulation, and cognitive processing (Drevets et al., 2008; McEwen, 2003). This atrophy is believed to result from chronic stress and neuroinflammation, both of which contribute to the onset and progression of depressive symptoms (Sapolsky, 2000). Functional brain abnormalities in depression often present as disruptions in connectivity and activity patterns. Functional MRI (fMRI) studies have found altered connectivity in "core" neurocognitive networks, including the default mode network (DMN), the salience network, and the central executive network, suggesting a critical role of these networks in mediating pathophysiological mechanisms in MDD (J. P. Hamilton et al., 2013; Menon, 2011). Additionally, altered activity patterns are characterized by hyperactivity in the amygdala and hypoactivity in the prefrontal cortex, reflecting impaired emotional processing and weakened regulatory control (Drevets et al., 2008; Pizzagalli, 2011). Neuroplasticity is another crucial factor of the structural and functional brain remodeling hypothesis. Depression has been linked to decreased neurogenesis and synaptic plasticity, particularly in the hippocampus (Duman & Monteggia, 2006). Antidepressant treatments, both pharmacological and psychotherapeutic, are believed to promote neuroplasticity and reverse some of these structural and functional changes, contributing to symptom improvement (Duman & Aghajanian, 2012).

#### NON-REWARD ATTRACTOR THEORY OF DEPRESSION

The non-reward attractor theory of depression, as described by Rolls, suggests that a key feature of depression is the diminished ability to anticipate or experience rewarding stimuli, leading to persistent negative emotions and motivational deficits (Rolls, 2016). According to this theory, depression results in a stable brain state known as the "non-reward" attractor state, where the brain's capacity to experience pleasure or anticipate rewards is severely reduced. This maladaptive neural state reinforces depressive symptoms by trapping the brain in a feedback loop of negative emotional responses (Rolls, 2000).

Central to this non-reward system is the right lateral OFC (R-LOFC), a region within the prefrontal cortex (PFC) that plays a crucial role

in processing the absence of expected rewards, and is instrumental in shaping negatively valenced cognition, emotion, and motivation (Rolls et al., 2020). Neuroimaging studies have confirmed altered activity in brain regions associated with reward processing in individuals with MDD, with persistent, heightened activity and increased sensitivity in the non-reward network, particularly within the R-LOFC (Rolls, 2000, 2016; Rolls et al., 2020).

Research has also found that individuals with depression often exhibit reduced activity in the ventral striatum, particularly the nucleus accumbens, a key area involved in reward anticipation and processing. This reduced activity is linked to impaired reward function, a core symptom of depression, with the ventral striatum projecting to both the lateral and medial OFC (Knutson & Greer, 2008). Additionally, disruptions in the dopaminergic system, which plays a central role in reward signaling, have been observed in depressed individuals, further supporting the notion that the reward system is impaired (Nestler & Carlezon, 2006; Rolls, 2013).

The non-reward attractor theory implies that therapeutic approaches aimed at enhancing reward sensitivity or increasing engagement in rewarding activities may be particularly effective. For instance, behavioral activation therapies, which encourage patients to engage in activities that provide positive reinforcement, align with this theory and have been shown to effectively disrupt the maladaptive state, thereby alleviating depressive symptoms (Dimidjian et al., 2008; Jacobson et al., 2001).

The non-reward attractor theory of depression identifies specific brain regions and circuits, including the R-LOFC and its striatal projections, as key targets for brain stimulation treatments due to their role in persistent non-reward processing.

#### CAUSAL MAPPING IN DEPRESSION

Causal mapping in depression aims to bridge the gap between brain regions merely associated with depressive symptoms and those directly responsible for them (Siddiqi et al., 2022).

Traditional brain mapping techniques rely on correlational data from neuroimaging methods such as MRI. Connectivity analyses have identified key brain regions involved in depression. Functional connectivity analyses, measured through fMRI, has shown disrupted connectivity within the DMN, a network critical for self-referential thinking and mood regulation, as well as altered connectivity between the DMN and other networks, like the salience and central executive networks, reflecting impaired cognitive and emotional processing (J. P. Hamilton et al., 2011; Kaiser et al., 2015; Menon, 2011; Sheline et al., 2010). Additionally, the most effective TMS targets have been found to be functionally anti-correlated with the subgenual cingulate cortex (SCC) (Fox et al., 2012). In parallel, structural connectivity studies using diffusion tensor imaging (DTI) have demonstrated that reduced connectivity between the PFC and amygdala is linked to impaired emotional regulation and increased vulnerability to depression (Korgaonkar et al., 2014). Furthermore, the most effective DBS targets overlap with white matter tracts connecting the SCC to the OFC and the limbic system (Riva-Posse et al., 2014).

While traditional brain mapping techniques provide valuable insights, they fail to distinguish between brain regions that cause, compensate for, or are incidentally related to symptoms. In contrast, causal mapping integrates data from various methods to identify neural circuits directly contributing to depression (Siddiqi et al., 2022). Traditional lesion mapping, historically demonstrated through cases like Phineas Gage and H.M., showed that damage to specific brain regions can lead to distinct functional deficits (Harlow, 1848; Scoville & Milner, 1957). For instance, in depression, early incidental stroke studies revealed that lesions affecting the dorsolateral PFC (DLPFC) often resulted in depressive symptoms, and targeting this region with TMS was later found to alleviate these symptoms in clinical trials (Pascual-Leone et al., 1996; Robinson et al., 1984). However, Boes et al. (2015) noted that this method is limited as it fails to account for complex network dynamics—lesions can affect distant but connected regions, leading to symptoms that do not correspond neatly to the lesion site. To address this limitation, they introduced lesion network mapping, which uses normative connectivity data to identify brain networks associated with symptoms, allowing for

more precise localization even when lesion sites differ (Boes et al., 2015). Siddiqi and colleagues (2021) expanded on this by showing that brain lesions associated with depressive symptoms were functionally connected to the same TMS and DBS targets, converging into a common depression-related brain network (Siddiqi et al., 2021). This convergence between lesion-induced symptoms and stimulation-based treatments strengthens the argument for the causal involvement of these circuits in depression.

Overall, causal mapping in depression offers a powerful framework for identifying and refining therapeutic targets. By focusing on the causal relationships between brain regions and depressive symptoms, rather than merely correlational data, this approach paves the way for more precise and effective interventions. Techniques like TMS and DBS can be better tailored to target specific neural circuits directly involved in mood regulation. This method bridges the gap between neuroimaging findings and clinical applications, providing a roadmap for improving outcomes in TRD and potentially other neuropsychiatric disorders.

## INNOVATIVE NEUROANATOMICALLY FOCAL TREATMENTS: TMS

### CONVENTIONAL TMS PROTOCOLS

As noted earlier, TMS is a non-invasive neuromodulation technique that uses magnetic fields to generate electric currents in targeted brain regions through a coil placed on the scalp, effectively modulating neural circuitry for therapeutic purposes (Hallett, 2007; Valero-Cabré et al., 2017). Developed in the 1980s, TMS has evolved significantly and is now a well-established therapeutic intervention for various neuropsychiatric disorders, particularly MDD (Barker et al., 1985; Lefaucheur et al., 2014; McClintock et al., 2018; Sackeim et al., 2020).

In 2019, a Dutch-Belgian consensus recommended high-frequency TMS targeting the left DLPFC (L-DLPFC), a region implicated in mood regulation and cognitive functions (George et al., 1995; O'Rear-

don et al., 2007), or alternatively low-frequency TMS to the right DLPFC), as a first-line treatment for depression (Arns et al., 2019). The consensus further emphasized that stimulation protocols should deliver over 1000 pulses per session, with an average of 20-30 sessions, typically administered 2-5 sessions per week (Arns et al., 2019). Retrospective studies examining real-world effectiveness have reported remission rates ranging from 24% (Hutton et al., 2023) to 36% (Sackeim et al., 2020), and increasing to 56 % when combined with psychotherapy (Donse et al., 2018). RCTs have shown substantial improvement in depressive symptoms for patients with MDD who have not responded to at least one antidepressant (O'Reardon et al., 2007). Long-term efficacy has also been documented, with sustained symptom improvements lasting up to a year post-treatment (Carpenter et al., 2012; Donse et al., 2018).

Another effective TMS target is the dorsomedial PFC (DMPFC), which also involves high-frequency TMS, similar to the DLPFC (Bakker et al., 2015). High-frequency TMS targeting the DMPFC has been shown to alleviate depressive symptoms in TRD, with remission rates reported between 29% and 39% in an open-label study (Dunlop et al., 2015). However, a placebo-controlled trial failed to show significant improvement over sham, possibly due to unintended neural stimulation caused by the Transcutaneous Electrical Nerve Stimulation (TENS) sham condition (Dunlop et al., 2020). Additionally, some studies suggest that DMPFC stimulation may be more effective for certain depression subtypes, such as those with comorbid anxiety, compared to DLPFC stimulation (Drysdale et al., 2017), though this could not be independently replicated due to overfitting (Dinga et al., 2019).

However, several limitations must be acknowledged. Not all patients respond to TMS, with one subpopulation showing a marked clinical response while another exhibits only marginal improvements in depression scores; indeed the distribution of TMS outcomes in depression has actually been shown to be bimodal by several independent groups (Bakker et al., 2015; Downar et al., 2014; Fitzgerald et al., 2016). Factors contributing to this variability may include differences in individual neuroanatomy, disease severity, and treatment history

(Burke et al., 2019). Moreover, recent findings indicate that sequential bilateral DLPFC-TMS does not show superiority over unilateral high-frequency L-DLPFC-TMS in a large naturalistic case series (Aaronson et al., 2022). These findings suggest that MDD patients unresponsive to DLPFC or DMPFC stimulation might benefit from alternative targets.

Another limitation is that while some patients experience long-term benefits, others may relapse, necessitating maintenance TMS sessions (Carpenter et al., 2012; Janicak et al., 2002). TMS is generally well-tolerated, with common side effects such as scalp discomfort and headaches typically classified as mild and transient, though they can still impact adherence (Machii et al., 2006). In rare instances, more serious adverse events like seizures have been reported (Rossi et al., 2009, 2021).

TMS is also relatively expensive, and access may be restricted by geographic and insurance limitations, reducing its availability to a broader population (McClintock et al., 2018). Additionally, the optimal stimulation parameters (frequency, intensity, duration) for both DLPFC and DMPFC are still under investigation, and individualizing treatment protocols remains a challenge (Lefaucheur et al., 2014).

Advancements in TMS technology and research are addressing some of these limitations. Efforts are underway to personalize TMS protocols based on individual neuroimaging data and biomarkers, potentially improving response rates (Klooster et al., 2022; Voetterl, Sack, et al., 2023). Combining TMS with other treatments, such as psychotherapy or pharmacotherapy, may enhance the efficacy and durability of antidepressant effects (Donse et al., 2018; Rakesh et al., 2024). Understanding the neurobiological mechanisms underlying TMS effects can guide the development of more effective protocols and expand the search for new therapeutic targets, both within the prefrontal cortex and other brain regions and networks involved in depression, potentially improving outcomes for patients with TRD (Burke et al., 2019).

## ALTERNATIVE TMS PROTOCOLS AND TARGETS

TMS is a well-established non-invasive neuromodulation technique primarily used for treating MDD. While the conventional high-frequency TMS targeting the DLPFC has been effective for many patients, there is growing interest in alternative TMS protocols and brain targets to enhance therapeutic outcomes, particularly for those with TRD.

One notable advancement in TMS protocols is theta burst stimulation (TBS). Unlike traditional TMS, which involves delivering continuous stimulation at a fixed frequency, intermittent TBS (iTBS) delivers triplets bursts of high-frequency (50Hz) stimulation repeated every 200 milliseconds, in a pattern that mimics the brain's endogenous theta rhythms (Huang et al., 2011). iTBS has been shown to be non-inferior to standard 10 Hz rTMS in reducing depressive symptoms in TRD patients, with comparable remission rates (10 Hz: 27%; iTBS: 32%; Figure 1). Its major advantage is efficiency, as iTBS sessions last around 3 minutes compared to 40 minutes for 10 Hz TMS, making it a more practical and time-efficient option for patients (Blumberger et al., 2018). Continuous TBS (cTBS) is another variant of TBS, involving a single continuous train of 50Hz triplet bursts of stimulation. While less common in the clinical settings, studies have reported that cTBS can effectively reduce depressive symptoms and may offer benefits in specific patient populations or as an adjunct to other treatments (Huang et al., 2009). Overall, TBS protocols are becoming increasingly integrated into clinical practice for MDD due to their efficacy (comparable outcomes to standard TMS) and convenience (reduced session durations), making it a valuable and practical option for patients with MDD.

In recent years, the R-LOFC has gained attention as a potential target for TMS in treating MDD. The OFC is integral to reward processing, decision making, and emotional regulation (Kringelbach & Rolls, 2004). As noted earlier, the 'non-reward attractor theory of depression' proposes that MDD symptoms stem from ongoing activity and increased sensitivity within the OFC (Rolls, 2016). Neuroimaging studies have shown that individuals unresponsive to stimulation of DLPFC and DMPFC may exhibit distinct patterns of

pathological connectivity (Downar & Daskalakis, 2013), along with specific symptoms like anhedonia (Downar et al., 2014). Supporting this, an abnormal nexus of functional connectivity in the R-LOFC was found for biotype 2 patients, who showed weak responses to DMPFC-TMS (Drysdale et al., 2017). Further supporting this theory, an MRI study found enhanced functional connectivity between the LOFC and other parts of the non-reward system, exacerbating negative self-perception in depression (Cheng et al., 2016). Additionally, a meta-analysis highlighted abnormal PFC activation (target F8) across various psychiatric disorders, including MDD, indicating a transdiagnostic pattern (McTeague et al., 2017). Moreover, DBS targeting the LOFC has shown potential for rapid mood improvement in individuals with moderate-to-severe depression (Rao et al., 2018). These findings collectively suggest that the OFC could be a promising target for non-invasive brain stimulation. While the scientific evidence supporting TMS targeting the R-LOFC in psychiatry remains limited, there are promising findings. A PET study demonstrated a greater reduction in R-OFC metabolism in patients with obsessive-compulsive disorder (OCD) who received active R-OFC stimulation compared to those who received sham stimulation (Nauczyciel et al., 2014). Moreover, a case study reported improvements in mood, anxiety, and anhedonia in an MDD patient following 1 Hz-R-LOFC TMS (targeting Fp2), after failure to respond to DLPFC- and DMPFC-TMS treatments (Fettes et al., 2017). A subsequent case-series replicated the tolerability, safety, and efficacy of this approach (Feffer et al., 2018). Another case series demonstrated that sequential bilateral DLPFC-TMS augmentation using R-LOFC (targeting Fp2) stimulation in MDD patients unresponsive to L-DLPFC stimulation led to improvements in mood, negative rumination, and overall depression severity (Tadayonnejad et al., 2023). These studies suggest that R-LOFC is a viable alternative target for TMS in MDD, highlighting the need for further research to understand the potential benefits of R-LOFC-TMS for TRD.

Based on Figure 1, comparing response and remission rates for TRD patients with data from the STAR*D study shows that for individuals with 2-3 failed treatments, TMS protocols—particularly 10 Hz L-DLPFC and iTBS—demonstrate higher efficacy than continuing

with antidepressant treatments (Blumberger et al., 2018; Rush et al., 2006). These findings suggest that TMS may be a more effective alternative for TRD patients after multiple failed pharmacological attempts. The figure further highlights that switching to or adding the alternative TMS target, R-LOFC, maintains stable response and remission rates between 20-30%, reinforcing its potential utility in TRD cases (Feffer et al., 2018; Tadayonnejad et al., 2023). Additionally, another study found that TMS was significantly more effective in reducing depressive symptoms than switching antidepressant medications in patients with moderate TRD, with remission rates of 27.1% for TMS versus 4.9% for antidepressants (Dalhuisen et al., 2024). Overall, these findings underscore the growing evidence that TMS offers a promising and more effective treatment option for TRD patients compared to traditional pharmacological approaches.

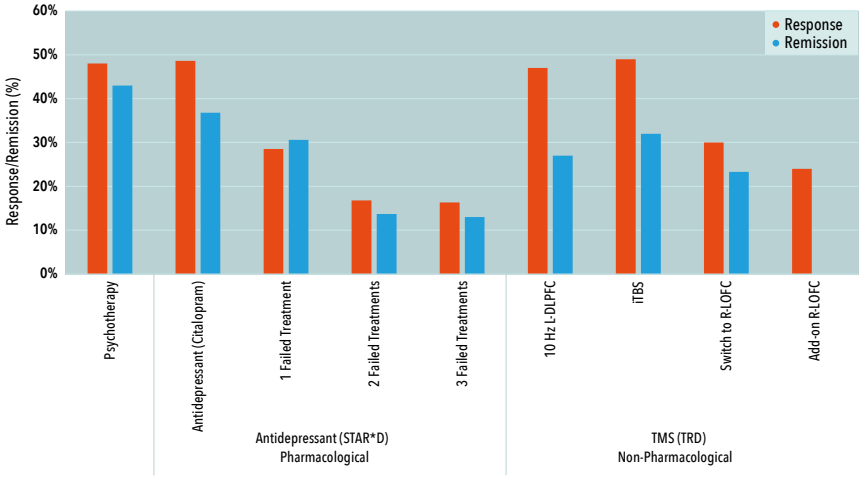


*Figure 1 Response and remission rates for patients with depression undergoing psychotherapy, antidepressants (including successive treatment failures), or TMS (various protocols and targets) in treatment-resistant depression (TRD)*

**Note.** Data for psychotherapy comes from Cuijpers et al. (2014) (Cuijpers, Karyotaki, et al., 2014), antidepressant data from the STAR*D study (Rush et al., 2006), and TMS data from Blumberger et al. (2018), Feffer et al. (2018), and Tadayonnejad et al. (2023) (Blumberger et al., 2018; Feffer et al., 2018; Tadayonnejad et al., 2023).

## MARKERS FOR DEPRESSION DIAGNOSIS AND TREATMENT SELECTION

### OVERVIEW OF BIOMARKERS IN DEPRESSION

Biomarkers, or biological markers, are measurable indicators that provide information about physiological or pathological processes or responses to treatment interventions (Biomarkers Definitions Working Group., 2001). In the context of MDD, these markers are essential for identifying individuals at risk, monitoring the progression of the disease, and predicting treatment response (Aronson & Ferner, 2017). Biomarkers can be broadly classified into several categories: neuroimaging, biochemical, and electrophysiological. Neuroimaging biomarkers use techniques like MRI and positron emission tomography (PET) to visualize and measure brain structures and functions linked to MDD. Common findings include structural abnormalities, like reduced hippocampal volume, particularly in patients with untreated depression, which worsens illness duration (Sheline et al., 2003), and functional changes, like decreased prefrontal cortex and increased amygdala activity, linked to emotional dysregulation in depression (Drevets, 2001). However, the large-scale ENIGMA (Enhancing Neuro-Imaging Genetics Through Meta-Analysis) consortium study showed no significant brain structural asymmetry changes in MDD, suggesting asymmetry may not be central to the disorder's etiology (de Kovel et al., 2019). Biochemical biomarkers refer to alterations in neurotransmitters, hormones, and other molecules found in blood, cerebrospinal fluid, or tissues. A key area of research is inflammation, where elevated levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-$\alpha$), have been associated with MDD (Dowlati et al., 2010).

### ELECTROENCEPHALOGRAPHIC MARKERS

Electroencephalography (EEG) is a non-invasive technique that measures the brain's electrical activity by placing electrodes on the scalp. This method captures spontaneous brain activity, which appears as oscillatory waves across various frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (>30 Hz).

Each frequency band corresponds to different brain states, ranging from slow rhythms during sleep to faster oscillations associated with cognitive processes (Buzsáki & Draguhn, 2004). EEG, with its high temporal resolution, affordability, scalability, and reliability, holds greater promise than MRI for advancing precision psychiatry by enabling sensitive, clinically relevant biomarkers (Etkin & Mathalon, 2024); its widespread use in clinical and research settings allows for real-time brain function assessment, making it invaluable for uncovering the neurophysiological basis of various conditions (Niedermeyer, 2011). In patients with MDD, abnormal EEG patterns have been observed, offering insights into the disorder's neurobiological underpinnings and showing potential as predictive markers for treatment response, though further validation is needed in clinical practice.

#### PREDICTIVE VALUE OF EEG MARKERS IN DEPRESSION

While EEG markers have previously been associated with MDD, well-powered studies and meta-analyses now suggest that no specific EEG metrics are consistently linked to MDD symptoms (Olbrich & Arns, 2013; van der Vinne et al., 2017). However, EEG metrics have shown promise in predicting treatment outcomes, offering valuable insights for identifying patients who may respond favorably to particular interventions (Arns et al., 2016).

Frontal alpha asymmetry (FAA) has shown promise as a predictor of antidepressant treatment response. In a study by Arns and colleagues (2016), it was found that in females, higher right FAA was associated with better remission rates when treated with SSRIs like escitalopram and sertraline. This effect was not observed in males, nor with the SNRI venlafaxine (Arns et al., 2016). These findings were replicated in an independent study (Ip et al., 2021). Additionally, the study found that using FAA to guide antidepressant selection could improve remission rates by 7-14%, supporting earlier findings (Bruder et al., 2001). These findings highlight FAA's potential utility in optimizing personalized treatment strategies for depression.

Theta power has shown mixed associations with treatment outcomes. The large Establishing Moderators and Biosignatures of An-

tidepressant Response for Clinical Care (EMBARC) biomarker study concluded that increased baseline rostral anterior cingulate cortex (rACC)-theta activity represented a nonspecific prognostic marker of treatment outcome, as patients with higher levels improved both on sertraline and on placebo (Pizzagalli et al., 2018). However, the International Study to Predict Optimized Treatment in Depression (iSPOT-D) biomarker study found that patients with high baseline rACC-theta activity exhibited poorer responses to escitalopram, sertraline, or venlafaxine, with this effect being more pronounced in a subgroup of patients who had experienced previous treatment failures (Arns et al., 2015).

Individual alpha peak frequency (iAPF), an individual's most pronounced alpha oscillations (Posthuma et al., 2001), has also been studied as a predictor of treatment response in depression. Low iAPF has been linked to better responses to sertraline (Arns et al., 2017) and initially to non-response in DLPFC-TMS (Arns et al., 2010, 2012). However, follow-up research could not replicate the non-response findings (Krepel et al., 2018; Widge et al., 2013). More recent studies clarified these discrepancies, showing that iAPF specifically predicts outcomes for 10 Hz TMS but not for 1 Hz-R-DLPFC-TMS. This effect was found using an average reference method, which captures more focal activity (Krepel et al., 2018; Voetterl, van Wingen, et al., 2023). Additionally, the association between iAPF and symptom improvement was revealed to be quadratic rather than linear, with the distance of iAPF to 10 Hz negatively correlating with symptom improvement after 10 Hz TMS (Corlier et al., 2019; Roelofs et al., 2021). Further validation research retrospectively found that using Brainmarker-I (an iAPF-based biomarker normalized for age and sex) decile scores significantly improved treatment outcomes, increasing remission rates by 14% for patients with high decile scores undergoing 1 Hz TMS and by 38% for those with low decile scores receiving ECT (Voetterl, Sack, et al., 2023). These results highlight the utility of iAPF-based stratification in optimizing treatment strategies for depression.

## STRATIFIED PSYCHIATRY

The traditional "one-size-fits-all" approach to depression treatment often relies on trial and error, leading to delayed recovery and increased risk of TRD (Arns et al., 2022). Stratified psychiatry offers a more precise alternative by tailoring psychiatric treatments to patient subgroups identified through biomarkers, clinical features, and other measurable data (see Figure 2) (Arns et al., 2023). This approach addresses the variability in depressive symptoms, treatment responses, and underlying biological mechanisms, as highlighted in studies like STAR*D (Rush et al., 2006), aiming to improve remission rates.

EEG biomarkers play a key role in stratified psychiatry for depression, helping clinicians in identifying neurophysiological patterns linked to specific depressive subtypes or treatment responses (Arns et al., 2022). The integration of multiple EEG biomarkers with clinical data and machine learning algorithms has shown considerable promise, achieving up to 88% accuracy in predicting antidepressant treatment responses when all features are included (Jaworska et al., 2019). This multi-marker approach supports the goals of stratified psychiatry, enabling more personalized and effective treatment strategies for depression.

The field of biomarker identification and application for depression treatment selection is rapidly evolving, with significant potential to improve patient outcomes. While neuroimaging and biochemical biomarkers provide valuable insights into the pathophysiology of MDD, EEG biomarkers have shown promise in predicting treatment response. Integrating these biomarkers into personalized treatment plans enables clinicians to better tailor treatments to individual patients, thereby improving overall remission outcomes and reducing the burden of TRD.

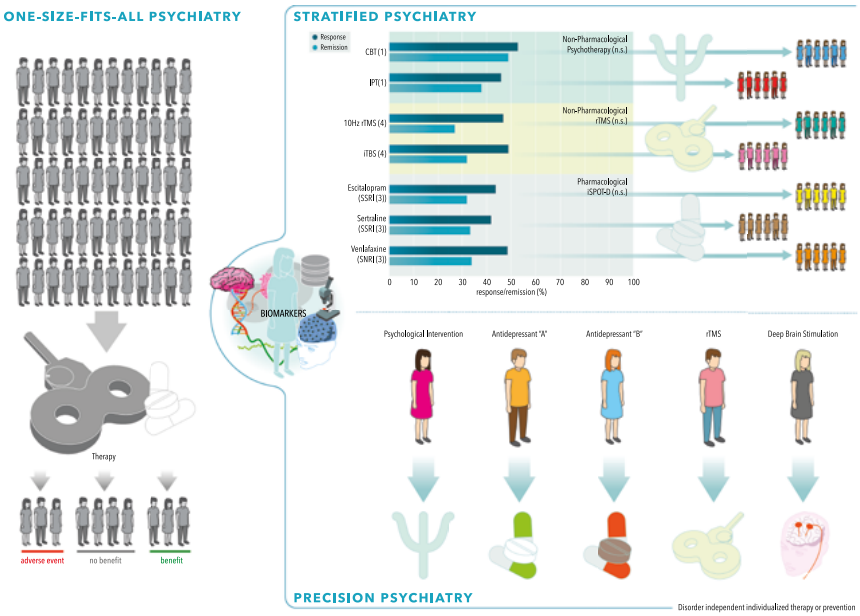


*Figure 2. Transition from One-Size-Fits-All Psychiatry to Stratified and Precision Psychiatry*
**Note.** An infographic illustrating the shift from traditional, diagnostic-based, 'one-size-fits-all psychiatry' that is currently in use (left), to more personalized, prognostic models such as 'Stratified Psychiatry' (right-top) and 'Precision Psychiatry' (right-bottom), which incorporate biomarkers and tailored treatments to improve therapeutic outcomes.

## SUMMARY / PHD THESIS AIMS

Depression remains a highly prevalent and challenging mental health issue, with conventional treatments often proving inadequate for a substantial number of individuals, particularly those diagnosed with TRD (or DTD). Despite the availability of psychotherapy and pharmacotherapy, many patients continue to struggle with depression, highlighting the urgent need for new approaches and a deeper understanding of the mechanisms driving treatment resistance. This thesis seeks to address this gap by focusing on two key areas. First, it aims to define and understand TRD through the lens of rACC-theta activity, which may serve as a critical biomarker for identifying treatment resistance. By exploring the role of rACC-theta in TRD, the aim is to stratify patients based on their likelihood of respond-

ing to certain treatments, ultimately enabling more personalized and precise therapeutic interventions. Second, investigation of the potential of R-LOFC-TMS as a rescue option for patients who do not respond to DLPFC-TMS, a commonly used protocol, will be conducted. R-LOFC-TMS holds promise as an alternative treatment avenue as it is believed to target a distinct neural network involved in depression. Validating this target across various protocols will be essential in determining its efficacy and potential for broader clinical application. Together, these two approaches—defining TRD through rACC-theta activity and exploring R-LOFC-TMS as an alternative treatment—form the central theme of this work, with the goal of advancing both the understanding and treatment of TRD.

## THESIS CHAPTERS OVERVIEW

In **Chapter 2**, we explore the relationship between rACC-theta activity and varying levels of treatment resistance in MDD. Building on the findings from the iSPOT-D study (Arns et al., 2015), which linked higher rACC-theta activity to poorer treatment responses—particularly in patients with multiple prior treatment failures— this study expands the analysis to a larger cohort. Using eLORETA, we analyzed oscillatory power across multiple frequency bands (delta, theta, alpha, beta, gamma) in over 500 MDD patients at different stages of treatment resistance (psychotherapy, antidepressants, TMS, ECT). In **Chapter 3**, we continue the research on the novel TMS target, the R-LOFC (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023). We evaluated its effectiveness in TRD patients who did not respond to standard TMS protocols targeting the DLPFC. This study included patients from two sites—one in the U.S. (N = 16) and one in the Netherlands (NL; N = 25)—with the TMS protocol modified to deliver low-frequency 1 Hz pulses to the R-LOFC, either as a singular treatment (NL, targeting FP2) and as an augmentation (U.S., targeting AF8). **Chapter 4** builds on this by examining outcomes in a new, larger sample of patients (N = 54) who did not respond to a full 36-session course of sequential bilateral (SBL) DLPFC-TMS, and subsequently switched to complete an additional full 36-session course of 1 Hz R-LOFC-TMS (targeting F8). Finally, in **Chapter 5**, we

investigated whether initiating treatment with the combined R-LOFC/L-DLPFC protocol from the first session provides additional benefits over standard bilateral DLPFC-TMS, in a large naturalistic sample (N > 3000) of TMS-naive MDD patients. Treatment effectiveness was compared between two groups: one treated with the conventional SBL-DLPFC-TMS protocol (1 Hz F4 + 20 Hz F3) and another with a 'hybrid' protocol, in which the right-sided sequence of 1 Hz stimulation was delivered at site F8 (overlying the R-LOFC) instead of F4.

# 2

# ROSTRAL ANTERIOR CINGULATE CORTEX OSCILLATORY POWER INDEXES TREATMENT-RESISTANCE TO MULTIPLE THERAPIES IN MAJOR DEPRESSIVE DISORDER

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## ABSTRACT

*Introduction:* High rostral anterior cingulate cortex (rACC) activity is proposed as a nonspecific prognostic marker for treatment response in major depressive disorder, independent of treatment modality. However, other studies report a negative association between baseline high rACC activation and treatment response. Interestingly, these contradictory findings were also found when focusing on oscillatory markers, specifically rACC-theta power. An explanation could be that rACC-theta activity dynamically changes according to number of previous treatment attempts and thus is mediated by level of treatment-resistance.

*Methods:* Primarily, we analyzed differences in rACC- and frontal-theta activity in large national cross-sectional samples representing various levels of treatment-resistance and resistance to multimodal treatments in depressed patients (psychotherapy [$n$ = 175], antidepressant medication [AD; $n$ = 106], repetitive transcranial magnetic stimulation [rTMS; $n$ = 196], and electroconvulsive therapy [ECT; $n$ = 41]), and the respective difference between remitters and non-remitters. For exploratory purposes, we also investigated other frequency bands (delta, alpha, beta, gamma).

*Results:* rACC-theta activity was higher ($p < 0.001$) in the more resistant rTMS and ECT patients relative to the less resistant psychotherapy and AD patients (psychotherapy-rTMS: $d$ = 0.315; AD-rTMS: d = 0.320; psychotherapy-ECT: $d$ = 1.031; AD-ECT: $d$ = 1.034), with no difference between psychotherapy and AD patients. This association was even more pronounced after controlling for frontal-theta. Post hoc analyses also yielded effects for delta, beta, and gamma bands.

*Conclusion:* Our findings suggest that by factoring in degree of treatment-resistance during interpretation of the rACC-theta biomarker, its usefulness in treatment selection and prognosis could potentially be improved substantially in future real-world practice. Future research should however also investigate specificity of the theta band.

## INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability in the world, with symptoms ranging from mild anhedonia to social and occupational malfunctioning and death by suicide (World Health Organization, 2017). It is believed to be characterized by a disruption in the frontal-limbic circuitry (Pizzagalli, 2011), in which there is a deficit in switching between the default mode network and the central executive network (Zheng et al., 2015). Various therapies aim to modify the pathological network activity in depression using different modi operandi (Mayberg, 2003), and are usually delivered in a stepped-care model. This means that patients start with less invasive treatments (e.g., psychotherapy and/or antidepressant medication (AD)) and progress to more intensive treatments accompanied with higher costs and side effects (e.g., intranasal or intravenous ketamine, repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT)) once prior treatments have failed (van Straten et al., 2010). Remission rates for treatments in the early stages are around 35% (Arns et al., 2019; Blumberger et al., 2018; Cuijpers, Karyotaki, et al., 2014; Hollon et al., 2002; Saveanu et al., 2015) and decrease to around 13-14% after 2-3 failed treatments (Rush et al., 2006), after which a patient's de-

pression is categorized as treatment-resistant depression (TRD), also named "difficult-to-treat depression" (Rush et al., 2006). To help treat MDD more efficiently, current research aims to identify biomarkers (i.e., prognostic metrices based on the brain network activity at baseline) that can identify likely TRD cases at an early stage, and predict which treatments are likely to be more effective in such cases.

One brain region of interest for biomarker discovery in depression is the rostral anterior cingulate cortex (rACC). High rACC activity has been proposed to be a non-specific prognostic marker for treatment response (Pizzagalli, 2011; Pizzagalli et al., 2018). Studies using EEG, fMRI, or PET have found that patients with high rACC activity are more likely to achieve a positive treatment outcome, independent of modality (e.g., AD, sleep deprivation, rTMS)(Pizzagalli, 2011). However, other studies using PET/SPECT have reported the opposite finding of a negative association between baseline rACC activation and treatment response (Pizzagalli, 2011). These contrary findings were reported for treatments with paroxetine, venlafaxine, cognitive behavioral therapy (CBT), ECT, and rTMS (Brody et al., 1999; Konarski et al., 2009; McCormick et al., 2007; Mottaghy et al., 2002; Pizzagalli, 2011).

A similar apparent contradiction is seen in this region with theta power on EEG. A recently published follow-up to the large EMBARC biomarker study reported that patients with high baseline rACC-theta activity were more likely to improve with treatment in general, whether on sertraline or on placebo (Pizzagalli et al., 2018). However, in contrast, the iSPOT-D biomarker study reported the opposite finding, that patients with high baseline rACC-theta showed poorer response in general, to escitalopram, sertraline, or venlafaxine (Arns et al., 2015).

One proposal to reconcile these findings is that the predictive value of rACC-theta may depend on the degree of treatment-resistance. For example, Hunter et al. found that antidepressant-naïve patients with high rACC-theta had greatest treatment improvement, and that for antidepressant-experienced patients it was those with low rACC-theta that showed greatest treatment improvement (Hunter et al., 2013). In keeping with this pattern, EMBARC patients (who were required to be fairly treatment-naïve, with no failed medication trials in the cur-

rent episode) with high rACC-theta showed the greatest treatment improvement (Pizzagalli et al., 2018), while iSPOT-D patients with more treatment failures showed the strongest relationship between high rACC-theta and poor treatment response (Arns et al., 2015).

Following these studies, we may question whether high rACC-theta should be considered a general (treatment non-specific) marker of depressive symptom improvement (prognostic marker) (Pizzagalli, 2011), whether rACC-theta is a biological marker correlated to treatment-resistance (trait), or whether rACC-theta dynamically changes according to the number of previous treatment attempts and thus is mediated by the level of treatment-resistance (Arns et al., 2015; Hunter et al., 2013). The aim of the present study was therefore to clarify this issue, by first determining whether the degree of treatment-resistance correlates with baseline rACC-theta activity, and second, whether rACC-theta activity can be used to predict treatment outcome more effectively when the degree of treatment-resistance is integrated in prediction analyses. We hypothesized that baseline rACC-theta activity would change with increasing levels of treatment-resistance, and that patients with high treatment-resistance and co-occurring high baseline rACC-theta activity would show poorer treatment outcomes.

We set out to test this hypothesis in a new, large, naturalistic dataset comprising of four Dutch national open-label datasets, in which patients were allocated to treatment in a stepped-care model according to structured clinical guidelines (Craighead & Dunlop, 2014; Donse et al., 2018; Spijker et al., 2013). The use of these datasets provided some assurance that patients were truly referred to treatments based on their level of depression severity and resistance level. The datasets covered a variety of treatment modalities: psychotherapy and AD for patients with low treatment-resistance, rTMS for patients with medium treatment-resistance, and ECT for patients with high treatment-resistance (Kellner et al., 2012; Voigt et al., 2019; Weissman et al., 1979). This study focused on rACC-theta and frontal-theta activity as this study was an a priori planned extension of the earlier 2015 iSPOT-D study (Arns et al., 2015). Pre-treatment EEG recordings and standardized clinical questionnaires obtained before and after treatment enabled assessment of rACC-theta at different levels of treat-

ment-resistance, as well as assessment of whether rACC-theta was associated with remission for any treatment modality.

## MATERIALS AND METHODS

### PARTICIPANTS

Five hundred eighteen EEG-recordings of participants from different clinics were collected for this study and were categorized into four datasets (see below for details). These datasets were national open-label datasets, collected under naturalistic conditions, in which patients were allocated to treatment in a stepped-care-model according to structured clinical guidelines (Craighead & Dunlop, 2014; Donse et al., 2018; Spijker et al., 2013). We also used the healthy control group from the iSPOT-D study (Arns et al., 2015) ($n$ = 336) to visualize how rACC-theta activity compared to the following datasets in the remission section. All participants provided written informed consent.

*Dataset 1: Psychotherapy*
The psychotherapy dataset consisted of patients diagnosed with non-psychotic MDD or dysthymia and a Beck Depression Inventory second edition (BDI-II) (Van der Does, 2002b) score ≥14 at baseline, who received any form of psychotherapy as monotherapy ($n$ = 175). Patients could further be divided in having received CBT ($n$ = 94) or other types of psychotherapy (Other; $n$ = 81). BDI-II was recorded before and after treatment. Details about this sample are described elsewhere (Meijs et al., 2022).

*Dataset 2: Antidepressants*
The AD dataset consisted of patients diagnosed with non-psychotic MDD or dysthymia and a BDI-II score ≥14 at baseline, who received AD, either as monotherapy or in combination with psychotherapy ($n$ = 106). This sample was taken from van der Vinne et al. (van der Vinne et al., 2021). BDI-II was recorded before and again after 8 weeks of medication (monotherapy) or at the end of psychotherapy if this preceded the 8 weeks of medication (combination).

*Dataset 3: rTMS*
The rTMS dataset consisted of 196 patients, diagnosed with non-psychotic MDD or dysthymia and BDI-II ≥14 at baseline, who underwent protocolized rTMS treatment concurrent with psychotherapy. Patients received high-frequency TMS (10 Hz left dorsolateral prefrontal cortex, DLPFC), low-frequency TMS (1 Hz right DLPFC), or both 1 Hz and 10 Hz sequentially. All patients completed at least 10 sessions of treatment and filled in the BDI-II at baseline and at the last session (on average session 21). Details about this sample are described elsewhere (Donse et al., 2018; Meijs et al., 2022; van Dijk et al., 2022) and data are part of the open access dataset TDBRAIN (https://brainclinics.com/resources/) (van Dijk et al., 2022).

*Dataset 4: ECT*
The fourth dataset consisted of 41 patients, treated with complete ECT-courses at the Rijnstate Hospital. Most patients suffered from TRD. Depression severity was scored with the Hamilton Rating Scale for Depression ($HRSD_{17}$), within one week before start of ECT and within one week after the course. ECT was administered according to Dutch standards, and right unilateral and bifrontotemporal electrode placements were applied according to the psychiatrists' discretion. The ECT-course was terminated after reaching remission (HRSD17 score ≤ 7), or when patients did not improve any further after one week, or if ten bilateral ECT-sessions did not show any change in depression.

#### EEG DATA COLLECTION AND PREPROCESSING

EEG data were collected using a standardized methodology and platform (Brain Resource Ltd., Australia). The EEG platform and methodology used in this study were identical to the iSPOT-D study (Arns et al., 2015), and details and validations have been published elsewhere (Arns et al., 2016; Paul et al., 2007; L. M. Williams et al., 2005).

In summary, patients were seated in a sound and light attenuated room within a clinical setting. As a naturalistic dataset, recordings occurred either in the morning or in the afternoon based on patient and room availability. EEG data were acquired from 26 channels: Fp1,

Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (ANT Waveguard-cap; NuAmps; 10-20 electrode international system). EEG was collected for two minutes with eyes open, with the patient asked to fixate on a red dot on the screen) and two minutes with eyes closed. The patient was instructed to remain relaxed for the duration of the recording. No intervention took place when drowsiness patterns were observed in the EEG. Data were referenced to averaged mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Impedances were kept below 10kΩ and the sampling rate was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

Data were filtered (0.3-100Hz and notch of 50Hz), EOG-corrected using a regression-based technique similar to that used by Gratton et al. (Gratton et al., 1983), and automatic artifact-detection and -removal were performed. Artifact signals included EMG, sharp channel-jumps (up and down), kurtosis, extreme voltage swing, residual eyeblinks, electrode bridging, and extreme correlations. Automatic artifact rejection was performed using a custom-built Python package (van Dijk et al., 2022). This package is based on the automated method employed in the iSPOT-D study (Arns et al., 2015), as it showed an agreement of 98.4% with "manual" artifact rejection by certified EEG expert (Arns et al., 2016) and was further validated by van Dijk et al. (van Dijk et al., 2022) [full python code available online (http://www.brainclinics.com/resources)].

## ANALYSIS

*EEG eLORETA analyses*

EEG analysis was performed identical to the prior report by Arns and colleagues (Arns et al., 2015), but in short: based on the scalp-recorded electric potential distribution, the exact low-resolution brain electromagnetic tomography (eLORETA) software (http://www.uzh.ch/keyinst/loreta.htm) was used to compute the cortical three-di-

mensional (3D) distribution of current density (i.e., the amount of electrical current flowing through a solid; unit: amperes per square meter, Å/m2).

Previous studies have demonstrated that eLORETA can outperform other linear inverse solutions (e.g., Minimum Norm Estimate, dynamic Statistical Parametric Mapping, Weighted Minimum Norm, Local Autoregressive Average, Dynamic Imaging of Coherent Sources, and Linearly Constrained Minimum Variance) under ideal, noise-free conditions (Carboni et al., 2022; Halder et al., 2018; Pascual-Marqui et al., 2018). It has also been reported that this linear inverse solution for the EEG has the unique property of having exact (zero-error) localization for point test sources anywhere in the brain, albeit with low spatial resolution (Gerrits et al., 2019; Pascual-Marqui, 2007; Pascual-Marqui et al., 2011, 2018).

Previous studies cross-validated the LORETA algorithm to ensure eLORETA's confidence estimates in the respective inverse solutions, using not only EEG but also independent techniques of higher anatomical precision such as fMRI and PET. These studies showed that the anatomical localization provided by eLORETA's intracortical EEG-source estimates showed good concordance with independent measures of neural activation obtained via BOLD signals on fMRI, and via glucose metabolism on PET imaging (Mulert et al., 2004; Pizzagalli et al., 2004). eLORETA is an improvement over the original LORETA version (Pascual-Marqui et al., 1994) and the standardized version sLORETA (Pascual-Marqui et al., 2002). The eLORETA method is described in detail by Pascual-Marqui (Pascual-Marqui, 2007).

As eLORETA is deemed a valid way of analyzing rACC-theta activity (Pizzagalli et al., 2001), we used it to extract EEG current source density from the rACC (using the voxels reported by Pizzagalli et al. (Pizzagalli et al., 2001)) and frontal cortex during resting state conditions with eyes closed. The regions of interest (ROI) did not overlap. The employed frequency band for theta was 6.5–8 Hz (for exploratory analyses also delta (1.5-3.5 Hz), alpha (8-13 Hz), beta (14.5-30 Hz), and gamma (31-49 Hz) bands were assessed). Participants were excluded if extraction was not possible.

### STATISTICS

SPSS version 28 was used for statistical analyses. Remission was defined as a score ≤ 12 on the BDI-II post-treatment, and ≤ 7 on the $HRSD_{17}$ (see Participants).

In accordance with the iSPOT-D study (Arns et al., 2015), the primary analysis consisted of assessing whether there was a significant difference in the ROI (rACC and frontal) in the theta frequency band between treatments (psychotherapy, AD, rTMS, ECT) at baseline. Normal distribution of EEG measures was inspected, and theta measures were log transformed before statistical analysis. Differences in age, sex, and baseline depressive severity were tested using One-Way ANOVA or non-parametric tests (sex). In case of group differences in one of these measures, these variables were added as a covariate. To determine whether there is a difference in activity between rACC- and frontal-theta and the level of TRD, a repeated measures ANOVA was conducted with dependent variable rACC-theta and frontal-theta during EC; fixed factors treatment and sex; and covariate age. When significant interactions were found, we followed-up with univariate ANOVA-analyses.

For exploratory purposes, we repeated the analyses performed for theta band on the delta, alpha, beta, and gamma bands, and reported these in Supplementary Materials. As we are investigating an a priori defined analysis based on the 2015 iSPOT-D study (Arns et al., 2015), these exploratory analyses should be considered as post-hoc and secondary to the main analysis, and therefore more strict corrections were used for multiple testing ($p = 0.05/61$).

The secondary analysis consisted of comparing rACC-theta activity between remitters and non-remitters. A univariate ANOVA was conducted with dependent variable rACC-theta during EC; fixed factors treatment (CBT, Other, AD, rTMS, ECT), sex, and remission; and covariates age and baseline severity. When significant interactions were found, we followed-up with univariate ANOVA-analyses. To test for protocol specific effects, we also performed a univariate ANOVA analysis comparing rACC-theta activity between remitters vs non-remitters across the 1Hz vs 10 Hz protocol groups, with sex, age,

and baseline BDI as covariates of non-interest (demographic features are presented in Supplementary Materials).

For main effects, significance level was set at $\alpha = .05$ and for post-hoc comparisons a Bonferroni-corrected p-value was used (determined by the number of comparisons). Effect sizes of main effects are reported in Cohen's *d*.

## RESULTS

The final demographic features and depression severity of participants included in the analyses following exclusion criteria (e.g., no EEG data) are presented in Table 1.

| | Datasets | | | | |
|---|---|---|---|---|---|
| | psychotherapy | | AD | rTMS | ECT |
| | CBT | other | | | |
| Full datasets | | | | | |
| Sample size, *n* | 175 | | 106 | 196 | 41 |
| | 94 | 81 | | | |
| Included in analysis | | | | | |
| Sample size, *n* | 140 | | 97 | 193 | 28 |
| | 74 | 66 | | | |
| Males *n* (%) | 50 (36) | | 41 (42) | 95 (49) | 11 (39) |
| | 32 (43) | 18 (27) | | | |
| Age, mean (SD), years | 37 (14.1) | | 40 (14.2) | 43 (13.4) | 50 (14.2) |
| | 35 (14.1) | 40 (14.1) | | | |
| Baseline BDI-II/$HRSD_{17}$ | 31.6 | | 32,5 | 31,2 | 20,9 |
| | 30.2 | 33.0 | | | |
| Post-treatment BDI-II/$HRSD_{17}$ | 20.1 | | 22,9 | 14,1 | 13,28 |
| | 20.1 | 20,1 | | | |

Sample size included in analysis reflects the number of people with complete baseline data who finished treatment and with successful eLORETA extraction. Dataset psychotherapy was divided into participants having received cognitive behavioral therapy (CBT) and other types of psychotherapy (other). AD, antidepressant medication; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy; CBT, cognitive behavioral therapy; SD, standard deviation; BDI-II, Beck Depression Inventory; $HRSD_{17}$, Hamilton Rating Scale for Depression.

*Table 1. Key demographic features and depression severity of the patient sample*

## PRIMARY ANALYSES: ROI ACTIVITY AND TRD-LEVELS

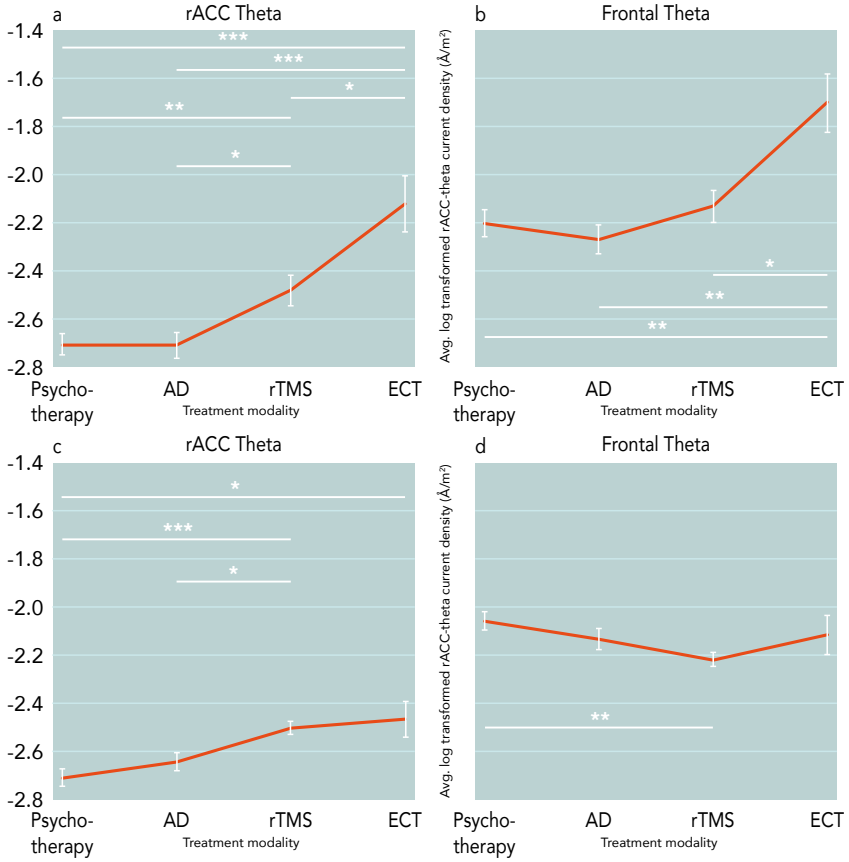



*Fig. 1. rACC-theta and frontal-theta power levels across treatment modalities. a Illustrates rACC-theta activity being higher as treatment-resistance level increases, with no significant difference found between psychotherapy and AD. b Illustrates frontal-theta activity being higher in ECT compared to the other treatments. c Illustrates rACC-theta activity covaried by frontal-theta activity, and shows higher rACC-theta activity in rTMS compared to psychotherapy and AD, and in ECT compared to psychotherapy. d Illustrates frontal-theta activity covaried by rACC-theta activity, and shows lower frontal-theta activity in rTMS compared to psychotherapy. Significance level was Bonferroni-corrected. Error bars represent standard error of the mean. *p < 0.008, **p < 0.0017, ***p < 0.00017.*

No significant correlation was found between baseline BDI-II and rACC-theta and frontal-theta activity when grouping the psychotherapy, AD and rTMS datasets ($p$ = .826 and $p$ = .929), nor between baseline HRSD17 and rACC-theta and frontal-theta activity for the

ECT dataset ($p$ = .231 and $p$ = .160). As one dataset used $HRSD_{17}$ and the other three datasets used BDI-II, we removed baseline severity as covariate from further analyses in this section.

Repeated measures ANOVA, using age as a covariate, yielded for frontal and rACC-theta a significant effect of treatment ($F(3, 449) = 7.607$; $p < .001$), ROI ($F(1, 449) = 53.809$; $p < .001$), age ($F(1, 449) = 17.437$; $p < .001$), an interaction effect of ROI X treatment ($F(3, 449) = 4.949$; $p = .002$), and of ROI X sex ($F(1, 449) = 6.298$; $p = .012$). Post-hoc analyses revealed a significant difference between the two ROIs across treatments ($p < .001$).

Following up on the interaction ROI X treatment, a univariate ANOVA, using age as covariate, was conducted for rACC-theta and yielded a significant main effect of treatment ($F(3, 449) = 10.186$; $p < .001$), and of age ($F(1, 449) = 16.382$; $p < .001$). Pairwise comparisons revealed a significant difference in rACC-theta activity between all types of treatments [ECT patients had higher rACC-theta activity than psychotherapy, AD, and rTMS patients (psychotherapy-ECT: $p < .001$, $d = 1.031$; AD-ECT: $p < .001$, $d = 1.034$; rTMS-ECT: $p = .005$, $d = .480$); rTMS patients had higher rACC-theta activity than psychotherapy and AD patients (psychotherapy-rTMS: $p < .001$, $d = .315$; AD-rTMS: $p = .004$, $d = .320$)], except between psychotherapy and AD ($p = 726$, $d = .008$; shown in Fig. 1. a).

Furthermore, a univariate ANOVA for frontal-theta, using age as covariate, yielded a significant main effect of treatment ($F(3, 449) = 5.071$; $p = .002$), and of age ($F(1, 449) = 15.783$; $p < .001$). Pairwise comparisons revealed only a significant difference in frontal-theta activity between ECT and the other types of treatments [ECT patients had higher rACC-theta activity than psychotherapy, AD, and rTMS patients (psychotherapy-ECT: $p < .001$, $d = 1.769$; AD-ECT: $p < .001$, $d = .913$; rTMS-ECT: $p = .003$, $d = 546$; shown in Fig. 1. b)].

Due to the ROI X treatment interaction found in the repeated measures ANOVA, a mediation analysis was performed to rule out that rACC-theta effects were mediated by frontal-theta (Baron & Kenny, 1986). Univariate ANOVA, using age and frontal-theta as covari-

ate, yielded for rACC-theta a significant main effect of treatment ($F$(3, 448) = 8.901; $p$ < .001), frontal-theta ($F$(1, 448)= 1095.624; $p$ < .001), and of sex ($F$(1, 448) = 5.128; $p$ = .024). Pairwise comparisons revealed rACC-theta activity to be significantly higher in rTMS and ECT patients compared to psychotherapy patients (psychotherapy - rTMS: $p$ < .001, $d$ = .541; psychotherapy - ECT: $p$ = .003, $d$ = .628) and in rTMS patients compared to AD patients ($p$ = .003, $d$ = .374; shown in Fig. 1. c).

Finally, univariate ANOVA, using age and rACC-theta as covariate, yielded for frontal-theta a significant main effect of treatment ($F$(3, 448)= 3.837; $p$ = .010), rACC-theta ($F$(1, 448) = 1095.624; $p$ < .001), and of sex ($F$(1, 448)= 6.179; $p$ = .013). Pairwise comparisons only revealed frontal-theta activity to be significantly lower in rTMS patients compared to psychotherapy patients ($p$ < .001, $d$ = .380; shown in Fig. 1. d).

For the other frequency bands, an exploratory analysis found that a significant interaction between ROIs and treatment groups was evident for delta (rACC), beta and gamma (rACC and frontal) bands, but not for the alpha band. The results remained significant when mediated by the respective frequency band in the frontal region (Supplementary Materials).

#### SECONDARY ANALYSES: RACC-THETA AND REMISSION

When investigating whether rACC-theta activity was associated with remission, we divided the data further into five treatments: CBT, other psychotherapy forms (Other), AD, rTMS, and ECT. A one-way ANOVA with remission as factor determined that baseline severity was significant for each treatment, except for ECT (CBT $p$ = .006; Other $p$ = .006; AD $p$ < .001; rTMS $p$ < .001; ECT $p$ = .568). We therefore took baseline severity into account for the following analyses of this section. We accounted for the difference between questionnaires (BDI-II and $HRSD_{17}$) by performing a Z-score transform.

Univariate ANOVA, using age and baseline severity as covariates, yielded for rACC-theta in relation to remission a significant main effect of treatment ($F$(4, 432) = 5.793; $p$ < .001), age ($F$(1, 432) = 17.456; $p$ < .001), and an interaction effect of treatment X remission ($F$(4, 432)

= 4.591; $p$ = .001). Repeating the analysis for every treatment independently only revealed a significant difference in rACC-theta activity between remitters and non-remitters for AD (remitters had higher rACC-theta activity than non-remitters: $p < .001$, $d$ = .781), but not for CBT, Other, rTMS or for ECT ($p$ = .014; $p$ = .019; $p$ = .089; $p$ = .820; respectively shown in Fig. 2, in which the reader can also visually compare the results to a healthy control group extracted from the iSPOT-D study (Arns et al., 2015)).

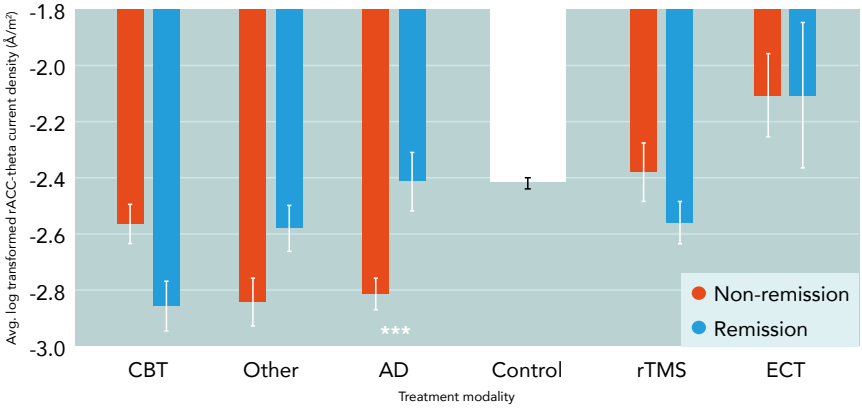



*Fig. 2. rACC-theta and frontal-theta power levels across treatment modalities, and healthy controls (n = 336, from the iSPOT-D study (Arns et al., 2015)), in relation to remission. Graph shows higher rACC-theta activity in rTMS and ECT compared to psychotherapy and AD, with healthy controls in between these two levels of treatment-resistance. A significant difference in rACC-theta activity between remitters and non-remitters was only found in the AD dataset, with rACC-theta activity being higher in remitters. Significance level was Bonferroni-corrected. Error bars represent standard error of the mean. *p < 0.01, **p < 0.002, ***p < 0.0002.*

The exploratory analysis, testing for protocol specific effects, revealed no significant interaction between remission and rTMS protocol groups ($p$ = .900).

## DISCUSSION

Following up on the iSPOT-D study (Arns et al., 2015), we investigated whether there are differences in pre-treatment frontal- and rACC-theta activity across treatments with various levels of TRD. We found that rACC-theta activity differed between first line care (i.e., psychotherapy and AD; low activity) and second/third line care (i.e., rTMS and ECT; high activity), and these effects were not mediated by frontal-theta activity. Therefore, the data suggests that these results are specifically associated with TRD level and rACC-theta, which is in favor of our hypothesis that baseline rACC-theta activity changes with increasing levels of treatment-resistance.

Furthermore, we only found a significant difference in rACC-theta between remitters and non-remitters for the patients treated with AD, with higher rACC-theta found in remitters compared to non-remitters. We believe that this result shows an interesting consistency with the previously reported findings in the fairly treatment-naïve patients of the EMBARC study: those with high rACC-theta activity likewise showed greater improvement on ADs than those with lower rACC-theta activity (Pizzagalli et al., 2018). Intriguingly, resemblance to the iSPOT-D study finding, that patients with high rACC-theta activity and higher levels of treatment-resistance showed poorer response to treatment (Arns et al., 2015), can be found in the current rTMS group. Close inspection of Figure 2 reveals a similar trend in the rTMS group (who had relatively higher levels of treatment-resistance): higher rACC-theta activity in non-remitters compared to remitters. However, this finding is not significant. Summarized, the present findings offer some suggestive evidence towards a reconciliation of the EMBARC and the iSPOT-D findings regarding rACC-theta and remission.

We also found that rACC-theta for healthy controls is situated in between first line care (lower rACC-theta) and second/third line care (higher rACC-theta). Based on these large sample sizes ($n$ = 518 MDD, $n$ = 336 healthy controls), it is interesting to find this scattered pattern as it further demonstrates that high rACC-theta activity is not a non-specific prognostic biomarker for patients with depression (Piz-

zagalli, 2011), with overall more variable effects and lower effect sizes relative to the primary analysis focused on treatment-resistance level, lending more support for an association with treatment-resistance. It is recommended that studies do follow-up EEGs in depressed patients (longitudinal studies) using a within-subject design.

Our finding that rACC-theta differed across TRD levels lends support to the suggestion that rACC-theta is not simply mediated by placebo response (since lower placebo response is expected with higher TRD level). Furthermore, as the EMBARC study determined that rACC-theta activity remained stable between baseline and week 1 for patients given either sertraline or placebo, rACC-theta is most likely not mediated by acute pharmacological effects nor placebo effects (Pizzagalli et al., 2018). We must therefore question whether the difference in rACC-theta across TRD levels is a pre-existing biomarker for resistance to first line treatments, or whether it is instead associated with prior (pharmacological) treatment exposures. The results however are in line with our earlier iSPOT-D report (Arns et al., 2015) where the MDD population as a whole had higher rACC-theta compared to the control group – a finding which we can now interpret as a consequence of enrolling an MDD population with a fairly high TRD level, relative to our psychotherapy and AD samples.

It is also possible that the baseline differences in rACC-theta between the patient groups in our study reflect a process of neuroplasticity in response to illness progression and successive treatment failures. rACC-theta has been found to change in an individual over time within a single episode of MDD, meaning rACC-theta may capture some state-related aspect of brain functioning that is associated with subsequent response to medication (Arns et al., 2015; Hunter et al., 2013). An MRI study reported that MDD patients with larger ACC volumes had fewer previous hospitalizations than patients with smaller ACC volumes (Frodl et al., 2008). Duman et al. further associated the extent of ACC volume reduction with severity of depression, duration of illness, and time length of treatment (Duman et al., 2016). The process of neuroplasticity in response to illness progression and successive treatment failures would be an interesting issue for further studies to pursue.

The understanding of the pathophysiology of MDD has shifted to a model based on dysfunctional connectivity between neural networks, rather than abnormalities in the activity of a single neuroanatomical location (Kaiser et al., 2015). In this view, we should consider the activity of the rACC as a node integrated in more complex neural brain networks with different patterns of connectivity and predictive capacities between different levels of response or resistance to treatments. We suggest an enhancement of our current analyses by incorporating connectivity with rACC and its association with treatments with levels of TRD, and also by comparing connectivity pre- and post-treatment.

Of note, the exploratory analyses for the other frequency bands in the ROIs also revealed significant differences between treatment groups in the delta (rACC), beta and gamma (rACC and frontal) bands. The relatively treatment-resistant ECT patients had significantly higher power in beta and gamma bands in both rACC and frontal regions compared to the other, less treatment-resistant, patient samples. For the delta band, the rTMS patients had significantly higher power in the rACC compared to the psychotherapy and AD patients. In addition, when mediated by the respective frontal band, rTMS patients had significantly higher (delta, beta, gamma) power in the rACC compared to psychotherapy patients. These results could suggest that the effects of treatment-resistance are more specific to the theta band. However, since the literature on the role of these frequency bands in treatment-resistance is currently limited, and the focus of this paper is on rACC-theta, it falls beyond the scope of the present work to examine these findings in comprehensive detail. However, based on our results, we do suggest further exploration of frequency bands other than theta, and whether they may also play an important role in treatment selection or outcome prediction in TRD, or instead, whether they reflect other potential cofounding factors such as medication effects, sleep disturbance, or other factors yet to be determined.

The use of a large naturalistic dataset in this study offers benefits in terms of generalization to real world practice. However, it also engenders a number of limitations that should be acknowledged. Demo-

graphic differences (e.g., premorbid IQ, social and economic status, ethnicity, smoking and drinking status, the history of drug abuse and other psychiatric and neurological diseases) may affect a person's resistance to treatment, and therefore may have influenced our results. However, such data were not systematically collected for all datasets. Furthermore, in selecting confounds for our model, we were as comprehensive as possible given the available data in this large naturalistic community sample. Future research could consider collecting a wider array of variables to address other potential confounding factors. Regarding regions of interest, as the present work was an a priori planned follow-up study drawing upon the findings of the earlier 2015 iSPOT-D study (Arns et al., 2015), in which the effects of interest were seen specifically in theta activity of the rACC and frontal regions, we here exclusively focused on these regions as a measure to limit Type-I error. Exploring other regions may be of interest to future studies. In this study, the datasets were collected with the intention to identify predictors of treatment response; thus, post-treatment EEG was not systematically collected. Future studies could investigate the longitudinal development of the rACC-TRD association through within-subject designs, by comparing pre- and post-treatment EEGs. Since this dataset was collected under naturalistic conditions, standardized therapy regimens were sometimes influenced by clinical judgement. Although the lack of treatment standardization conform RCTs is a limitation to be acknowledged, it also offers the advantage of representing real-world clinical practice. As such, the findings are likewise more likely to translate successfully to real-world settings. While it would have been interesting to analyze the differences between specific ADs in relation to rACC-theta and levels of treatment-resistance, the number of participants for each AD was too small to perform a meaningful statistical analysis (there were a total of 24 different AD combinations, comprising of seven major group classes, for 106 subjects), reflecting the naturalistic research setting. Future research could focus on AD-specific markers. Although it is theoretically possible that MDD patients starting with different ADs have different levels of baseline rACC-theta activity, we consider this less likely due to previously reported results from the EMBARC study showing no differences in rACC-theta between unmedicated (baseline) and medicated (week 1) patients (Pizzagalli et al., 2018).

In conclusion, our study found that rACC-theta differs across treatments for MDD, with higher rACC-theta activity found in second/third line care (i.e., rTMS and ECT), and lower activity in first line care (i.e., psychotherapy and AD). Furthermore, our study found AD remitters to have higher rACC-theta activity compared with AD non-remitters, which is consistent with the EMBARC findings (Pizzagalli et al., 2018). Our study also found suggestive evidence that other frequency bands outside of theta could potentially be useful in treatment selection or outcome prediction - an interesting topic for future study. Overall, the findings of the present study provide a new perspective on a known biomarker, by refining upon the older theory that high rACC activity is a non-specific prognostic biomarker for patients with depression (Pizzagalli, 2011). By factoring in the degree of treatment-resistance during interpretation of the rACC-theta biomarker, its usefulness in treatment selection and prognosis could potentially be improved substantially in future real-world practice.

## SUPPLEMENTARY MATERIALS

***Table S1*** *Key demographic features and depression severity of the rTMS patient sample.*

| | rTMS | | |
|---|---|---|---|
| | 10 Hz L | 1 Hz R | Both |
| Full datasets | 196 | | |
| Sample size, *n* | 74 | 115 | 7 |
| Included in Exploratory Analysis | 186 | | |
| Sample size, *n* | 73 | 113 | |
| Males *n* (%) | 93 (50%) | | |
| | 37 (51%) | 56 (50%) | |
| Age, years, mean (SD) | 43 (13.3) | | |
| | 41 (13.4) | 45 (13.4) | |
| Baseline BDI-II | 30.8 | | |
| | 30.2 | 31.3 | |
| Post-treatment BDI-II | 13.9 | | |
| | 13.1 | 14.5 | |

Note. Sample size included in exploratory analysis reflects the number of people who received either high frequency protocol over the left dorsolateral prefrontal cortex (DLPFC) or low frequency protocol over the right DLPFC, with complete baseline data who finished treatment and with successful eLORETA extraction. rTMS = repetitive transcranial magnetic stimulation; 10 Hz L = 10 Hz left DLPFC; 1 Hz R = 1 Hz right DLPFC; Both = both protocols sequentially; SD = standard deviation; BDI-II = Beck Depression Inventory.

A repeated measure ANOVA was performed for each of the other frequency bands (delta, alpha, beta and gamma), with within-subject: region of interest (ROI; frontal and rACC); between-subject: treatment group (Tx; psychotherapy, antidepressant (AD), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT)) and sex; and covariate: age. The interaction result between ROI and treatment group for each frequency band can be found in Table S1.

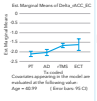
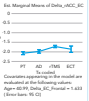
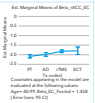
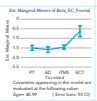
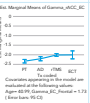
*Table S2 ROI x Tx results according to each frequency band*

| Frequency band | df | F | ρ |
|---|---|---|---|
| Delta | 3,449 | 13.732 | < .001 |
| Alpha | no significant dif for the ROI x Tx was found | | |
| Beta | 3,449 | 6.985 | < .001 |
| Gamma | 3,449 | 10.354 | < .001 |

We followed up with univariate ANOVAs for each significant frequency band (delta, beta, gamma) according to each ROI (rACC and frontal). If Tx remained significant, pairwise comparisons were assessed.

We then performed univariate ANOVAs for rACC activity of the significant frequency bands (delta, beta, gamma) mediated by frontal activity of the respective frequency band. Finally, if Tx remained significant, pairwise comparisons were assessed.
Significant results are found in Table S2.

*Table S3 Overview of the significant results from the follow-up analyses*

| | | | | | | | | | rACC mediated by Frontal | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Frequency Band | ROI | Treatment | | | | Pairwise comparison | | | Treatment | | | | Pairwise comparison | | |
| | | df | F | ρ | Graph | Treatment contrasts | ρ | d | df | F | ρ | Graph | Treatment contrasts | ρ | d |
| Delta | rACC | 3,449 | 9.966 | <.001 |  | Psychotherapy - rTMS | <.001 | 0.488 | 3,448 | 18.575 | <.001 |  | Psychotherapy - rTMS | <.001 | 0.488 |
| | | | | | | AD - rTMS | <.001 | 0.414 | | | | | | | |
| Beta | rACC | 3,449 | 13.856 | <.001 |  | Psychotherapy - ECT | <.001 | 1.181 | 3,448 | 8.016 | <.001 |  | Psychotherapy - rTMS | <.001 | 0.349 |
| | | | | | | AD - ECT | <.001 | 1.128 | | | | | | | |
| | | | | | | rTMS - ECT | <.001 | 0.815 | | | | | | | |
| | Frontal | 3,449 | 11.66 | <.001 |  | Psychotherapy - ECT | <.001 | 1.192 | | | | | | | |
| | | | | | | AD - ECT | <.001 | 1.438 | | | | | | | |
| | | | | | | rTMS - ECT | <.001 | 1.154 | | | | | | | |
| Gamma | rACC | 3,449 | 10.147 | <.001 |  | Psychotherapy - ECT | <.001 | 1.121 | 3,488 | 10.308 | <.001 |  | Psychotherapy - rTMS | <.001 | 0.239 |
| | | | | | | AD - ECT | <.001 | 1.169 | | | | | | | |
| | | | | | | rTMS - ECT | <.001 | 0.854 | | | | | | | |
| | Frontal | 3,449 | 10.226 | <.001 |  | Psychotherapy - ECT | <.001 | 1.013 | | | | | | | |
| | | | | | | AD - ECT | <.001 | 1.286 | | | | | | | |
| | | | | | | rTMS - ECT | <.001 | 1.2 | | | | | | | |

# 3

# 1 HZ RIGHT ORBITOFRONTAL TMS BENEFITS DEPRESSED PATIENTS UNRESPONSIVE TO DORSOLATERAL PREFRONTAL CORTEX TMS

This chapter is published as:
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**DEAR EDITOR,**

Major depressive disorder (MDD) remains a significant global health challenge. Patients failing to achieve remission despite multiple conventional therapeutic interventions (i.e., difficult-to-treat or treatment-resistant depression, TRD) constitute nearly 30 % of MDD cases (Rush et al., 2006). Repetitive transcranial magnetic stimulation (TMS) has gained traction as a promising non-invasive approach in TRD, conventionally targeting the dorsolateral prefrontal cortex (DLPFC) (Janicak & Dokucu, 2015). While high-frequency TMS applied to the left DLPFC has demonstrated remission rates ranging from 19 % to 37 % (Berlim et al., 2014; Carpenter et al., 2012) but augmented 1Hz-R-DLPFC results in no extra beneficial effect (Sackeim et al., 2020), many patients remain non-responders, and alternative stimulation sites and protocols may be required. An emerging candidate target is the orbitofrontal cortex (OFC), a region pivotal in processing reward/'non-reward' and implicated in MDD pathophysiology (Rolls et al., 2020). Neuroimaging and deep brain stimulation studies have suggested that the right-lateral-OFC (R–OFC) may be a fruitful target for neuromodulation (Cheng et al., 2016; Rao et al., 2018). Encouragingly, a case study reported improved mood and anhedonia in an MDD patient through 1Hz-TMS over the R–OFC, fol-

lowing non-response to DLPFC and dorsomedial PFC (DMPFC)-TMS (DMPFC) (Fettes et al., 2017). A follow-up case series in patients unresponsive to DMPFC-TMS found 30 % response and 24 % remission after a course of 1Hz R–OFC–TMS (Feffer et al., 2018) and a recent study established mood improvement after OFC augmentation to combined DLPFC 10Hz and iTBS (Tadayonnejad et al., 2023).

Here we report on the clinical effectiveness of 1Hz-R–OFC–TMS in individuals previously unresponsive to conventional DLPFC-TMS, both as a singular treatment and as an augmentation. Drawing from patient samples in both the Netherlands (NL) and the United States (US), we assessed mood, anxiety and, for the Dutch sample, sleep outcomes. Additionally, we explored whether particular baseline demographic characteristics or clinical symptoms predict remission/non-remission following 1Hz-R–OFC–TMS.

Our retrospective, naturalistic study enrolled 41 patients with non-psychotic TRD (i.e., at least two failed evidence-based treatments; nNL = 25; nUS = 16; detailed demographic/clinical characteristics are presented in Table S1). Data were collected from neurocare Clinics/neurocare Centers (www.neurocaregroup.com; https://neurocarecoa.com). Inclusion criteria consisted of: confirmed non-psychotic MDD diagnosis, established through standardized interviews (M.I.N.I., SCID); baseline Beck Depression Inventory (BDI-II) scores≥14; non-response to prior DLPFC-TMS treatment (defined by BDI-II scores decreased by<50 %). Pregnant patients, those with epilepsy, current psychosis, cardiac pacemakers, or cranial metal implants were excluded. Patients were switched to 1Hz-R–OFC–TMS after non-response to 42.4 ± 21.6 (NL) or 20.4 ± 7.4 (US) sessions of DLPFC-TMS, according to clinical judgment. Informed consent was obtained from all patients.

In the NL sample, patients underwent an average of 24.4 ± 16.4 1Hz-R–OFC–TMS only sessions (1Hz, 60s on, 30s off, 15 trains, 120 % lower limb RMT) at Fp2, using a figure-8 coil with 120°-angled windings (Deymed DuoMag XT-100 with 90BFVT-LQC coil or MagVenture R30 with D-B80 coil; Fig. 1A). In the US sample, patients received an average of 20.1 ± 6.7 1Hz-R–OFC–TMS augmented to DLPFC stim-

ulation (1Hz, 1200 pulses continuously, 120 % finger twitch RMT) at AF8, using a NeuroStar iron-core coil, positioned at an angle of +35°. In Supplementary Fig. S1 we provide SimNIBS simulations of the electric fields induced by Fp2 and AF8 stimulation (OFC), to show their differential modulation compared to F4 stimulation (DLPFC; https://simnibs.github.io/simnibs/build/html/).

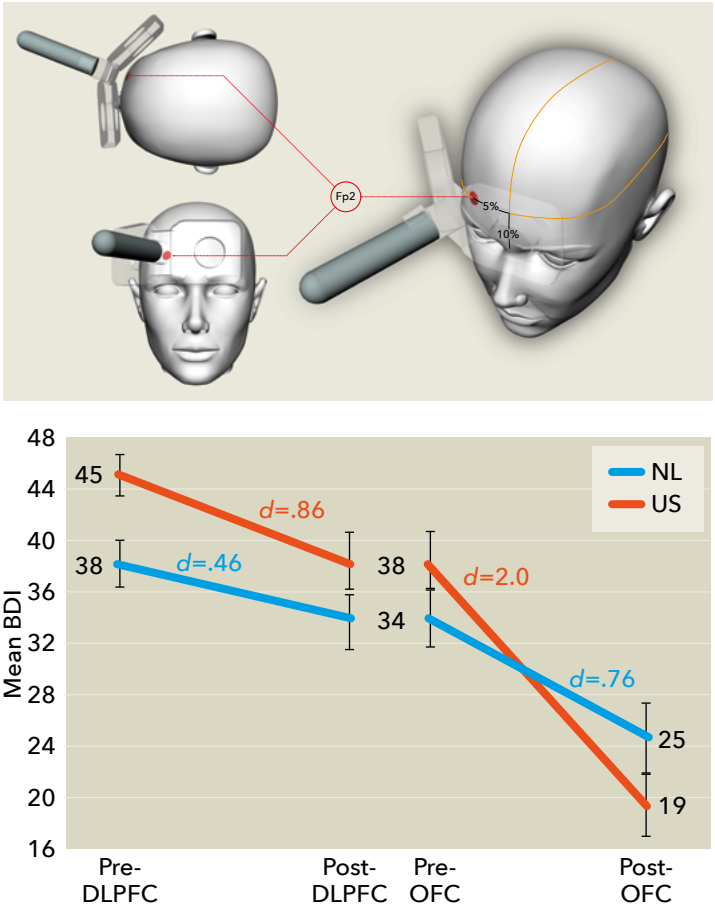



*Fig. 1(A) For the NL-sample, Deymed DuoMag XT-100 with 90BFVT-LQC coil over the right OFC at the Fp2 location in the 10–20 system. (B) Decrease in mean BDI score between pre- and post-TMS treatment (DLPFC and OFC) for the NL and US-samples. Error bars represent SEM, and effect sizes are reported with Cohen's d. BDI=Beck Depression Inventory; DLPFC = dorsolateral prefrontal cortex; NL = Dutch sample; OFC = orbitofrontal cortex; TMS = transcranial magnetic stimulation; US=American sample.*

Depression severity was assessed using BDI-II, with subscales representing symptom clusters (Table S2). Anxiety levels were measured using the Depression Anxiety and Stress Scale (DASS). For the NL-sample, sleep disturbances were evaluated using the Pittsburg Sleep Quality Index (PSQI), and objective measures of sleep-wake patterns and activity were captured using an Actigraphy watch.

Statistical results revealed no significant differences between the two samples regarding age, sex, antidepressant use, baseline depression severity, or comorbidities (Table S1). Detailed clinical outcomes are presented in Table S3. To summarize, 1Hz-R–OFC–TMS achieved response in 6/25 (24 %; NL), 8/16 (50 %; US), and remission in 6/25 (24 %; NL), 5/16 (31 %; US). Repeated measures ANOVA revealed significant reductions in depression severity (BDI-II scores) for both samples following 1Hz-R–OFC–TMS ($F(1,39) = 64.921$, $p < .001$). Notably, the mood improvement associated with 1Hz-R–OFC–TMS was especially pronounced in the US sample (Fig. 1B), also evidenced by the significant interactions between TMS protocol and country sample ($F(1,39) = 9.540$, $p = .004$) and between TMS protocol and time ($F(1,39) = 17.337$, $p < .001$; detailed statistical results in Table S4). Furthermore, repeated measures ANOVAs revealed significant improvements ($p \leq .001$) following 1Hz-R–OFC–TMS in anxiety, anhedonia, non-anhedonia, cognitive-affective, somatic and performance, cognitive, and non-cognitive symptom clusters, as well as sleep on PSQI global score ($p = .008$; Table S5 and Fig. S2). None of the available demographic/clinical characteristics (age, sex, antidepressant usage, baseline BDI-II, symptom clusters, anxiety, sleep) showed any significant predictive association with 1Hz-R–OFC–TMS remission/non-remission status following Bonferroni correction, although patients with higher anhedonia showed a trend towards higher probability of remission (Table S6).

The remission rates, ranging from 24 % (NL) to 31 % (US), collectively propose that a strategic shift in stimulation site, thereby impacting another independent neural circuit, holds promise for patients unresponsive to DLPFC-TMS. These findings align with prior studies (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023), and underscore the clinical significance of 1Hz-R–OFC–TMS given that remission rates reported for DLPFC-TMS span between 19 % and 37

% (Berlim et al., 2014; Carpenter et al., 2012). Moreover, the more pronounced mood improvement associated with 1Hz-R–OFC–TMS in the US sample could be linked to distinctions between the two samples: different sites for OFC stimulation (NL:Fp2; US:AF8), and US patients transitioned from DLPFC-TMS to 1Hz-R–OFC–TMS much sooner on average than their NL counterparts (NL:42.4, US:20.4 DLPFC sessions). Therefore, we cannot discount the potential impact of a higher number of DLPFC-TMS sessions. While our study found no significant predictive associations between clinical characteristics and 1Hz-R–OFC–TMS remission/non-remission, electroencephalogram-derived biomarkers (e.g., Brainmarker-I, OFC-theta band activity) may offer promise due to their demonstrated associations in prior research (Rao et al., 2018; Voetterl, van Wingen, et al., 2023). Additionally, with the non-significant trend found towards anhedonia, future research focused specifically on anhedonia could be of interest in determining whether it truly can predict remission/non-remission following 1Hz-R–OFC–TMS.

Limitations (more extensively discussed in the supplement) include a relatively small sample size (which may be underpowered to detect subtle predictors), the absence of a control group, the differential administration of OFC-TMS as either a full switch or augmentation, and heterogeneity of baseline characteristics and intervention parameters between the two samples. However, given the heterogeneity in terms of length of treatment but similar remission rates in the samples, the established treatment effects are possibly not just a consequence of more sessions. This is supported by the recent finding of Tadayonnejad et al. (Tadayonnejad et al., 2023), where a greater rate of symptom improvement was established after the addition of right OFC augmentation. The robustness and scope of the observed improvements despite this heterogeneity is promising for generalizability of the findings. Future studies on 1Hz-R–OFC–TMS incorporating control groups (sham, continued DLPFC-TMS) and larger sample sizes would address limitations of the currently available literature on 1Hz-R–OFC–TMS.

In conclusion, our study supports the clinical utility of 1Hz-R–OFC–TMS for TRD in patients unresponsive to conventional DLPFC-TMS. The robust effects seen in these two open-label samples encourage fu-

ture large-scale randomized trials of 1Hz-R–OFC–TMS. Further work to compare a continued DLPFC stimulation treatment arm (10Hz or 1Hz) with a switch to 1Hz-OFC, and to elucidate specific clinical and/or biological markers (e.g., EEG) of 1Hz-R–OFC–TMS responders might play a crucial role in patient selection, ultimately enhancing treatment outcomes.

# SUPPLEMENTARY MATERIAL

## SUPPLEMENTARY TABLES:

*Supplementary Table S1. Baseline demographic and clinical characteristics of the study.*

| Characteristics | NL | US | Statistical Analysis | |
|---|---|---|---|---|
| | N=25 | N=16 | *F or χ2* | *p* value |
| Age (years; SD) | 51.5 (13.7) | 41.2 (16.4) | 4.705 | .036 |
| Age range (years) | 25-73 | 21-77 | | |
| Sex (M : F) | 13 : 12 | 5 : 11 | 0.610 | .435 |
| Antidepressant use, N | 12 | 3 | 2.951 | .086 |
| Baseline depression severity (i.e., average pre-DLPFC BDI-II (SD)) | 38.2 (9.1) | 45.1 (6.5) | 6.879 | .012 . |
| Comorbidities, N | 12 | 4 | 1.976 | 160 |
| No comorbidities, N | 13 (52%) | 12 (75%) | | |
| Bipolar I, N | 2 (8%) | 0 (0%) | | |
| Anxiety disorder, N | 4 (16%) | 4 (25%) | | |
| Excoriation disorder, N | 0 (0%) | 1 (6%) | | |
| Dysthymia, N | 0 (0%) | 1 (6%) | | |
| ASD, N | 2 (16%) | 0 (0%) | | |
| PTSD, N | 3 (13%) | 0 (0%) | | |
| Personality disorders, N | 3 (12%) | 0 (0%) | | |
| Panic disorder, N | 3 (12%) | 0 (0%) | | |
| ADHD, N | 1 (4%) | 0 (0%) | | |

Note: Following Bonferroni correction, there were no significant differences in age, sex, antidepressant use, baseline depression severity (pre-DLPFC-TMS BDI-II), and co-morbidities between NL and US samples. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BDI-II, Beck Depression Inventory second version; F, females; M, males; N, number of patients with; NL, Netherlands; PTSD, post-traumatic stress disorder; SD, standard deviation; US, United States.

*Supplementary Table S2. Symptom clusters (BDI-II subscales) with their corresponding BDI-II items*

| Symptom Cluster (BDI-II subscale) | BDI-II items | Reference |
|---|---|---|
| Anhedonia | 4, 12, 21 | Leventhal et al., 2006 |
| Non-anhedonia | 1-3, 5-11, 13-20 | Leventhal et al., 2006 |
| Cognitive-affective | 1-13 | Trentini et al. 2005 |
| Somatic and Performance | 14-21 | Trentini et al. 2005 |
| Cognitive | 2, 3, 5-9, 14 | Kumar et al. 2002 |
| Non-cognitive | 1, 4, 10-13, 15-21 | Kumar et al. 2002 |

Note: BDI-II, Beck Depression Inventory second version.

*Supplementary Table S3. OFC-TMS (and DLPFC-TMS in blue for reference) treatment outcome results of MDD patients from the Netherlands and the United States*

| | OFC-TMS [DLPFC-TMS in blue for reference] | |
|---|---|---|
| Country | NL | US |
| Response, N (%) | [0 (0%)] 6 (24.0%) | [0 (0%)] 8 (50.0%) |
| Remission, N (%) | [0 (0%)] 6 (24.0%) | [0 (0%)] 5 (31.3%) |
| Average Pre-BDI-II (SD) | [38.2 (9.1)] 33.9 (10.9) | [45.1 (6.5)] 38.4 (8.9) |
| Average Post-BDI-II (SD) | [33.6 (10.6)] 24.6 (13.8) | [38.4 (8.9)] 19.4 (9.9) |
| BDI percentage change | [-12.4%] -29.40% | [-14.9%] -47.1% |

Note. The post-DLPFC and pre-OFC BDI means within the Dutch sample slightly differ due to two participants having unequal BDIs post-DLPFC and pre-OFC TMS. BDI-II, Beck Depression Inventory second version; DLPFC, dorsolateral prefrontal cortex; MDD, major depressive disorder; N, number; NL, Dutch sample; OFC, orbitofrontal cortex; TMS, transcranial magnetic stimulation; US, American sample; SD, standard deviation.

***Supplementary Table S4.*** *Significant results for effectiveness of OFC-TMS on depression severity (BDI-II)*

| Statistical model | Variable | | Effect | F | *p* | DF |
|---|---|---|---|---|---|---|
| | Dependent | Independent | | | | |
| Repeated measures ANOVA: treatment effect in general | BDI-II pre and post DLPFC, BDI-II pre and post OFC | Country | Protocol | 96.387 | <.001 | 1,39 |
| | | | Time | 101.857 | <.001 | 1,39 |
| | | | Protocol X Country | 9.540 | .004 | 1,39 |
| | | | Time X Country | 8.924 | .005 | 1,39 |
| | | | Protocol X Time | 17.337 | <.001 | 1,39 |
| Repeated measures ANOVA: DLPFC-TMS effect in general | BDI-II pre and post DLPFC | Country | Time | 32.966 | <.001 | 1,39 |
| | | | Country | 4.51 | .04 | 1,39 |
| Repeated measures ANOVA: OFC-TMS effect in general | BDI-II pre and post OFC | Country | Time | 64.921 | <.001 | 1,39 |
| | | | Time X Country | 7.501 | .009 | 1,39 |
| Repeated measures ANOVA: OFC-TMS effect per country | BDI-II pre and post OFC | | NL | 26.960 | <.001 | 1,24 |
| | | | US | 31.346 | <.001 | 1,15 |

Note. BDI-II, Beck Depression Inventory second version; country, NL and US; DLPFC, dorsolateral prefrontal cortex; NL, Dutch sample; OFC, orbitofrontal cortex; protocol, DLPFC-TMS and OFC-TMS; time, pre and post treatment; TMS, transcranial magnetic stimulation; US, American sample.

***Supplementary Table S5.*** *Significant results for effectiveness of OFC-TMS on symptom cluster (BDI-II subscale) scores, anxiety scores, and sleep measures per country (sleep (PSQI) only for NL sample)*

| | Country | F | *p* | *d* | DF |
|---|---|---|---|---|---|
| Symptom Cluster (BDI-II subscale) | | | | | |
| Anhedonia | NL | 13.867 | 0.001 | 0.598 | 1,22 |
| | US | 16.589 | <.001 | 1.224 | 1,15 |
| Non-anhedonia | NL | 17.825 | <.001 | 0.621 | 1,22 |
| | US | 32.144 | <.001 | 2.005 | 1,15 |
| Cognitive-affective | NL | 14.641 | <.001 | 0.564 | 1,22 |
| | US | 30.482 | <.001 | 1.939 | 1,15 |
| Somatic and Performance | NL | 19.324 | <.001 | 0.683 | 1,22 |
| | US | 19.997 | <.001 | 1.457 | 1,15 |
| Cognitive | NL | 13.921 | 0.001 | 0.597 | 1,22 |
| | US | 27.404 | <.001 | 1.500 | 1,15 |
| Non-cognitive | NL | 17.11 | <.001 | 0.564 | 1,22 |
| | US | 29.677 | <.001 | 1.840 | 1,15 |
| Anxiety | | | | | |
| | NL | 14.293 | .001 | .737 | 1,22 |
| | US | 16.860 | <.001 | 1.133 | 1,14 |
| PSQI | | | | | |
| Global score | NL | 9.991 | .008 | .577 | 1,13 |

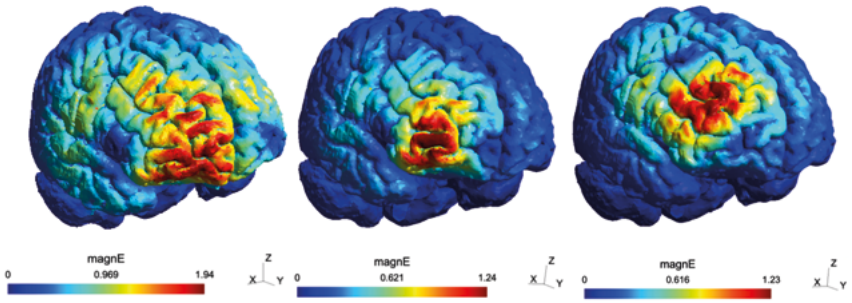
Note. Repeated measures ANOVA revealed significant decreases in BDI-II subscale scores during OFC-TMS in both country samples; in NL-sample, significant decrease in PSQI was only found in PSQI global score. BDI-II, Beck Depression Inventory second version; d, effect size; NL, Dutch sample; PSQI, Pittsburg Sleep Quality Index; US, American sample.

***Supplementary Table S6.*** *Univariate ANOVA results for potential predictors (baseline characteristics, symptom cluster (BDI-II subscale) scores, anxiety scores, and sleep measures) of OFC-TMS remitters and non-remitters per country*

| | Country | F | *p* |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age | NL | 1.295 | .267 |
| | US | 1.625 | .223 |
| Sex | NL | 1.061 | .314 |
| | US | 0.385 | .545 |
| Antidepressant use | NL | 0.012 | .915 |
| | US | 2.180 | .162 |
| MDD symptom severity (pre-DLPFC BDI-II) | NL | 3.423 | .077 |
| | US | 1.063 | .320 |
| **Symptom Cluster (BDI-II subscale)** | | | |
| Anhedonia | NL | 0.003 | .958 |
| | US | 5.056 | .041 |
| Non-anhedonia | NL | 3.070 | .096 |
| | US | 2.886 | .111 |
| Cognitive-Affective | NL | 2.739 | .114 |
| | US | 0.012 | .915 |
| Somatic and Performance | NL | 0.453 | .509 |
| | US | 1.171 | .297 |
| Cognitive | NL | 0.677 | .421 |
| | US | 1.478 | .244 |
| Non-cognitive | NL | 2.089 | .165 |
| | US | 0.662 | .429 |
| **Anxiety** | | | |
| | NL | 1.997 | .174 |
| | US | 0.882 | .363 |
| **PSQI** | | | |
| Global score | NL | 0.007 | .934 |
| Subjective sleep duration (hrs.) | NL | 0.001 | .972 |
| Sleep onset latency (m.) | NL | 0.970 | .338 |
| **Actigraphy** | | | |
| Sleep efficiency (%) | NL | 0.214 | .651 |
| Objective sleep duration (hh:mm) | NL | 0.301 | .593 |
| Sleep onset latency (m.) | NL | 0.810 | .384 |
| Wakefulness after sleep onset (m.) | NL | 0.948 | .348 |

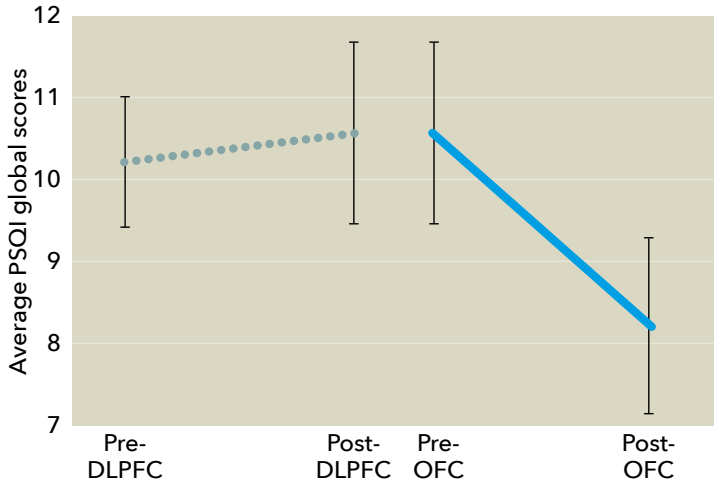
Note. Following Bonferroni correction, there were no significant differences in baseline BDI-II subscales, anxiety scores, or sleep measures between OFC remitters and non-remitters in either country sample. BDI-II, Beck Depression Inventory second version; DLPFC, dorsolateral prefrontal cortex; hrs/hh, hours; m/mm, minutes; MDD, major depressive disorder; NL, Dutch sample; OFC, orbitofrontal cortex; PSQI, Pittsburg Sleep Quality Index; TMS, transcranial magnetic stimulation; US, American sample.

## SUPPLEMENTARY FIGURES




***Supplemental Figure S1.*** *SimNIBS simulations of the electric fields induced in OFC by A) Fp2 stimulation with the Deymed 120 angle coil and B) AF8 stimulation with the MagVenture B70 coil (similar to NeuroStar), to show their differential modulation compared to C) F4 DLPFC stimulation with the MagVenture B70 coil (https://simnibs.github.io/simnibs/build/html/)*

*Note. the differential effect was previously demonstrated by Nauczyciel et al (2014) with a DB80 coil over FP2, after which PET scans showed that the area modulated was different from the DLPFC (Naucyzciel et al., 2014).*




***Supplemental Figure S2.*** *Average PSQI global score (sleep) during OFC-TMS (and during DLPFC-TMS, for reference in grey) in the NL sample*

*Note. Significant decrease in PSQI global scores (sleep) was found during OFC-TMS, but not during DLPFC TMS, in the NL sample. Error bars indicate SEM. DLPFC = dorsolateral prefrontal cortex; PSQI = Pittsburg Sleep Quality Index; OFC= orbitofrontal cortex*

## SUPPLEMENTARY DISCUSSION: EXTENDED EVALUATION OF LIMITATIONS

Given the limited availability of (open label) studies on OFC TMS in major depressive disorder (MDD), this study serves as a foundational investigation intended to provide guidance for subsequent follow-up research. Nonetheless, a notable limitation of our study lies in its small sample size, which should be extended in the future.

Due to certain ambiguities in the original publication by Fettes and colleagues (Fettes et al., 2017) and possible disparities in reimbursement policies between the two countries, several differences between our two samples could potentially contribute for the variations observed in the results: different sites for OFC stimulation (NL: Fp2; US: AF8), different utilized TMS coils (NL: figure-8 coil with 120°-angled windings; US: NeuroStar iron core coil), US patients transitioned from DLPFC-TMS to OFC-TMS much sooner on average than their NL counterparts (NL: 42.4; US: 20.6 DLPFC sessions), the US sample contained relatively more females, younger patients, and had less comorbidities compared to the NL sample. Another important distinction between the two datasets is the differential administration of OFC-TMS, either as a full switch from DLPFC to the singular target OFC, or the augmentation of OFC to DLPFC-TMS. Furthermore, as a result of comparing the Fp2 and AF8 targets to F4 in Fig. S1, it is visible that not only F4 stimulation leads to different electric fields, but also that F2 and AF8 seem to differ. The latter two are still considered an entry point into the OFC, nonetheless we suggest future studies to investigate the ramifications of using both targets.

These differences could be perceived both as limitations and fortuitous aspects of the study, as they underscore the robustness of the OFC protocol. Notably, remission rates were similar in both samples (NL: 24%; US: 31%), although a steeper improvement in depression severity was observed among the US patients in comparison to the NL patients during OFC-TMS. This could partly be due to a regression to the mean, but we should not overlook the possibility that it might be a result of augmentation to DLPFC stimulation instead of a full switch.

Another limitation to consider is that our study exclusively focused on patients who underwent OFC-TMS subsequent to not responding to DLPFC-TMS, and did not include a control group. Consequently, we are not yet able to definitively establish OFC-TMS specific effects on individuals with MDD. To address this, forthcoming research could consider conducting sham-controlled studies, or compare DLPFC non-responders who continue DLPFC-TMS to patients who made the transition to OFC-TMS. This last approach would more comprehensively capture the advantages associated with changing TMS targets in terms of treatment outcomes for patients with MDD.

# 4

# CLINICAL EFFECTIVENESS OF SWITCHING TO RIGHT LATERAL ORBITOFRONTAL-TMS AFTER A FAILURE OF SEQUENTIAL BILATERAL DORSOLATERAL PREFRONTAL-TMS IN MAJOR DEPRESSION

This chapter is under review at *Transcranial Magnetic Stimulation*

## ABSTRACT

**Background:** When patients with major depression fail to respond to TMS using a conventional dorsolateral prefrontal cortex (DLPFC) protocol, several published case series have suggested that switching to or adding-on 1 Hz right lateral orbitofrontal cortex (R-LOFC) TMS may succeed. However, many of these case series are hampered by relatively short courses of treatment (i.e., <25 sessions) for either the DLPFC, the R-LOFC, or both protocols.

**Methods:** Here we report clinical outcomes for a case series of N=54 patients in a community setting who underwent a full course of 36 sessions of sequential bilateral (SBL) DLPFC-TMS (right/left, 1Hz/20Hz, 60s on 30s off/2s on 4s off, 360 pulses/1200 pulses, both 120% RMT) without response, then completed a full course of another 36 sessions of 1 Hz-R-LOFC-TMS (1Hz, 60s on 30s off, 360 pulses).

**Results:** Following the R-LOFC course, 15/54 (27.8%) achieved response and 9/54 (16.7%) achieved remission on PHQ-9, with a mean score improving from 14.2±4.1 to 9.5±5.3 points. Responders showed a distinctive discontinuity in response trajectory immediately following the switch from DLPFC to R-LOFC, with a significant sharp drop in symptoms suggesting causal effect.

**Conclusion:** Switching to 1 Hz-R-LOFC-TMS yields a sharp change in response trajectory in a subset of SBL-DLPFC-TMS unresponsive patients, implying a distinctive therapeutic mechanism rather than the accumulative effects of additional sessions. Future randomized controlled studies may establish definitive efficacy for 1 Hz-R-LOFC-TMS in depression among non-responders to conventional DLPFC-TMS.

## INTRODUCTION

Major depressive disorder (MDD) is one of the most debilitating and widespread conditions globally (Gutiérrez-Rojas et al., 2020). Patients who do not respond to two or more pharmacotherapy trials are considered to have treatment-resistant depression (TRD), also referred to as difficult-to-treat depression, affecting approximately 30% of those with MDD (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006). Recently, repetitive transcranial magnetic stimulation (TMS) has become an increasingly widely adopted treatment option in TRD, due to its ability to achieve clinically meaningful response and remission rates in medication-resistant cases (Rossi et al., 2009, 2021). Large retrospective studies of real-world effectiveness have noted remission rates between 24% (Hutton et al., 2023) and 36% (Sackeim et al., 2020), with up to 69% of patients achieving responder criterion of at least 50% improvement in symptoms (Sackeim et al., 2020). Importantly, the trajectory of TMS response has recently been shown to be non-linear over time, with a sharp improvement in the initial sessions slowing to a more gradual improvement in later sessions, most effectively modeled with an exponential decay function (Berlow et al., 2023).

The dorsolateral prefrontal cortex (DLPFC) is the most frequently targeted area for TMS in MDD cases (Fitzgerald et al., 2011; Janicak & Dokucu, 2015). Various TMS protocols have been developed for treating MDD. Notably, low-frequency (LF; 1 Hz) TMS applied to the right DLPFC (R-DLPFC) has shown similar effectiveness to high-frequency (HF; >5 Hz) TMS on the left DLPFC (L-DLPFC) (Cao et al., 2018; Isenberg et al., 2005). Initially, it was hypothesized that a sequence involving LF-R-DLPFC sessions followed by HF-L-DLPFC sessions, known as sequential bilateral (SBL) TMS, would be more effective than unilateral HF-TMS. However, retrospective reviews of real-world effectiveness have found no significant difference in outcomes between unilateral left versus bilateral DLPFC-TMS (Aaronson et al., 2022).

Despite the effectiveness of current DLPFC-TMS protocols, approximately 30% of patients remain treatment non-responders (Carpenter et al., 2021; Cole et al., 2022; Sackeim et al., 2020), prompting exploration of other brain regions as treatment targets in MDD. Recently, the right lateral orbitofrontal cortex (R-LOFC) has gained attention as a promising target for TMS in MDD treatment. The lateral OFC is crucial in processing non-reward signals—situations where expected rewards are not obtained or when negative outcomes occur—while the medial OFC is essential for processing positive reward signals (Rolls et al., 2020). The "non-reward attractor theory of depression" suggests that in depression, the OFC enters a maladaptive attractor state, persistently underestimating or failing to respond to positive reinforcement, leading to a prolonged non-reward experience (Rolls, 2016). This results in an inability to shift attention to positive reinforcement, driven by an imbalance in OFC activity: hyperactivity in the lateral OFC and underactivity in the medial OFC (Xie et al., 2021). This dysregulation leads to rumination and anhedonia, trapping individuals in a cycle of negative thinking and impairing their ability to experience or anticipate pleasure (Rutherford et al., 2023).

Supporting this theory, an fMRI study found enhanced functional connectivity with the LOFC, exacerbating negative self-perception in depression (Cheng et al., 2016). Additionally, a meta-analysis revealed abnormal PFC activation (target F8) across various psychiatric disorders, including MDD, indicating a transdiagnostic pattern (McTeague et al.,

2017). Moreover, stimulating the LOFC through deep brain stimulation (DBS) has shown potential for rapid mood improvement in individuals with moderate-to-severe depression (Rao et al., 2018). Similarly, neuroimaging studies indicate that individuals unresponsive to DLPFC- and DMPFC-TMS may have distinctive abnormal connectivity patterns (Downar & Daskalakis, 2013), along with specific symptoms such as anhedonia (Downar et al., 2014). These findings collectively suggest that the R-LOFC could be a promising target for non-invasive brain stimulation.

The clinical literature supporting the effectiveness of TMS targeting the R-LOFC in psychiatry remains limited to date. An early study on patients with obsessive-compulsive disorder (OCD) found that 1 Hz TMS targeting R-LOFC (1 Hz-R-LOFC-TMS) significantly improved both depression and OCD symptoms compared to sham stimulation. Additionally, FDG-PET imaging indicated that this protocol effectively reduced metabolic activity in the targeted OFC region (Nauczyciel et al., 2014). In a subsequent case study, an individual with MDD, who had not responded to DLPFC and DMPFC-TMS treatments, achieved remission and showed improvements in mood, anxiety, and anhedonia after 1 Hz-R-LOFC-TMS (targeting Fp2) (Fettes et al., 2017). A follow-up case-series (targeting AF8) replicated the tolerability, safety, and effectiveness of this approach, achieving remission in 23.3% of patients unresponsive to DLPFC- or DMPFC-TMS (Feffer et al., 2018). Another case series demonstrated that SBL augmentation using add-on R-LOFC (targeting Fp2) stimulation, in MDD patients unresponsive to unilateral L-DLPFC-TMS, yielded a response rate of 24% (remission rates were not reported) and improvements in mood, negative rumination, and depression symptom severity (Tadayonnejad et al., 2023). Additionally, a different case series found a 24% remission rate when switching to 1 Hz-R-LOFC-TMS (targeting Fp2), a 31.3% remission rate when using 1 Hz-R-LOFC-TMS (targeting AF8) as an add-on, and overall improvements in depression severity, anxiety, and sleep in MDD patients who received 1 Hz-R-LOFC-TMS after non-response to DLPFC-TMS (Prentice et al., 2023). These studies suggest that the R-LOFC may serve as a promising alternative target for TMS in patients with MDD who are unresponsive to DLPFC-TMS. However, it needs clarification whether the improvements seen following a switch to R-LOFC-TMS part-

way through the course are indeed due to the switch, or whether they would have occurred anyway by simply delivering more sessions of DLPFC-TMS.

Here we present results from a retrospective case review among patients who had failed to respond to a full clinical course (36 sessions) of conventional SBL-DLPFC-TMS, who then received an additional full course (36 sessions) of 1 Hz-R-LOFC-TMS. A primary aim of this study was to investigate the clinical effectiveness of full courses of 1 Hz-R-LOFC-TMS in individuals unresponsive to full courses of conventional SBL-DLPFC-TMS, replicating and extending the findings of Prentice and colleagues (2023). Based on the previous case series reviewed above, we hypothesized that 1 Hz-R-LOFC-TMS would result in improvements in mood, anhedonia, sleep, suicidality, and rumination. A secondary aim was to determine if any clinical characteristics could predict remission, response, or percentage improvement outcomes.

## METHODS AND MATERIALS

### PATIENT SAMPLE

This retrospective clinical effectiveness retrospective case-series drew upon data from consenting patients treated at one of 14 outpatient psychiatric care clinics located in urban and suburban communities in Texas, under standardized protocols for TMS treatment procedures and outcome assessments delivered in partnership with, or directly by, Salience TMS Neuro Solutions (Plano, TX; www.salienceneuro.com). As of July 1st 2024, data was collected from approximately 9700 patients who have undergone TMS treatment at one of the Salience sites since 2011, with an enrollment rate currently at ~1800 new TMS patients added per year. The data includes fields describing their demographic features, clinical diagnoses and comorbidities, medication history, treatment parameters for each TMS session delivered over their course of care, and outcome measures on standardized self-rated clinical scales for mood, anxiety, and suicidality symptoms (item-by-item PHQ-9, GAD-7) symptoms, assessed regularly before, during, and after

treatment. Data are stored in a centralized, HIPAA-compliant database, and patients are not required to consent to include their data in order to receive treatment.

This large-retrospective real world effectiveness chart review included patients according to the following criteria. Retrospective data were initially retrieved for eighty-five individuals with non-psychotic MDD who were prescribed and agreed to proceed with 1 Hz-R-LOFC-TMS, after non-response (PHQ-9 improvement <50% versus baseline) to a full (36 sessions) course of SBL-DLPFC-TMS (1 Hz right F4/20 Hz left F3), between December 2019 and May 2020. These participants were all unique individuals who received at least one R-LOFC-TMS session following unsuccessful SBL-DLPFC-TMS treatment. Patients provided informed consent to pursue this non-standard protocol given the lack of response to a full course of standard treatment as well as their expressed desire to continue pursuing TMS. Exclusions included age less than 18 years at the time of treatment (N=4) and protocols including stimulation at additional sites beyond DLPFC and R-LOFC (N=3). Patients with comorbid diagnoses of bipolar disorder, schizophrenia, and/or autism were excluded (N=4). Furthermore, patients were excluded if they had a baseline (pre-SBL-DLPFC-TMS) Patient Health Questionnaire-9 (PHQ-9) score (Kroenke et al., 2001) of less than 10 (N=10), indicating only mild severity of baseline depressive symptoms. We also defined a per protocol subsample by excluding patients (N=10) who did not complete the full R-LOFC-TMS course (36 sessions). Therefore, the included (per protocol) sample consisted of 54 patients (32 females, mean age 45.0 ± 15.2).

#### TMS TREATMENT PARAMETERS

For the SBL-DLPFC-TMS protocol, patients underwent 36 sessions of treatment, once daily, 5 times per week on weekdays, with right followed by left DLPFC treatment on each session. 1 Hz-R-DLPFC-TMS was delivered to a target site defined using a right-sided reflection of the BeamF3 scalp heuristic, 60 s on 30 s off, 6 trains, 360 pulses total, at 120% of the resting motor threshold for the upper extremity; 20 Hz L-DLPFC-TMS was delivered to the BeamF3 scalp site, 2 s on 4 s off, 30 trains, 1200 pulses, again at 120% of the resting motor threshold for the upper extremity.

Having failed to respond to the SBL-DLPFC-TMS protocol, patients then switched to 36 sessions of 1 Hz-R-LOFC-TMS, again once daily, 5 times per week on weekdays. TMS was delivered to the R-LOFC at the F8 location in the 10-20 EEG system (Figure 1). This localization was achieved by measuring 10% of the nasion-inion measure to localize point FPz, followed by measuring 15% of the total head circumference to the right along the head circumference line to localize region F8. We specifically chose to target F8 rather than more anterior locations like AF8 because F8 has been shown to exhibit abnormal functional connectivity at rest in MDD (Rolls, 2016) and in MDD patients with low response rates to DMPFC-TMS (Drysdale et al., 2017). Additionally, F8 demonstrates abnormal activation across a variety of axis I disorders during emotion regulation tasks, including MDD (McTeague et al., 2017). R-LOFC stimulation was delivered in 1 Hz trains, 60 s on and 30 s off for 6 trains, 360 pulses total, at 120% of the resting motor threshold for the upper extremity; for patients unable to tolerate this intensity, the intensity was adjusted to 100% resting motor threshold. All treatments were performed on a MagVenture MagVita (R30) system with a Cool-B65 coil. For R-LOFC treatment, the B65 coil was oriented with the handle pointing downward, perpendicular to the head circumference (i.e., current flow upward).

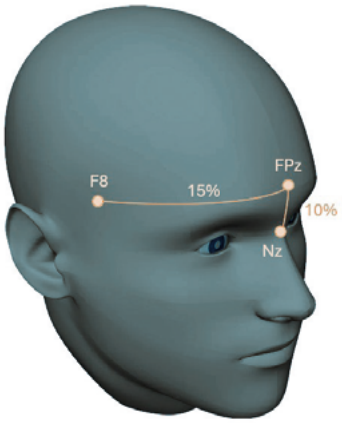



***Figure 1.*** *Coil placement procedures for R-LOFC-TMS, targeting F8*
*Note. The F8 stimulation site was located by first measuring 10% of the nasion-to-inion distance along the sagittal midline (corresponding to the 10–20 EEG site FPz), followed by measuring 15% of the head circumference to the right. This location corresponds to the F8 site in the 10–20 EEG system. Model of human head from https://www.3dcadbrowser.com/3d-model/human-head-47967*

### CLINICAL ASSESSMENT

Depression severity was evaluated using the PHQ-9, administered at baseline and weekly during treatment (Beck et al., 1996; Van der Does, 2002a). Anhedonia, sleep, and suicidality were evaluated through the item scores of PHQ-9 [anhedonia: item 1 "Q1. Interest or Pleasure in Doing Things"; sleep: item 3 " Q3. Trouble with Sleep"; suicidality: item 9 "Q9. Thoughts of Suicide or Self-Hurting"] (Beck et al., 1996; Van der Does, 2002a). Anxiety severity was evaluated using the GAD-7, administered on the same schedule as the PHQ-9. The GAD-7 item 2 ("Not being able to stop or control worrying") was employed as a proxy for rumination in the absence of a dedicated rumination scale in available naturalistic data (Spitzer et al., 2006).

### STATISTICAL ANALYSIS

To evaluate the clinical outcomes or effectiveness of R-LOFC-TMS, we initially conducted an iterative multiple linear regression on percentage improvement, using baseline characteristics identified in previous studies (Aaronson et al., 2022; Blumberger et al., 2018; Hutton et al., 2023; Sackeim et al., 2020) as the independent variables. These variables included age, sex, depression severity (pre-R-LOFC PHQ-9), illness duration, and the number of previously failed antidepressants. The goal was to identify any significant relationships between these variables and clinical outcomes, which would justify their inclusion as covariates or as full factors for examining interactions (e.g., sex).

Next, in accordance with the findings from Berlow and colleagues indicating that the trajectory of response to TMS follows an exponential decay function (Berlow et al., 2023), we plotted the trajectory of the PHQ-9 scores over SBL-DLPFC- and R-LOFC-TMS treatment. Examination of the trajectories of improvement among responders and non-responders enabled an assessment of whether the improvement followed a single continuous exponential decay curve (suggesting a simple cumulative effect of the 36 additional sessions in the second course), or instead followed a *discontinuous* curve with a second exponential decay beginning at the point of switch to R-LOFC-TMS (which would suggest a distinctive therapeutic mechanism rather than simply the additional mass effect of more sessions (Marinescu et al., 2018)).

To determine whether there is a difference in the degree of change in the slope of PHQ-9 improvement following protocol switch (i.e., PHQ-9 change from session 26-36 vs session 36-46) between R-LOFC-TMS responders and non-responders and between males and females, we conducted separate t-tests.

Subsequently, we performed a repeated measures ANOVA to determine the significance of changes in depression severity (PHQ-9) through the courses of SBL-DLPFC- and R-LOFC-TMS. PHQ-9 measurements at three time points were employed as dependent variables (pre-SBL-DLPFC-TMS, post-SBL-DLPFC/pre-R-LOFC-TMS, and post-R-LOFC-TMS), and sex as the independent variable.
Next, we examined the effectiveness of R-LOFC-TMS on the specific symptom subdomains of anhedonia, sleep, suicidality, and rumination proxy (PHQ-9 item 1, 3, 9, and GAD-7 item 2), by performing a repeated measures ANOVA for each symptom, using the scores at two time points (pre- and post-R-LOFC-TMS) as the dependent variables and sex as independent variable.
For each of the repeated measures ANOVAs, if a significant interaction was found, post hoc analyses were conducted, involving data separation based on variables from the interaction and repeating the same analysis accordingly.

Lastly, in order to identify potential predictors of the clinical outcome for R-LOFC-TMS, we constructed a new multiple linear regression model incorporating baseline characteristics (age, sex, depression severity (preR-LOFC PHQ-9), illness duration, number of previously failed antidepressants) as well as baseline individual items (anhedonia, sleep, suicidality, and rumination proxy), to determine if there was a predictive association with remission, response, or percentage improvement outcome.

Response was defined as 50% reduction in PHQ-9 scores at final assessment relative to pre-TMS baseline and remission was defined as a final PHQ-9 score less than 5. All data were analyzed using IBM SPSS version 28. Where indicated, Bonferroni correction was used to adjust for multiple comparisons. The effect sizes were reported using Cohen's d (*d*).

## RESULTS

### CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

The demographic and clinical characteristics are summarized in Table 1. Multiple linear regression determined that sex ($p$ = .008) had an influence on percentage improvement. Therefore, sex was used as a between-subject factor in analyses and/or analyses were split according to sex, as appropriate.

*Table 1. Demographic and clinical characteristics for MDD patients undergoing 1 Hz-R-LOFC-TMS, with correlation to percentage improvement (n = 54)*

| | Sample Characteristic | Pearson correlation to % improvement on R-LOFC-TMS | |
|---|---|---|---|
| | | F | *p*- value* |
| Age (mean ± SD) | 45.0 ± 15.2 | 0.219 | 0.056 |
| Sex (% female) | 59.3 | -0.326 | **0.008*** |
| Illness duration (years; mean ± SD) | 20.9 ± 13.0 | 0.220 | 0.055 |
| Number of previously failed antidepressants (mean ± SD) | 7.4 ± 4.1 | -0.179 | 0.098 |
| Baseline PHQ-9 (pre-R-LOFC-TMS; mean ± SD) | 14.2 ± 4.1 | -0.009 | 0.475 |

Note. **Bold** represents statistically significant p-values. **p*-value for the correlation with percentage improvement.

### PRIMARY ANALYSES: CLINICAL OUTCOMES/EFFECTIVENESS OF R-LOFC-TMS

Clinical outcomes are summarized in Table 2. Among the 54 patients included in this study, 15 (27.8%) achieved response and 9 (16.7%) achieved remission on the PHQ-9 following 36 sessions of R-LOFC-TMS.

*Table 2. Treatment outcomes in MDD patients after SBL-DLPFC-TMS and R-LOFC-TMS, with R-LOFC-TMS results by sex subgroups and statistical significance of sex differencs.e*

| | SBL-DLPFC-TMS (*n* = 54) | R-LOFC-TMS (*n* = 54) | | |
|---|---|---|---|---|
| | | Female (*n* = 32) | Male (*n* = 22) | Significance (sex difference) |
| % improvement | – | 32.9 ± 31.6 | | |
| | | 41.4 ± 32.5 | 20.6 ± 25.5 | **$p$ = 0.013,** t(52) = -2.581 |
| Response | 0 (0%) | 15/54 (27.8%) | | |
| (*n*, (%)) | | 12/32 (37.5%) | 3/22 (13.6%) | $p$ = 0.069, Fisher's exact test |
| Remission | 0 (0%) | 9/54 (16.7%) | | |
| (*n*, (%)) | | 7/32 (21.9%) | 2/22 (9.1%) | $p$ = 0.283, Fisher's exact test |
| Baseline PHQ-9 Score | 16.8 ± 4.5 | 14.2 ± 4.1 | | |
| (Mean ± SD) | | 14.5 ± 4.3 | 13.7 ± 4.0 | $p$ = 0.485, t(52) = -0.704 |
| End PHQ-9 Score | 14.2 ± 4.1 | 9.5 ± 5.3 | | |
| (Mean ± SD) | | 8.6 ± 5.4 | 10.9 ± 5.1 | $p$ = 0.115, t(52) = 1.605 |

Note. MDD = major depressive disorder; *n* = number of patients; PHQ-9 = Patient Health Questionnaire (9-item); R-LOFC-TMS = right lateral orbitofrontal cortex transcranial magnetic stimulation; SBL-DLPFC-TMS = sequential bilateral dorsolateral prefrontal cortex transcranial magnetic stimulation; SD = standard deviation.
**Bold** indicates statistically significant results ($p < 0.05$). Fisher's exact test was used for categorical variables, and independent samples *t*-test for continuous variables.

Figure 2 presents mean PHQ-9 score trajectories over the course of SBL-DLPFC-TMS and subsequent R-LOFC-TMS, plotted separately for responders and non-responders. Notably, R-LOFC-TMS responders show a distinctive sharp drop in scores over the first 10 days following the switch from SBL-DLPFC-TMS to R-LOFC-TMS, while R-LOFC-TMS non-responders showed no such change in the slope of the trajectory at the point of switching from SBL-DLPFC- to RLOFC-TMS.

Comparing R-LOFC-TMS responders versus non-responders, a significant difference was found in the degree of change in the slope of PHQ-9 improvement following protocol switch (i.e., PHQ-9 change from session 26-36 vs session 36-46; $t(52) = 2.89$; $p = .006$). In other words, a difference was found between R-LOFC-TMS responders versus non-responders for the rate of change in PHQ-9 scores, when examining the slope of the trajectory for the 10 sessions before and after the transition to R-LOFC-TMS (cf Figure 2).

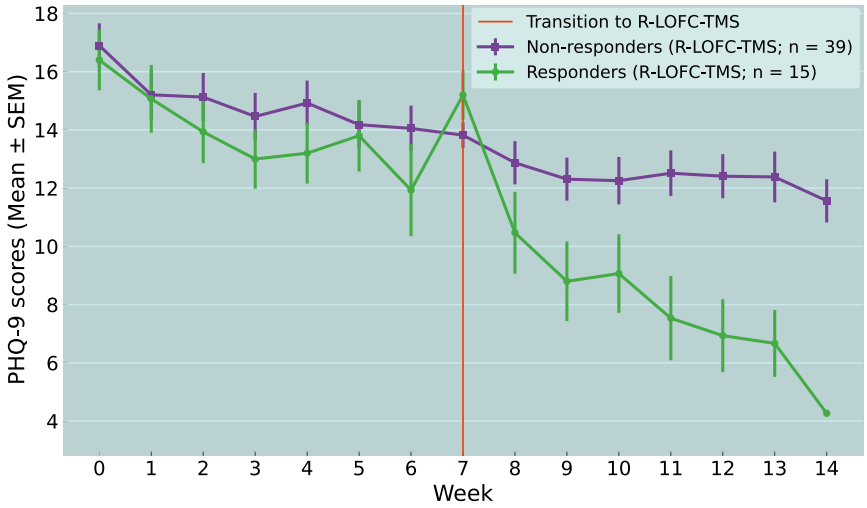



***Figure 2.*** *Average PHQ-9 scores over the course of SBL-DLPFC-TMS (36 sessions) and subsequent R-LOFC-TMS (36 sessions), plotted separately for R-LOFC-TMS responders (n = 15) and R-LOFC-TMS non-responders (n = 39).*
*Note. Figure shows a distinctive sharp drop in scores in R-LOFC-TMS responders over the first 10 sessions (or first 2 weeks) following the switch from SBL-DLPFC-TMS to R-LOFC-TMS, rather than a steady continuous improvement over the entire 72 sessions of treatment. Error bars represent SEM. Responders n = 15; non-responders n = 39. PHQ-9 = nine-item Patient Health Questionnaire; R-LOFC= right lateral orbitofrontal cortex; SBL-DLPFC = sequential bilateral dorsolateral prefrontal cortex; SD = standard deviation; TMS = transcranial magnetic stimulation.*

Changes in depression severity over the course of the two protocols for both males and females are illustrated in Figure 3. For depression severity (PHQ-9), the repeated measures ANOVA yielded significant effects of time ($F(2,52) = 67.49$; $p < .001$), interaction of time x sex ($F(2,52) = 4.25$; $p = .017$), but no significant effect of sex ($F(1,52) = .066$; $p = .798$). Pairwise comparison determined that there were no significant differences in PHQ-9 scores between males and females at each of the three time points (pre-SBL-DLPFC: $F(1,52) = .278$; $p = .600$; post-SBL-DLPFC/pre-R-LOFC: $F(1,52) = .485$; $p = .489$; post-R-LOFC: $F(1,52) = 2.521$; $p = .118$; Bonferroni correction: $p = 0.05/3 = 0.017$). In other words, while both sexes experienced a significant reduction in depression symptoms over the treatment course, the overall decrease did not significantly differ between males and females.

When analyzing the data separately by TMS protocol and sex, the repeated measures ANOVA revealed significant effects of time (pre-

vs. post-SBL-DLPFC-TMS) on PHQ-9 scores for both males ($F(1,21) = 17.54$, $p < .001$, $d = .72$) and females ($F(1,31) = 14.42$, $p < .001$, $d = .52$), indicating a significant reduction in PHQ-9 scores following SBL-DLPFC treatment in both sexes. Note that this decrease in symptoms did not reach response or remission levels. Similarly, for the PHQ-9 scores pre- and post-R-LOFC-TMS, the repeated measures ANOVA revealed significant effects of time for both males ($F(1,21) = 12.68$, $p = .002$, $d = .61$) and females ($F(1,31) = 43.40$, $p < .001$, $d = 1.22$), demonstrating a significant decrease in PHQ-9 scores from pre- to post-R-LOFC treatment in both sexes.

Comparing males versus females, there was no significant difference in the degree of change in the slope of PHQ-9 improvement following protocol switch (i.e., PHQ-9 change from session 26-36 vs session 36-46) ($t(52) = 0.42$; $p = .680$). In other words, no difference was found between males and females for the rate of change in PHQ-9 scores, when examining the slope of the trajectory for the 10 sessions before and after the transition to R-LOFC-TMS (cf Figure 3).

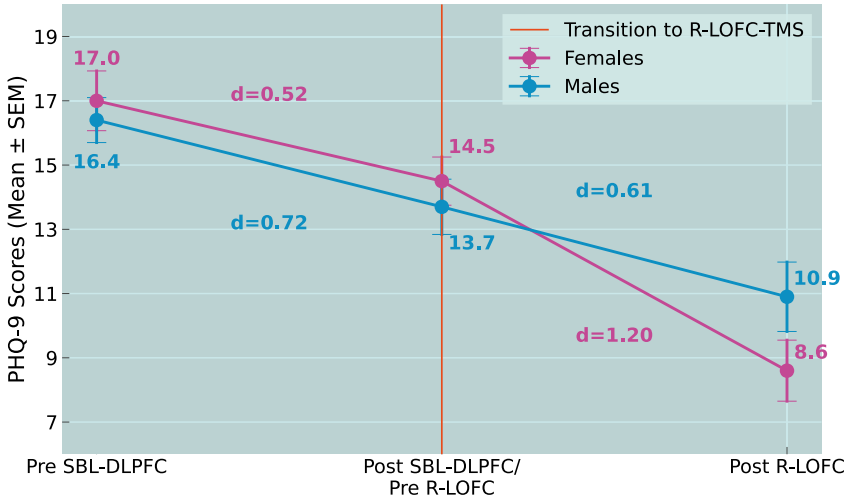



***Figure 3.*** *Changes in mean PHQ-9 scores between pre- and post-TMS treatment (SBL-DLPFC and R-LOFC) for males (n = 22) and females (n = 32).*
***Note.*** *Error bars represent SEM, and effect sizes are reported with Cohen's d. Females n = 32; males n = 22. MDD = major depressive disorder; PHQ-9 = nine-item Patient Health Questionnaire; R-LOFC= right lateral orbitofrontal cortex; SBL-DLPFC = sequential bilateral dorsolateral prefrontal cortex; SD = standard deviation; TMS = transcranial magnetic stimulation.*

Anhedonia results are presented in Figure 4. During R-LOFC-TMS, for the PHQ-9 item 1, the repeated measures ANOVA showed significant effects for time ($F(1,52) = 21.87$; $p < .001$), and for the interaction of time x sex ($F(1,52) = 6.32$; $p = .015$), but no significant effect for sex overall ($F(1,52) = 3.445$; $p = .069$). When performing separate analyses by sex, the repeated measures ANOVA revealed a significant decrease in PHQ-9 item 1 scores from pre- to post-R-LOFC treatment for females ($F(1,31) = 28.37$, $p < .001$, $d = 1.12$), but not for males ($F(1,21) = 2.392$, $p = .137$, $d = 0.33$). In other words, a significant decrease in anhedonia scores during R-LOFC-TMS was found only in females.

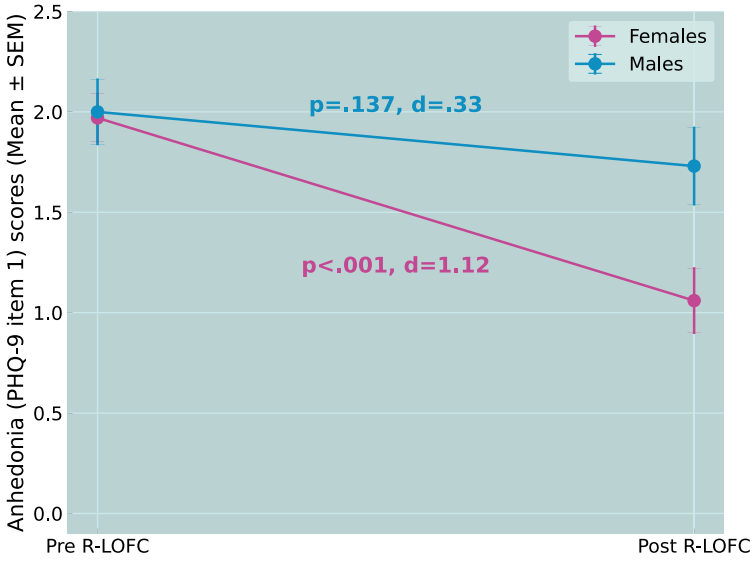



***Figure 4.*** *Changes in mean anhedonia scores between pre- and post-R-LOFC-TMS treatment for males (n = 22) and females (n = 32)*

***Note.*** *Significant difference in PHQ-9 item 1 scores (anhedonia) was found during R-LOFC-TMS for females (n = 32), but not for males (n = 22). Error bars represent SEM, and effect sizes are reported with Cohen's d. PHQ-9 = nine-item Patient Health Questionnaire; R-LOFC= right lateral orbitofrontal cortex; SD = standard deviation; TMS = transcranial magnetic stimulation.*

Sleep, suicidality, and rumination proxy results are presented in Supplementary Table S.1. Over the course of R-LOFC-TMS, examining separately each of these three items (PHQ-9 item 3, PHQ-9 item 9, and GAD-7 item 2), repeated measures ANOVA analyses showed significant effects of time (sleep: $F(1,52) = 11.56$; $p = .001$; suicidality:

F(1,52) = 9.73; $p$ = .003; rumination proxy: F(1,52) = 10.64; $p$ = .002), but no significant effect of sex or interaction of time x sex (Table 3). These results indicate that sleep, suicidality, and rumination proxy item scores decreased from pre- to post-R-LOFC treatment, with no significant differences between males and females.

#### SECONDARY ANALYSES: TREATMENT PREDICTORS

Results from the multiple linear regression model incorporating baseline characteristics (age, sex, illness duration, number of previously failed antidepressants, depression severity (PHQ-9)) and baseline individual items (anhedonia, sleep, suicidality, and rumination proxy) to predict percentage improvement, remission, and response outcomes can be found in Supplementary Table S.2. This multiple linear regression model indicated that none of the variables showed a significant relationship with percentage improvement during the R-LOFC-TMS phase of treatment after applying the Bonferroni correction. A trend was observed in which females appeared to predict a greater outcome ($t$ = -2.663, $p$ = .011); however, as just noted, this did not hold up under Bonferroni correction ($p$ = 0.05/9 = 0.0056). Moreover, when analyzing the outcomes categorically, using remission and response rates instead of percentage improvement from baseline, none of the variables mentioned above were found to be significant predictors of outcome.

## DISCUSSION

The primary aim of this study was to assess the clinical effectiveness of a full, 36-session course of 1 Hz-R-LOFC-TMS in MDD patients who were non-responders to a full 36-session course of SBL-DLPFC-TMS. Building on the findings of Prentice and colleagues (2023) and others (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023), we sought to expand upon outcome findings reported for R-LOFC-TMS after partial courses of DLPFC- and DMPFC-TMS. Our findings revealed that 15 out of 54 patients (27.8%) achieved response, and 9 out of 54 (16.7%) achieved remission after completing an additional 36 sessions of 1 Hz-R-LOFC-TMS. When consolidating these

findings with previous studies, remission rates for R-LOFC-TMS range from 16.7% to 31.3%, depending on the protocol (switch or add-on) and targeted site (Fp2, AF8, or F8) (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023).

A prominent observation in the present study was that R-LOFC-TMS responders experienced a distinct shift in their improvement trajectory at the transition between TMS protocols. Specifically, a statistically significant sharp decline in PHQ-9 scores was found during the first 10 sessions following the switch from SBL-DLPFC-TMS to R-LOFC-TMS. In contrast, non-responders showed a continuous, steady improvement across all 72 treatment sessions, with no statistically significant changes or discontinuities in their trajectory. This discontinuity found in R-LOFC-TMS responders aligns with previously reported findings that the TMS trajectory conforms to an exponential decay function (Berlow et al., 2023), implying that the observed response reflects the onset of a new therapeutic effect rather than simply the accumulating residual effects of additional sessions (Marinescu et al., 2018). Additionally, the continuity observed among non-responders aligns with earlier studies, where no significant change in the depression severity trajectory was observed even after 51 sessions of DLPFC-TMS (Chen et al., 2024).

Notably, females showed a non-significant trend towards greater improvement in depression severity versus males on this R-LOFC-TMS protocol, consistent with earlier studies on sex difference in DLPFC-TMS efficacy (Sackeim et al., 2020). When assessing the effectiveness of R-LOFC-TMS on specific symptom subdomains (anhedonia, sleep, suicidality, and rumination proxy), we found that R-LOFC-TMS significantly improved each of these symptoms. Of note, a significant difference was found in anhedonia effects between males and females, with females showing improvement after undergoing R-LOFC-TMS, while males did not. Overall, these outcomes are consistent with prior findings (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023) indicating that 1 Hz-R-LOFC-TMS can achieve improvements in mood, anhedonia, sleep, and rumination in MDD patients unresponsive to previous treatment at DLPFC/DMPFC. Our study strengthens the evidence

for 1 Hz-R-LOFC-TMS as a first-choice off-label treatment in clinical guidelines for TRD, particularly in patients unresponsive to DLPFC-TMS, given its consistent efficacy across studies and its potential to target symptom domains that may vary by sex.

Our examination of potential predictive associations between R-LOFC-TMS outcomes and baseline clinical or demographic factors did not reveal any significant predictors of overall improvement. A non-significant trend was observed suggesting a possible association between females and percentage improvement, consistent with previous findings that females are more likely to have a positive outcome with DLPFC-TMS (Sackeim et al., 2020). However, the limited number of patients available in this dataset may not have provided sufficient statistical power to identify predictors for greater overall improvement (such as rumination, previously found to predict R-LOFC-TMS response in a report by Tadayonnejad and colleagues (2023)).

Due to the reliance upon a fairly limited set of clinical outcome scales, this retrospective review was unable to offer detailed psychometric assessments of the predictive value or treatment effect for symptoms such as rumination, suicidal ideation, obsessionality, neuroticism, or other domains potentially relevant to the R-LOFC-TMS target. For example, as noted above, rumination has previously been identified as a predictor for R-LOFC-TMS (Tadayonnejad et al., 2023). While we investigated rumination using item 2 of the GAD-7 as the nearest available proxy, a more valid assessment would be achieved using the Ruminative Response Scale (RRS) (Nolen-Hoeksema & Morrow, 1991). Larger samples and a broader, prospectively assembled battery of psychometric tests would be useful in future work for identifying differential predictors of R-LOFC-TMS and DLPFC-TMS response.

Incorporating electroencephalographic (EEG) and fMRI-biomarkers could also potentially be beneficial for protocol selection in individual patients. As examples of potential candidate biomarkers, a recent study noted that deep brain stimulation not only alleviates depressive symptomatology but also mitigates the baseline hyperactivity of OFC-theta power (Rao et al., 2018). Additionally, changes in frontal theta power were found to correlate with improvements following

R-LOFC-TMS (Feffer et al., 2018, 2022). Similarly, using resting-state fMRI, Drysdale and colleagues identified an abnormal nexus of functional connectivity in the R-LOFC for biotype 2 patients, who showed weak responses to DMPFC-TMS (Drysdale et al., 2017). Future investigations could explore the potential of these EEG and fMRI-biomarkers for stratification towards R-LOFC-TMS by conducting EEG and fMRI analyses that directly compare theta band activity with R-LOFC- and DLPFC-TMS treatments.

Considering the scarcity of (open label) studies on R-LOFC-TMS in MDD, this study serves as a foundational investigation aimed at informing future follow-up research. However, a significant limitation of our study is its small sample size, which should be expanded in future studies. Another important limitation to acknowledge is that our study focused exclusively on patients who received R-LOFC-TMS *after* not responding to SBL-DLPFC-TMS, without including a control group. Therefore, we are currently unable to conclusively establish the specific effects of R-LOFC-TMS on individuals with MDD. To address this, future research could consider conducting randomized sham-controlled studies on R-LOFC-TMS, or studies randomizing DLPFC-TMS non-responders to either continuing DLPFC-TMS or switch to R-LOFC-TMS. Pending the arrival of results from such studies, however, the present work offers at least some evidence to suggest that some patients who are not responding to DLFPC-TMS may move from a non-response to a response trajectory if they are switched to R-LOFC-TMS.

In conclusion, as an initial exploration into R-LOFC-TMS research, our results indicate that individuals who do not respond to a full course of 36 sessions of SBL-DLPFC-TMS may benefit from a switch to a full course of R-LOFC-TMS. Further research is essential to optimize the parameter of stimulation (including pulse pattern, pulse number, and exact R-LOFC target), as well as to identify predictive biomarkers that might distinguish R-LOFC-TMS responders from conventional DLPFC-TMS responders prior to embarking upon a course of treatment. Our findings support the potential importance of R-LOFC-TMS as a therapeutic option worth considering in DLPFC-TMS non-responders, before proceeding to more invasive or more poorly tolerated treatment modalities.

## SUPPLEMENTARY MATERIALS

***Table S.1.*** *Repeated measures ANOVA results for PHQ-9 item 3 (sleep), PHQ-9 item 9 (suicidality), and GAD-7 item 2 (rumination proxy) during R-LOFC-TMS*

| | Time | | | Time x Sex | | | Sex | | |
|---|---|---|---|---|---|---|---|---|---|
| | *F* | *p* | *df* | *F* | *p* | *df* | *F* | *p* | *df* |
| Sleep (PHQ-9 item 3) | 11.56 | **0.001** | 1,52 | 0.03 | 0.872 | 1,52 | 0.19 | 0.663 | 1,52 |
| Suicidality (PHQ-9 item 9) | 9.73 | **0.003** | 1,52 | 0.02 | 0.882 | 1,52 | 1.05 | 0.311 | 1,52 |
| Rumination proxy (GAD-7 item 2) | 10.64 | **0.002** | 1,52 | 3.60 | 0.063 | 1,52 | 0.81 | 0.371 | 1,52 |

**Note.** GAD-7 = Generalized Anxiety Disorder-7 scale; PHQ-9 = Patient Health Questionnaire-9. p-value threshold is 0.05. **Bold** denotes statistically significant *p*-values.

*Table S.2. Results from multiple linear regression models incorporating baseline characteristics and baseline individual items to predict percentage improvement, remission, and response outcomes*

| Correlation to % improvement | Standardized coefficients $\beta$ | $t$ | $p$ |
|---|---|---|---|
| Age | 0.229 | 1.32 | 0.194 |
| Sex | -0.364 | -2.66 | 0.011 |
| Illness duration | 0.084 | 0.50 | 0.620 |
| Number of previously failed antidepressants | -0.270 | -1.98 | 0.054 |
| Baseline PHQ-9 (pre-R-LOFC-TMS) | 0.152 | 0.65 | 0.517 |
| Anhedonia (PHQ-9 item 1) | -0.111 | -0.64 | 0.524 |
| Sleep (PHQ-9 item 3) | -0.103 | -0.57 | 0.571 |
| Suicidality (PHQ-9 item 9) | -0.059 | -0.38 | 0.707 |
| Rumination proxy (GAD-7 item 2) | -0.160 | -1.02 | 0.314 |
| **Correlation to remission** | Standardized coefficients $\beta$ | $t$ | $p$ |
| Age | 0.094 | 0.51 | 0.613 |
| Sex | -0.163 | -1.12 | 0.270 |
| Illness duration | 0.142 | 0.79 | 0.436 |
| Number of previously failed antidepressants | -0.044 | -0.30 | 0.762 |
| Baseline PHQ-9 (pre-R-LOFC-TMS) | -0.204 | -0.83 | 0.414 |
| Anhedonia (PHQ-9 item 1) | -0.005 | -0.03 | 0.977 |
| Sleep (PHQ-9 item 3) | -0.036 | -0.19 | 0.853 |
| Suicidality (PHQ-9 item 9) | -0.151 | -0.91 | 0.369 |
| Rumination proxy (GAD-7 item 2) | -0.016 | -0.10 | 0.923 |
| **Correlation to response** | Standardized coefficients $\beta$ | $t$ | $p$ |
| Age | 0.234 | 1.29 | 0.203 |
| Sex | -0.282 | -1.97 | 0.055 |
| Illness duration | -0.014 | -0.08 | 0.935 |
| Number of previously failed antidepressants | -0.275 | -1.93 | 0.060 |
| Baseline PHQ-9 (pre-R-LOFC-TMS) | 0.106 | 0.44 | 0.665 |
| Anhedonia (PHQ-9 item 1) | 0.100 | -0.56 | 0.582 |
| Sleep (PHQ-9 item 3) | 0.013 | 0.07 | 0.944 |
| Suicidality (PHQ-9 item 9) | -0.063 | -0.39 | 0.699 |
| Rumination proxy (GAD-7 item 2) | -0.024 | -0.15 | 0.883 |

**Note.** R-LOFC-TMS = right lateral orbitofrontal cortex transcranial magnetic stimulation.
Bonferroni-corrected $p$-value threshold is 0.0056 for the three analyses (0.05/9).

# 5

# OUTCOMES OF SEQUENTIAL BILATERAL DORSOLATERAL PREFRONTAL VERSUS RIGHT LATERAL ORBITOFRONTAL/ LEFT DORSOLATERAL PREFRONTAL TMS FOR MAJOR DEPRESSION

This chapter was published as a Letter to the Editor: Prentice, A., Arns, M., Middleton, V., Bowman, J., Donachie, N., Kriske, J., ... & Downar, J. (2025). Sequential bilateral dorsolateral prefrontal versus right lateral orbitofrontal/left dorsolateral prefrontal TMS for major depression: a large naturalistic case series. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation.*

## ABSTRACT

**Background:** Sequential bilateral dorsolateral prefrontal cortex (SBL-DLPFC)-TMS recently failed to show superiority to unilateral high-frequency left (L)-DLPFC-TMS in a large naturalistic case series by Aaronson et al. (2022). However, other case series have found that adding 1 Hz right lateral orbitofrontal (R-LOFC)-TMS to L-DLPFC-TMS can achieve response in ≥25% of DLPFC-TMS non-responders. We therefore considered whether it may be beneficial to combine R-LOFC with standard L-DLPFC treatment, versus conventional SBL-DLPFC-TMS.

**Methods:** We performed a retrospective analysis of clinical outcomes in N=3562 patients who began a course of 36 sessions of TMS for major depression. Of these, N=2773 received a course of conventional SBL-DLPFC-TMS (right F4/left F3, 1Hz/20Hz, 60s on 30s off/2s on 4s off, 360 pulses/1200 pulses, both 120% RMT), while N=789 had the right-sided target stimulation delivered at F8 (R-LOFC) rather than F4, with all other parameters unchanged.

**Results:** Baseline demographic characteristics and illness severity did not differ between groups. Contrary to our hypothesis, the F8-F3 subgroup did not achieve better outcomes on either PHQ-9 or GAD-7 vs. the F3-F4 subgroup. Response and remission rates were similar for both groups (PHQ-9 response, 68.3% F3-F4 vs. 67.9% F8-F3; remission 41.2% F3-F4 vs. 40.8% F8-F3). Per-protocol analyses likewise showed no difference in outcomes.

**Conclusion:** While R-LOFC-TMS has previously shown promising results in DLPFC-TMS non-responders, simply offering F8-F3 treatment to all patients from the first session did not appear to improve treatment outcomes overall. Further parameter optimization for R-LOFC-TMS may be worthwhile in future work.

## INTRODUCTION

Major depressive disorder (MDD) ranks among the most incapacitating and prevalent conditions worldwide (Gutiérrez-Rojas et al., 2020). Following two or more unsuccessful trials of pharmacotherapy, patients are considered to have treatment-resistant depression (TRD), a term that has more recently evolved into difficult-to-treat depression, encompassing around 30% of the MDD patient population (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006). In recent years, repetitive transcranial magnetic stimulation (TMS) has gained significant traction as a treatment for MDD (including TRD), offering excellent safety and tolerability along with increasingly superior remission rates compared to further medication trials (Dalhuisen et al., 2024; Rossi et al., 2009, 2021).

The dorsolateral prefrontal cortex (DLPFC) is the most common target for TMS in MDD (Fitzgerald et al., 2011; Janicak & Dokucu, 2015), with remission rates ranging from 19 to 37% for high-frequency (HF; > 5 Hz) TMS applied to the left DLPFC (L-DLPFC) (Berlim et al., 2014; Carpenter et al., 2012). Notably, studies have found no

significant difference in response between 10 Hz L-DLPFC-TMS and 1 Hz right DLPFC-TMS (Fitzgerald et al., 2003). Interestingly, TMS outcomes seem to exhibit a bimodal distribution, with some patients showing a marked clinical response, while others achieve only marginal improvements (Bakker et al., 2015; Downar et al., 2014; Fitzgerald et al., 2016). Although sequential bilateral (SBL)-DLPFC-TMS (i.e., right then left DLPFC) has been widely used in an attempt to increase remission rates, a recent large naturalistic case series failed to show superiority of this approach versus unilateral high-frequency L-DLPFC-TMS (Aaronson et al., 2022). Together, these findings indicate that the subpopulation of MDD patients who do not respond to DLPFC or DMPFC stimulation could potentially derive benefits from alternative stimulation targets.

I

n recent literature, the orbito-frontal cortex (OFC) has garnered increased attention as a potential site for TMS stimulation in MDD. In humans and nonhuman primates, the right lateral portion of the OFC (R-LOFC) responds to the absence of expected rewards (Rolls et al., 2020). The 'non-reward attractor theory of depression' postulates that MDD symptoms emerge due to self-perpetuating persistent activity and heightened sensitivity within a corticostriatal "non-reward" network, analogous to the more widely studied medial prefrontal "reward network" but with a nexus in the R-LOFC (Rolls, 2016). Neuroimaging studies propose that individuals who do not respond to DLPFC and DMPFC stimulation may exhibit distinct profiles of resting-state functional connectivity on fMRI (Downar & Daskalakis, 2013; Drysdale et al., 2017), along with specific symptoms like anhedonia (Downar et al., 2014). Such patients might therefore be expected to respond better to stimulation of non-reward network targets, such as the R-LOFC.

Substantiating this hypothesis, Drysdale and colleagues used resting-state fMRI to identify a subgroup of MDD patients who showed poor response to DMPFC-TMS, and were characterized by a prominent nexus of atypical functional connectivity in the R-LOFC, which was not present in DMPFC-TMS responders (Drysdale et al., 2017). However, attempts to independently replicate these findings were unsuccessful, likely due to overfitting issues (Dinga et al., 2019).

Moreover, an fMRI study in patients with MDD found enhanced functional connectivity between the R-LOFC and other nodes of the non-reward system, potentially associated with the "attractor state" of negative rumination in depression (Cheng et al., 2016). Furthermore, a meta-analysis of fMRI studies of brain activation during emotional regulation found that hypo- or hyper-activation of the R-LOFC was a transdiagnostic abnormal feature across various psychiatric disorders, including MDD (McTeague et al., 2017). Lastly, closed-loop stimulation of white matter tracts serving the R-LOFC, via deep brain stimulation (DBS), has demonstrated the potential to rapidly improve mood in individuals with moderate-to-severe depression (Rao et al., 2018). Collectively, these findings suggest that the R-LOFC holds promise as an effective target for non-invasive brain stimulation in MDD patients unresponsive to treatment at conventional TMS targets.

Evidence supporting the clinical effectiveness of R-LOFC-TMS in psychiatric illness has steadily accumulated over the last decade. In one case-study, a patient with MDD, who initially had not responded to either DLPFC-TMS and DMPFC-TMS, exhibited improvements in mood, anxiety, and anhedonia following 1 Hz-R-LOFC-TMS (targeting Fp2) (Fettes et al., 2017). A subsequent case series confirmed the tolerability, safety, and effectiveness of this approach (1 Hz-R-LOFC-TMS at target AF8), with about 24% achieving remission despite previous nonresponse to DLPFC-/DMPFC-TMS (Feffer et al., 2018). In another recent case-series by a different research group, among patients not responding to conventional L-DLPFC-TMS, applying add-on 1 Hz-R-LOFC-TMS (targeting Fp2) stimulation prior to L-DLPFC-TMS treatment during each session was associated with improvement in mood, negative rumination and depression symptom severity (Tadayonnejad et al., 2023). Moreover, a subsequent case-series by yet another research group found improvement in depression severity, anxiety and sleep in MDD patients nonresponsive to DLPFC-TMS who received 1 Hz-R-LOFC-TMS (targeting Fp2 and AF8) (Prentice et al., 2023). These independently reported case series by different groups agree in suggesting that a subpopulation of MDD patients may respond better to R-LOFC-TMS (either alone or as an add-on) than to standard TMS targeting DLPFC alone. Moreover,

since SBL-DLPFC-TMS does not appear to improve overall outcomes in MDD under naturalistic conditions (Aaronson et al., 2022), these findings raise the question of whether outcomes could be improved by offering all patients R-LOFC-TMS (rather than R-DLPFC-TMS) in addition to L-DLPFC-TMS from the very first session.

Although a definitive comparison between sequential R-LOFC/L-DLPFC-TMS and the more conventional SBL-DLPFC-TMS would require a randomized controlled trial (RCT), recent years have seen significant contributions to protocol optimization, largely driven by retrospective analysis of outcomes from large treatment registries collected in naturalistic community settings. Examples include a study (N>3500 patients) comparing outcomes for L-DLPFC-TMS versus SBL-DLPFC-TMS in MDD (Aaronson et al., 2022), and another study (N>5000 patients) comparing outcomes for a conventional 37.5min 10Hz L-DLPFC-TMS protocol to the abbreviated 18.75min "Dash" protocol (Carpenter et al., 2021).

In line with these studies, we sought to compare clinical outcomes for patients in a large community practice who had undergone a course of TMS using one of two protocols: either the SBL-DLPFC-TMS protocol (i.e., 1 Hz-R-DLPFC-TMS followed by 20 Hz-L-DLPFC-TMS), or the sequential 1 Hz-R-LOFC-TMS followed by 20 Hz-L-DLPFC-TMS protocol. This retrospective review captured a variety of clinical and demographic variables, including depression severity and anxiety self-reports on standard scales. Our hypothesis postulated that the R-LOFC/L-DLPFC protocol would achieve higher response and remission rates than the SBL-DLPFC-TMS protocol. A secondary aim of the study was to ascertain whether any clinical characteristics could be associated with remitters versus non-remitters for each protocol.

## METHODS

### PATIENT SAMPLE

This retrospective clinical effectiveness retrospective case-series drew upon data from consenting patients treated at one of 14 outpatient psychiatric care clinics located in urban and suburban communities in Texas, under standardized protocols for TMS treatment procedures and outcome assessments delivered in partnership with, or directly by, Salience TMS Neuro Solutions (Plano, TX; www.salienceneuro.com). As of July 1, 2024, data was collected from approximately 9700 patients who have undergone treatment at one of the Salience sites since 2011, with an enrollment rate currently at ~1800 new TMS patients added per year. The data includes fields describing their demographic features, clinical diagnoses and comorbidities, medication history, treatment parameters for each TMS session delivered over their course of care, and outcome measures on standardized self-rated clinical scales for mood, anxiety, and suicidality symptoms (item-by-item PHQ-9, GAD-7) symptoms, assessed regularly before, during, and after treatment. Data are stored in a centralized, HIPAA-compliant database, and patients are not required to consent to including their data in order to receive treatment.

Figure 1 presents a flow chart depicting the definition of the patient sample for the analysis. Retrospective data were initially retrieved for 5591 patients with non-psychotic MDD who had undergone a course of TMS using either a SBL-DLPFC-TMS protocol (hereafter termed F4-F3 for convenience) or a protocol in which the right-sided 1 Hz stimulation sequence was delivered at R-LOFC (hereafter termed F8-F3). Patients who underwent one of these protocols of TMS between April 2019 and December 2023 were deemed eligible for this study. These participants were all unique individuals who received at least one TMS session following their decision to undergo treatment. The patients were prescribed either the F4-F3 or F8-F3 TMS protocol based on the prescriber's clinical judgment, in light of the evolving base of literature at the time (which, as described above in the Introduction, progressively revealed limited additional benefit for adding on R-DLPFC-TMS and possible additional benefit for adding on R-LOFC-TMS to conventional L-DLPFC-TMS treatment, thus

leading more prescribers to shift to the latter protocol for routine use). Although the allocation was not formally randomized, there was also no specific set of patient symptom features or other factors used to direct patients to one protocol or the other. Rather, over the time window of this sample, there was variability among sites and practitioners in the timing and degree of adoption of the F8-F3 protocol versus the continuance of the standard sequential bilateral F4-F3 protocol.

In this retrospective analysis of outcomes, the intent-to-treat (ITT) sample was defined as a subset of the initially identified 5591 patients by applying the following exclusions: age less than 18 years at the time of treatment (N=87), non-naivety to TMS (N=506), and not having a primary diagnosis of unipolar non-psychotic MDD (N=16). Patients with comorbid diagnoses of bipolar disorder, schizophrenia, and/or autism were also excluded (N=363). Furthermore, patients were excluded if no PHQ-9 assessment was done within 14 days prior to the first TMS session (N=90), if they did not have at least one PHQ-9 assessment following start of TMS (N=118), and/or if they did not have a baseline PHQ-9 of at least 10 (N=833), indicating at least moderate severity of baseline depressive symptoms. Finally, patients with insufficiently complete demographic data (N=7) and those who underwent an accelerated regiment of TMS (N=9) were also excluded. The resultant ITT sample comprised 3562 patients, of whom 2773 patients were prescribed a conventional F4-F3 protocol, and 789 patients were prescribed the F8-F3 protocol, as detailed below. To assess treatment effect for patients who successfully completed a course of typical length (Blumberger et al., 2018; Sackeim et al., 2020), a subset of the ITT sample was defined as the "Completer" sample (N=3202), from which patients were excluded if they were classified as non-responders and ended TMS after fewer than 30 sessions of treatment (N=360). Of the Completer sample, 2486 patients were in the F4-F3 group and 716 were in the F8-F3 group.

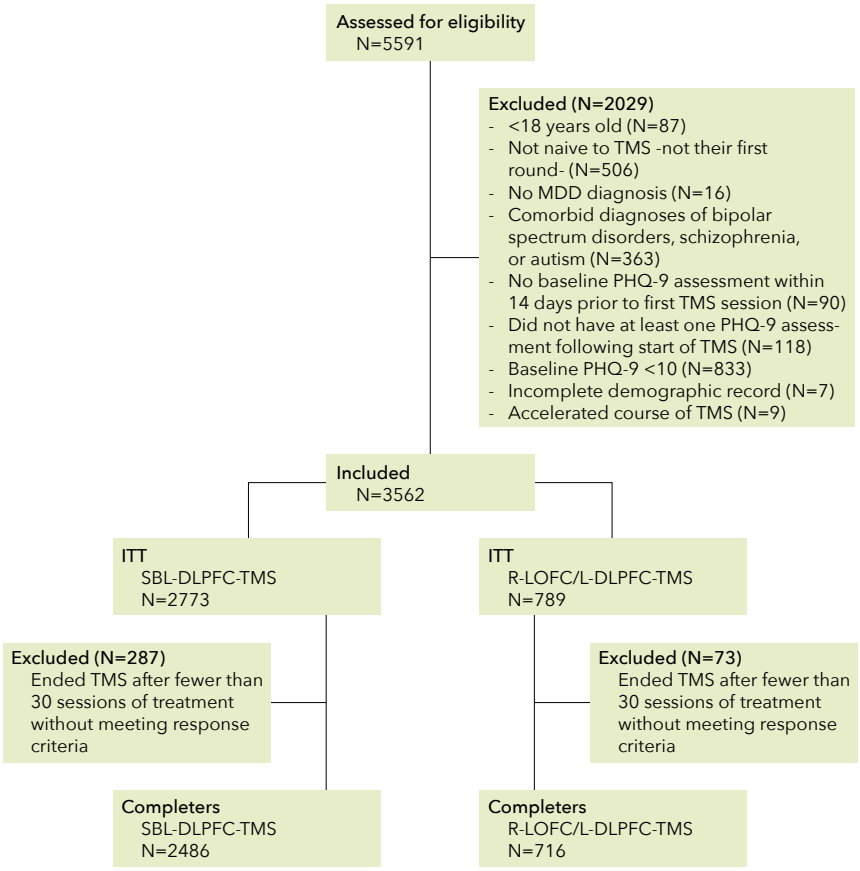



***Figure 1.*** *TREND Diagram illustrating inclusion and exclusion of patients for sample definition.*

*Note. Characteristics of the initial sample, inclusion and exclusion criteria, and final characteristics of the ITT and Completer subsamples are presented here. DLPFC = dorsolateral prefrontal cortex; ITT = intent-to-treat; L-DLPFC = left DLPFC; MDD = Major Depressive Disorder; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral-DLPFC-TMS; TMS=transcranial magnetic stimulation.*

#### TMS INTERVENTION PARAMETERS

The SBL-DLPFC protocol consisted of 360 pulses of 1 Hz to R-DLPFC (F4 target, 60s on 30s off, 6 trains, 8.5min) followed by 1200 pulses of 20 Hz (F3 target, 2s on 4s off, 30 trains, 3min) to L-DLPFC, both delivered at a target intensity of 120% resting motor threshold for upper extremity movements by visual inspection. The sequential R-LOFC/L-DLPFC protocol consisted of shifting the right-sided target from

DLPFC (F4 target) to OFC (F8 target), with all other parameters unchanged. Again, for both targets, the stimulation intensity was set at a target of 120% resting motor threshold for upper extremity movements by visual inspection. The F3 and F4 sites were localized using the BeamF3 scalp heuristic applied to the left or right hemisphere. The F8 location was localized at 15% of the head circumference rightwards from the frontal pole FPz as per the 10-20 EEG system. For both protocols, all stimulation (F3, F4, F8) was administered using a MagVenture MagVita TMS system and Cool-B-65 coil.

#### CLINICAL SYMPTOM ASSESSMENT

Depression severity was evaluated using the nine-item Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001). PHQ-9 items 1, 3, and 9 were also assessed individually as a secondary metrics of anhedonia, sleep, and suicidality, respectively (Kroenke et al., 2001; MacGregor et al., 2012; Na et al., 2018). Anxiety severity was also evaluated using the GAD-7, with item 2 ("not being able to stop or control worrying") assessed as a metric of rumination (Spitzer et al., 2006). For all the variables mentioned, the pre-TMS course and first available post-TMS-course scores (as detailed below) were utilized for statistical analyses of therapeutic effect.

#### STATISTICAL ANALYSES

The primary analyses were conducted in the ITT sample, then repeated in the Completer samples for confirmation. In the ITT sample, the final PHQ-9 was the last observation obtained post-baseline during the course of treatment (LOCF) and, in the Completer sample, the final PHQ-9 was obtained as the first available observation following the end of the course of active treatment. Descriptive statistics on demographic features, treatment parameters, and clinical outcomes are reported for each sample in Table 1. Comparison of demographic and clinical characteristics between F4-F3 and F8-F3 groups were done through t-tests and chi-squared analyses for continuous and categorical measures, respectively (Table 1). Response was defined as ≥50% reduction in PHQ-9 scores at final assessment relative to pre-TMS baseline, and remission was defined as a final PHQ-9 score less than 5. To compare PHQ-9 clinical outcomes (baseline PHQ-9, final

PHQ-9, difference in PHQ-9, percentage improvement, response rate, remission rate) between the F4-F3 and F8-F3 groups, separate one-way ANOVAs were used. Analyses with the GAD-7 were completed in a smaller subset of the sample used for PHQ-9 analyses, as only patients with a baseline GAD-7 score equal or more than 10 were analyzed to represent patients with clinically significant anxiety severity. On the GAD-7, response was defined as ≥50% reduction in GAD-7 scores at final assessment relative to pre-TMS baseline and remission was defined as a final GAD-7 score less than 5. The analyses of the GAD-7 scores followed the procedures used with the PHQ-9 scores. For exploratory purposes, sex was added in sensitivity analyses as an independent variable. Effect of treatment groups on the specific items for anhedonia, sleep, suicidality, and rumination proxy were assessed using a repeated measures ANOVA.

To identify overall predictors of clinical outcome, we subsequently performed multiple linear regression analyses incorporating baseline characteristics and treatment-related variables (age, sex, illness duration, number of previously failed antidepressants, depression severity (PHQ-9), anxiety severity (GAD-7), TMS protocol, PHQ-9 item 1 (anhedonia), PHQ-9 item 3 (sleep), PHQ-9 item 9 (suicidality), and GAD-7 item 2 (rumination proxy)), with percentage improvement as the dependent variable. Next, examining separately each of the two treatment groups F4-F3 and F8-F3, we applied the same analytic model (omitting the factor for TMS protocol). The same steps were performed for the categorical outcomes of remission and response; the results of these analyses can be found in Supplementary materials. Furthermore, to compare the two treatment protocols in predictors, an additional multiple linear regression was conducted. This analysis used the same baseline characteristics and treatment-related variables as before, adding percentage improvement as a covariate of non-importance and setting the interaction term of percentage improvement x TMS protocol as the dependent variable.

Descriptive statistics are reported as mean ± SD for continuous variables and frequency counts and percentages for categorical variables. Treatment parameters were averaged over all treatment sessions in the acute course. Significance values are two-tailed with an alpha of

0.05, and subsequent analyses are Bonferroni corrected. All p-values reported are without multiplicity adjustment. The effect sizes were reported using Cohen's d (*d*). All analyses were conducted using IBM SPSS version 28.

## RESULTS

Demographic and clinical characteristics are summarized in Table 1. The F4-F3 and F8-F3 groups did not differ in age, sex, illness duration, baseline depression severity (PHQ-9), or baseline anxiety severity (GAD-7). The average number of previously failed antidepressants trials was slightly higher in the F4-F3 group compared to the F8-F3 groups (6.4 ± SD 5.2 versus 5.6 ± SD 3.7). While this difference was statistically significant (p< .001), it is not large enough to be clinically meaningful.

*Table 1. Demographic and clinical characteristics of the ITT and Completer samples for the SBL-DLPFC-TMS and R-LOFC/L-DLFPC-TMS protocols.*

**PRIMARY ANALYSES: SELF-REPORT DEPRESSION SEVERITY**

| Intent-to-Treat Sample | SBL-DLPFC-TMS (F4-F3) (*n*=2773) | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=789) | P-Value* |
|---|---|---|---|
| Age | 41.6 ± 15.6 | 42.6 ± 16.4 | 0.134 |
| Sex (% female) | 68.6 | 65.4 | 0.087 |
| Illness duration (years) | 18.6 ± 13.4 | 17.8 ± 13.9 | 0.154 |
| Number of previously failed antidepressants | 6.4 ± 5.2 | 5.6 ± 3.7 | **<.001** |
| Baseline PHQ-9 | 16.7 ± 4.2 | 16.4 ± 4.2 | 0.089 |
| Baseline GAD-7 | 15.4 ± 3.3 | 15.2 ± 3.2 | 0.285 |
| **Completer Sample** | **SBL-DLPFC-TMS (F4-F3) (*n*=2486)** | **R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=716)** | **P-Value*** |
| Age | 41.7 ± 15.6 | 42.7 ± 16.4 | 0.147 |
| Sex (% female) | 68.3 | 65.9 | 0.222 |
| Illness duration (years) | 18.8 ± 13.5 | 17.9 ± 13.9 | 0.112 |
| Number of previously failed antidepressants | 6.4 ± 5.2 | 5.5 ± 3.5 | **<.001** |
| Baseline PHQ-9 | 16.5 ± 4.2 | 16.4 ± 4.2 | 0.279 |
| Baseline GAD-7 | 15.3 ± 3.3 | 15.1 ± 3.2 | 0.334 |

**Note.** DLPFC = dorsolateral prefrontal cortex; GAD-7 = Generalized Anxiety Disorder-7 scale; L-DLPFC= left DLPFC; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL=sequential bilateral.
* p-values derive from comparisons of the SBL-DLPFC and R-LOFC/L-DLPFC treatment groups.
**Bold** represents *p*-values that are statistically significant.

Clinical outcomes are presented in Table 2 and Figure 2. In the ITT and the Completer samples, no significant differences were found between the F4-F3 and F8-F3 groups for baseline severity (PHQ-9), last observed observation carried forward (PHQ-9), difference in PHQ-9, percentage improvement, response rates, or remission rates. Moreover, no significant differences were found between sexes for response rate, remission rate, or percentage improvement from baseline on PHQ-9.

*Table 2. PHQ-9 clinical outcomes for SBL-DLPFC and R-LOFC/L-DLPFC protocol groups in the ITT and the Completer samples.*

| **Intent-to-Treat Sample** | SBL-DLPFC-TMS (F4-F3) (*n*=2773) | | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=789) | | P-Value* |
|---|---|---|---|---|---|
| | Male (*n* = 870) | Female (*n* = 1903) | Male (*n* = 870) | Female (*n* = 1903) | |
| Baseline PHQ-9 | 16.7 ± 4.2 | | 16.4 ± 4.2 | | 0.089 |
| LOCF PHQ-9 | 6.9 ± 5.5 | | 6.9 ± 5.6 | | 0.845 |
| Difference (Pre-Post) | 9.8 ± 5.8 | | 9.4 ± 5.9 | | 0.157 |
| % improvement | 58.6 ± 31.1 | | 57.5 ± 31.9 | | 0.388 |
| | 56.4% | 59.6% | 54.4% | 59.2% | 0.572 |
| Response rate | 68.3% | | 67.9% | | 0.835 |
| | 64.8% | 69.9% | 64.1% | 70.0% | 0.859 |
| Remission rate | 41.2% | | 40.8% | | 0.832 |
| | 38.7% | 42.4% | 36.3% | 43.2% | 0.444 |
| **Completer Sample** | SBL-DLPFC-TMS (F4-F3) (*n*=2486) | | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=716) | | P-Value* |
| | Male (*n* = 787) | Female (*n* = 1699) | Male (*n* = 244) | Female (*n* = 472) | |
| Baseline PHQ-9 | 16.5 ± 4.2 | | 16.4 ± 4.2 | | 0.279 |
| End PHQ-9 | 6.0 ± 4.8 | | 6.0 ± 4.8 | | 0.874 |
| Difference (Pre-Post) | 10.6 ± 5.4 | | 10.3 ± 5.4 | | 0.328 |
| % improvement | 63.6 ± 28.0 | | 63.1 ± 27.2 | | 0.669 |
| | 60.7% | 64.9% | 60.3% | 63.1% | 0.995 |
| Response rate | 76.2% | | 74.9% | | 0.465 |
| | 71.5% | 78.3% | 71.7% | 76.5% | 0.595 |
| Remission rate | 46.0% | | 45.0% | | 0.634 |
| | 42.7% | 47.5% | 40.6% | 47.2% | 0.676 |

**Note.** DLPFC = dorsolateral prefrontal cortex; L-DLPFC = left DLPFC; LOCF = last observation carried forward; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral-DLPFC-TMS; TMS = transcranial magnetic stimulation.
**p*-values derive from comparisons of the SBL-DLPFC and R-LOFC/L-DLPFC treatment groups.

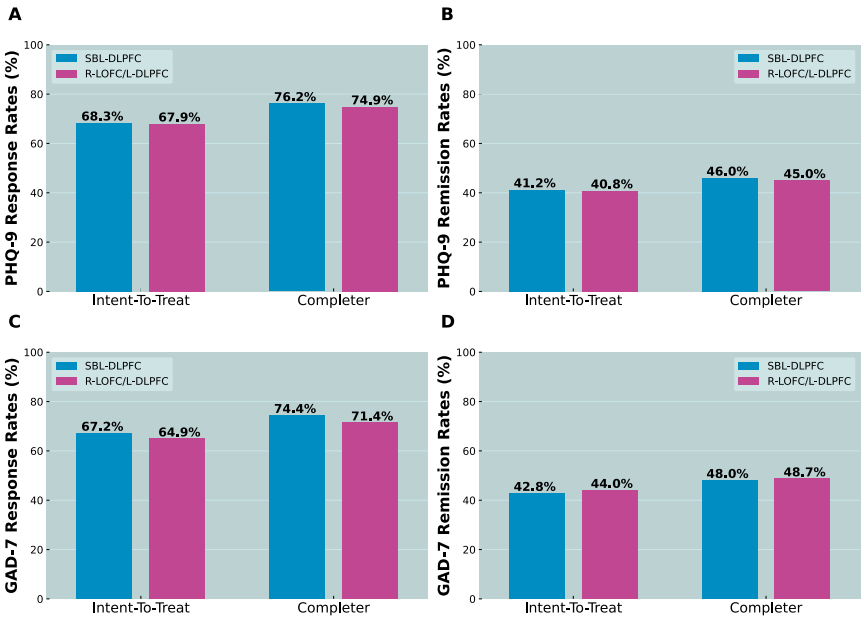



***Figure 2.*** *PHQ-9 and GAD-7 response and remission rates in the ITT and Completer samples for the SBL-DLPFC-TMS and R-LOFC/L-DLPFC-TMS groups*

*Note. (A) PHQ-9 response rates in the ITT and Completer samples across the SBL-DLPFC-TMS and R-LOFC/L-DLPFC-TMS groups. (B) PHQ-9 remission rates in the ITT and Completer samples for both treatment groups. (C) GAD-7 response rates in the ITT and Completer samples for both treatment groups. (D) GAD-7 remission rates in the ITT and Completer samples for both treatment groups. Error bars represent SEM. DLPFC = dorsolateral prefrontal cortex; GAD-7 = Generalized Anxiety Disorder-7; L-DLPFC = left DLPFC; PHQ-9 = Patient Health Questionnaire-9, R-LOFC = right lateral orbitofrontal cortex; SBL = sequential bilateral.*

In addition, in both the ITT and Completer samples, no significant Time x Protocol interaction effects were found for anhedonia (ITT: F(1,3521)= 2.436; $p$= .119; Completer: F(1,3186)= 1.116; $p$= .291), sleep (ITT: F(1,3521)= 3.611; $p$= .057; Completer: F(1,3186)= 2.148; $p$= .143), suicidality (ITT: F(1,3521)= 2.496; $p$= .114; Completer: F(1,3186)= 2.601; $p$= .107), and rumination proxy (ITT: F(1,3521)= 2.792; $p$= .095; Completer: F(1,3184)= 2.265; $p$= .132). In other words, no significant difference was found between the F4-F3 and F8-F3 groups for the degree of improvement from baseline in any of these four variables.

Regarding anxiety, GAD-7 outcomes for the F4-F3 and F8-F3 groups in the ITT and Completer samples are presented in Table 3 and Fig-

ure 2. For both the ITT and the Completer samples, no significant differences were found between the two protocols in baseline anxiety (GAD-7), last observed observation carried forward (GAD-7), difference in GAD-7, response rates, or remission rates.

*Table 3. GAD-7 clinical outcomes for SBL-DLPFC and R-LOFC/L-DLPFC protocol groups in the Intent-to-treat and the Completer samples.*

| Intent-to-Treat Sample | SBL-DLPFC-TMS (F4-F3) (*n*=2084) | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=595) | P-Value* |
|---|---|---|---|
| Baseline GAD-7 | 15.4 ± 3.3 | 15.2 ± 3.2 | 0.285 |
| LOCF GAD-7 | 6.6 ± 5.4 | 6.7 ± 5.4 | 0.755 |
| Difference (Pre-Post) | 8.8 ± 5.5 | 8.5 ± 5.4 | 0.341 |
| Response rate | 67.2% | 64.9% | 0.293 |
| Remission rate | 42.8% | 44.0% | 0.593 |
| **Completer Sample** | **SBL-DLPFC-TMS (F4-F3) (*n*=1844)** | **R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=538)** | **P-Value*** |
| Baseline GAD-7 | 15.3 ± 3.3 | 15.1 ± 3.2 | 0.334 |
| End GAD-7 | 5.7 ± 4.7 | 5.8 ± 4.7 | 0.624 |
| Difference (Pre-Post) | 9.6 ± 5.1 | 9.3 ± 5.0 | 0.279 |
| Response rate | 74.4% | 71.4% | 0.160 |
| Remission rate | 48.0% | 48.7% | 0.790 |

**Note.** DLPFC = dorsolateral prefrontal cortex; GAD-7 = Generalized Anxiety Disorder-7; LOCF = last observation carried forward; L-DLPFC = left DLPFC; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral-DLPFC-TMS; TMS = transcranial magnetic stimulation.
**p*-values derive from comparisons of the bilateral DLPFC and R-LOFC/L-DLPFC treatment groups.

#### SECONDARY ANALYSES: TREATMENT PREDICTORS

Table 4 presents the results of the analysis on candidate predictors of improvement among baseline characteristics and treatment-relevant variables: age, sex, illness duration, number of previously failed antidepressants, depression severity (PHQ-9), anxiety severity (GAD-7), TMS protocol, anhedonia (PHQ-9 item 1), sleep (PHQ-9 item 3), suicidality (PHQ-9 item 9), and rumination proxy (GAD-7 item 2). Predictor results for remission and response regarding the same variables are presented in Table S.1.

In the overall sample (pooling both protocols), a multiple linear regression, after Bonferroni correction, identified female sex and fewer previous failed antidepressants as significant predictors of greater

improvement (expressed as percent improvement from baseline). In the F4-F3 group, the same predictors were significant, along with longer illness duration and lower rumination proxy scores. For the F8-F3 group, only lower baseline anxiety severity (GAD-7) scores were a significant predictor of greater improvement.

*Table 4. Multiple linear regression results on predictors for percentage improvement regarding baseline characteristics and treatment-related variables.*

| **Correlation to PHQ-9 % improvement** | Overall (*n*=3202) | | | SBL-DLPFC-TMS (F4-F3) (*n*=2486) | | | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=716) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Standardized coefficients* | | | *Standardized coefficients* | | | *Standardized coefficients* | | |
| | *β* | *t* | *p* | *β* | *t* | *p* | *β* | *t* | *p* |
| Age | -0.057 | -2.631 | 0.009 | -0.068 | -2.715 | 0.007 | -0.038 | -0.862 | 0.389 |
| Sex | -0.073 | -4.111 | **<.001** | -0.068 | -3.382 | **<.001** | -0.091 | -2.384 | 0.017 |
| Illness duration | 0.053 | 2.446 | 0.015 | 0.074 | 2.932 | **0.003** | -0.005 | -0.109 | 0.913 |
| Number of previously failed antidepressants | -0.097 | -5.255 | **<.001** | -0.100 | -4.781 | **<.001** | -0.092 | -2.336 | 0.020 |
| Baseline PHQ-9 | 0.079 | 2.559 | 0.011 | 0.092 | 2.599 | 0.009 | 0.048 | 0.744 | 0.457 |
| Baseline GAD-7 | -0.032 | -0.971 | 0.332 | 0.017 | 0.445 | 0.657 | -0.200 | -2.890 | **0.004** |
| TMS protocol *(SBL-DLPFC, R-LOFC/L-DLPFC)* | -0.009 | -0.511 | 0.609 | / | / | / | / | / | / |
| Baseline PHQ-9 item 1 (anhedonia) | 0.008 | 0.353 | 0.724 | 0.008 | 0.293 | 0.769 | 0.012 | 0.250 | 0.803 |
| Baseline PHQ-9 item 3 (sleep) | 0.006 | 0.275 | 0.783 | -0.013 | -0.567 | 0.571 | 0.065 | 1.565 | 0.118 |
| Baseline PHQ-9 item 9 (suicidality) | -0.003 | -0.144 | 0.886 | -0.022 | -0.904 | 0.366 | 0.058 | 1.322 | 0.186 |
| Baseline GAD-7 item 2 (rumination proxy) | -0.064 | -2.068 | 0.039 | -0.109 | -3.054 | **0.002** | 0.078 | 1.224 | 0.221 |

**Note.** DLPFC = dorsolateral prefrontal cortex; L-DLPFC = left DLPFC; GAD-7 = Generalized Anxiety Disorder-7 scale; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral DLPFC transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.
*The Bonferroni-corrected p-value thresholds are 0.0045 for the overall analysis (0.05/11) and 0.005 for the SBL-DLPFC-TMS and R-LOFC/L-DLPFC-TMS analyses (0.05/10). **Bold** denotes statistically significant p-values.

Table S.2 presents the results of the analysis comparing predictors for the two treatment protocols, using the same baseline characteristics and treatment-related variables as before, with percentage improvement added as a covariate of non-importance and the interaction term of percentage improvement x TMS protocol as the dependent

variable. After Bonferroni correction, the analysis identified fewer previous failed antidepressant trials as correlated with differentially greater percentage improvement on the F4-F3 versus the F8-F3 protocol. To interpret this differential finding, we re-examined the coefficients for these groups individually (Table 4), noting that that fewer previous antidepressant trials was a relatively strong predictor of better outcome for the F4-F3 group, but this effect was much weaker and not significant for the F8-F3 group.

## DISCUSSION

The primary aim of this study was to compare the clinical effectiveness of SBL-DLPFC-TMS (1 Hz F4 + 20 Hz F3) to R-LOFC/L-DLPFC-TMS (1 Hz F8 + 20 Hz F3). Contrary to our hypothesis, the F8-F3 TMS group did not achieve better outcomes on either PHQ-9 or GAD-7 versus the F3-F4 TMS group, with similar response and remission rates between the two groups and no significant difference in percent improvement from baseline, despite the high power afforded by the large sample size. We also examined whether these two protocols showed differential effects on specific symptoms, including anhedonia, sleep, suicidality, and rumination proxy, using PHQ-9 and GAD-7 item scores. We found no significant difference between the two protocols. While R-LOFC-TMS has previously showed promising results in DLPFC-TMS non-responders (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023), these findings suggest simply offering combination R-LOFC/L-DLPFC (F8-F3) treatment to all patients from the first session does not appear to improve treatment outcomes.

Of note, a recent RCT fMRI study compared accelerated R-LOFC/L-DLPFC-TMS, accelerated L-DLPFC-TMS, and sham treatment (Cui et al., 2024). The study found that responders to the R-LOFC/L-DLPFC protocol initially demonstrated greater improvement immediately following treatment compared to those receiving unilateral DLPFC-TMS. However, by one week post-treatment, depression levels among L-DLPFC-TMS responders had improved, eliminating the significant difference between the two protocols. These findings are consistent with our results, which also indicate no difference in treatment effectiveness between standard DLPFC-TMS and R-LOFC/L-DLPFC-TMS. Therefore, while R-LOFC-TMS shows promise as a rescue strategy for DLPFC-TMS non-responders, its role as part of a combined first-line treatment approach remains uncertain.

A secondary aim of the study was to identify baseline characteristics predictive of greater improvement. Overall, female sex and fewer previous failed antidepressant trials emerged as significant predictors of better outcomes. These findings align with previous studies report-

ing that females and less treatment-resistant patients tend to achieve better results with TMS (Fregni et al., 2006; Sackeim et al., 2020). In the F4-F3 group, additional predictors included longer illness duration and lower baseline rumination proxy scores. In contrast, for the F8-F3 group, only lower anxiety (GAD-7) scores significantly predicted greater improvement. Interestingly, rumination did not emerge as a significant predictor in the F8-F3 group, contrary to expectations based on findings from UCLA (Tadayonnejad et al., 2023). However, this is consistent with our broader finding that outcomes for the two treatment protocols were very similar. When comparing predictors for the two treatment protocols, fewer previous failed antidepressant trials was found to correlate with differentially greater percentage improvement on the F4-F3 versus the F8-F3 protocol. This finding challenges earlier suggestions that R-LOFC-TMS might be particularly well-suited to patients with more severe anxiety, rumination, suicidality, anhedonia, or sleep disturbances.

There are a number of possible interpretations for the similarity of effects seen with F8-F3 and F4-F3 in the present study. The most prosaic interpretation is that the 1 Hz protocol was simply underdosed at 360 pulses, so that both groups may have effectively received only F3 stimulation. However, previous studies have shown positive outcomes from switching to R-LOFC stimulation for DLPFC/DMPFC non-responders using 360 pulses (Feffer et al., 2018; Fettes et al., 2017).

Another possible explanation for the similar effects observed with F8-F3 and F4-F3 in this study is that both protocols were delivered using the MagVenture MagVita TMS system and a Cool-B65 coil. The use of this coil may have limited the depth of cortical stimulation, potentially constraining the differentiation in outcomes between the protocols. It is conceivable that stronger effects, particularly for R-LOFC, might have been achieved with a deeper coil, such as the D-B80, which is designed to target deeper brain regions more effectively.

Another interpretation is that the lack of additional effect stems from the use of the F8 stimulus location rather than the more ante-

rior locations (i.e., Fp2 and AF8) used in some previous reports (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023). Currently there is no consensus on the optimal R-LOFC target, with options including FP2, AF8, and F8 (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023). In the present study, F8 was chosen as the R-LOFC target because it overlays a region that has been found to be abnormally activated during emotional processing across a wide variety of psychiatric diagnoses (McTeague et al., 2017). The F8 location falls closer to the right ventrolateral prefrontal cortex (R-VLPFC) rather than the R-LOFC per se, and although the R-LOFC belongs to a separate functional network from DLPFC, a recent study in both primates and humans has indicated a common connection between the R-VLPFC and the salience network (Trambaiolli et al., 2022). If these networks are anatomically and functionally connected, then stimulating the F8 location may actually be targeting the same network as F4 and F3, and might therefore fail to achieve additional benefit. Analogously, recent work has demonstrated that SBL-DLPFC-TMS does not outperform left unilateral DLPFC-TMS (Aaronson et al., 2022), again potentially because stimulation of L-DLPFC also achieves robust activation of a network of regions including R-DLPFC (Tik et al., 2023). By the same token, if the F8-F3 and F4-F3 protocols are simply stimulating the same network at different nodes, then their effects may prove to be similar. Recent work using TMS-fMRI has been fruitful in illustrating the neurophysiological effects of stimulation at DLPFC using real-world treatment protocols (Tik et al., 2023). Applying a similar approach to the R-LOFC could help determine the optimal target and stimulation protocol in future work.

One final possible explanation for the lack of significant differences between the two TMS protocols could relate to the concept of "specificity" in neuroplasticity. Effective neuroplastic changes require consistent stimulation of specific neural circuits, in line with Hebbian principles, often summarized as "what fires together, wires together." When protocols involve multiple targets, such as R-LOFC/L-DLPFC-TMS, this consistency may be disrupted, potentially overwhelming the brain's capacity to establish stable and long-lasting synaptic changes. Supporting this idea, a large cohort study (Aaronson et al.,

2022) demonstrated superior treatment outcomes for patients receiving unilateral DLPFC-TMS compared to those undergoing SBL-DLPFC-TMS, likely due to the more focused engagement of neural pathways afforded by unilateral stimulation, enhancing neuroplastic specificity. This theory aligns with findings from prior research which reported positive treatment outcomes in TRD patients treated with R-LOFC-TMS following unsuccessful DLPFC-TMS (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023). The ability of R-LOFC-TMS to preserve specificity after DLPFC-TMS may enable the brain to integrate this targeted approach more effectively, promoting more durable neuroplastic adaptations.

Notwithstanding the present findings regarding add-on stimulation, previous studies have shown that patients unresponsive to DLPFC-TMS can achieve remission with R-LOFC-TMS at other targets (Feffer et al., 2018; Fettes et al., 2017; Prentice et al., 2023; Tadayonnejad et al., 2023). Therefore, identifying a predictor would be potentially beneficial for guiding patients to the correct protocol without resorting to trial-and-error. Rumination (i.e., higher scores on the Ruminative Response Scale, RRS (Nolen-Hoeksema & Morrow, 1991)) has recently been identified as a predictor for better OFC-TMS response (Tadayonnejad et al., 2023). The present sample did not have this measure available, and using GAD-7 item 2 as a proxy for rumination did not appear to reveal any effects of interest. This limitation may have impacted our results; future studies should consider using the RRS for a more comprehensive and validated evaluation of rumination as a predictor of R-LOFC-TMS outcome.

Since clinical and demographic characteristics did not show significance as differential treatment outcome predictors in the present study, incorporating electroencephalogram (EEG) and fMRI-biomarkers could potentially fill this gap. For example, a study noted that deep brain stimulation not only alleviates depressive symptomatology but also mitigates the baseline hyperactivity of OFC-theta power (Rao et al., 2018). Additionally, changes in frontal-theta power were found to correlate with improvements following TMS protocols that activate other non-DLPFC regions, such as DMPFC-TMS and R-LOFC-TMS (Feffer et al., 2018, 2022). Similarly, using resting-state

fMRI, Drysdale and colleagues identified a biotype of MDD patients with poor response to DMPFC-TMS, showing a prominent abnormal nexus of connectivity in the R-LOFC, which was not present in responder types (Drysdale et al., 2017), though this could not be independently replicated due to overfitting issues (Dinga et al., 2019). Future investigations should explore the potential of these types of EEG and fMRI biomarkers for identifying stronger candidates for R-LOFC-TMS, for example, by conducting EEG and fMRI analyses that directly compare baseline neural activity among patients responsive and unresponsive to R-LOFC- and DLPFC-TMS treatments.

While the large sample size of this study helps mitigate some of the limitations inherent in its retrospective, naturalistic, open-label design, we acknowledge that only a formal RCT can definitively establish efficacy for R-LOFC-TMS. Of note, a recent fMRI study conducted a RCT with three arms: accelerated R-LOFC/L-DLPFC-TMS, accelerated L-DLPFC-TMS, and sham. While responders to the R-LOFC/L-DLPFC protocol initially showed greater improvement immediately post-treatment compared to those of unilateral DLPFC-TMS, by week 1 post-treatment, depression levels among L-DLPFC-TMS responders had improved to the extent that the significant difference between the two protocols was no longer observed (Cui et al., 2024). The latter result aligns with our findings, indicating no difference in treatment outcomes between standard DLPFC-TMS and R-LOFC/L-DLPFC-TMS. However, future research should continue to establish efficacy for R-LOFC-TMS by conducting RCTs comparing the following: R-LOFC-TMS versus sham stimulation, R-LOFC-TMS versus DLPFC-TMS, and R-LOFC/L-DLPFC versus SBL-DLPFC-TMS. The parameters of stimulation (particularly the exact R-LOFC target and the number of pulses delivered) may first require preclinical optimization with the aid of TMS-fMRI and TMS-EEG, given the lack of effect seen for the 360 pulse, 1 Hz, F8-targeted approach employed in the present study. Another limitation of this study is the absence of true randomization, which may have introduced prescriber bias. The F8-F3 protocol was more frequently selected for recent patients, while F4-F3 was predominantly chosen for earlier cohorts, likely reflecting shifts in clinical preferences over time. This historical imbalance, combined with a small but significant difference in the number

of prior antidepressant trials between groups, underscores the importance of implementing stricter controls in future RCTs to reduce confounding factors and strengthen causal conclusions.

In conclusion, our findings suggest that administering 360 pulses of 1 Hz stimulation to F8 (R-LOFC) did not confer additional benefit versus delivering the same 360 pulses of 1 Hz stimulation to F4, combined with high frequency L-DLPFC-TMS. If R-LOFC-TMS is to deliver overall gains in response and remission rates, then further optimization of parameters of stimulation (i.e., different number of pulses, a different pulse sequence, a different target, or all of the above) may need to be implemented. Further work is also required to clarify why a "switch" strategy from DLPFC- to R-LOFC-TMS does appear to deliver response and remission for some patients in previous case series, and to identify candidate biomarkers that may help identify these R-LOFC-TMS-responsive patients in advance of treatment. Structured as a formal randomized trial, such work may produce a viable personalization strategy for target selection in TMS patients, and thereby improve the overall chances of success for each individual patient presenting for treatment.

## SUPPLEMENTARY MATERIALS

*Table S1. Multiple linear regression results on predictors for remission and response regarding baseline characteristics and treatment-related variables.*
*(continues on facing page)*

| Correlation to PHQ-9 remission | Overall (*n*=3202) | | | SBL-DLPFC-TMS (F4-F3) (*n*=2486) | | | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=716) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Standardized coefficients* | | | *Standardized coefficients* | | | *Standardized coefficients* | | |
| | *β* | *t* | *p* | *β* | *t* | *p* | *β* | *t* | *p* |
| Age | -0.041 | -2.583 | 0.010 | -0.053 | -2.160 | 0.031 | -0.072 | -1.652 | 0.099 |
| Sex | -0.048 | -3.954 | **<.001** | -0.067 | -3.377 | **<.001** | -0.075 | -1.992 | 0.047 |
| Illness duration | -0.011 | 1.796 | 0.073 | 0.047 | 1.883 | 0.060 | 0.014 | 0.323 | 0.747 |
| Number of previously failed antidepressants | -0.094 | -4.034 | **<.001** | -0.088 | -4.276 | **<.001** | -0.001 | -0.020 | 0.984 |
| Baseline PHQ-9 | -0.195 | -5.491 | **<.001** | -0.178 | -5.113 | **<.001** | -0.121 | -1.905 | 0.057 |
| Baseline GAD-7 | -0.150 | -0.870 | 0.385 | 0.021 | 0.548 | 0.584 | -0.203 | -2.975 | **0.003** |
| TMS protocol *(SBL-DLPFC, R-LOFC/L-DLPFC)* | -0.006 | -0.645 | 0.519 | / | / | / | / | / | / |
| Baseline PHQ-9 item 1 (anhedonia) | -0.016 | 0.259 | 0.795 | 0.018 | 0.720 | 0.451 | -0.041 | -0.848 | 0.397 |
| Baseline PHQ-9 item 3 (sleep) | -0.068 | -0.002 | 0.998 | -0.013 | -0.599 | 0.549 | 0.043 | 1.047 | 0.295 |
| Baseline PHQ-9 item 9 (suicidality) | -0.077 | 0.942 | 0.346 | 0.010 | 0.423 | 0.672 | 0.050 | 1.162 | 0.246 |
| Baseline GAD-7 item 2 (rumination proxy) | -0.142 | -1.781 | 0.075 | -0.092 | -2.629 | 0.009 | 0.069 | 1.100 | 0.272 |

**Note.** For remitters, multiple linear regression revealed that overall sex (female), number of previously failed antidepressants (few), and baseline depression severity (PHQ-9; low score) are significant predictors. For the SBL-DLPFC-TMS group, the same variables were found to be significant in predicting remission. For the R-LOFC/L-DLPFC-TMS group, baseline anxiety severity (GAD-7; low score) was found to be a significant predictor of remission. For responders, multiple linear regression revealed that overall and in the bilateral DLPFC-TMS group sex (female) and number of previously failed antidepressants (few) are significant predictors. For the RLOFC/L-DLPFC-TMS group, no variable was found to be a significant predictor of response. DLPFC = dorsolateral prefrontal cortex; L-DLPFC = left DLPFC; GAD-7 = Generalized Anxiety Disorder-7 scale; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral DLPFC transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.
* Bonferroni-corrected p-value thresholds are 0.0045 for the overall analysis (0.05/11) and 0.005 for the SBL-DLPFC-TMS and R-LOFC/L-DLPFC-TMS analyses (0.05/10). **Bold** denotes statistically significant p-values.

*(Table S1, continued).*

| Correlation to PHQ-9 response | Overall (*n*=3202) | | | SBL-DLPFC-TMS (F4-F3) (*n*=2486) | | | R-LOFC/L-DLPFC-TMS (F8-F3) (*n*=716) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Standardized coefficients* | | | *Standardized coefficients* | | | *Standardized coefficients* | | |
| | *β* | *t* | *p* | *β* | *t* | *p* | *β* | *t* | *p* |
| Age | -0.021 | -1.905 | 0.057 | -0.041 | -1.637 | 0.102 | -0.053 | -1.203 | 0.229 |
| Sex | -0.069 | -4.094 | **<.001** | -0.074 | -3.650 | **<.001** | -0.074 | -1.927 | 0.054 |
| Illness duration | 0.018 | 2.197 | 0.028 | 0.062 | 2.451 | 0.014 | 0.004 | 0.093 | 0.926 |
| Number of previously failed antidepressants | -0.059 | -3.982 | **<.001** | -0.075 | -3.561 | **<.001** | -0.076 | -1.919 | 0.055 |
| Baseline PHQ-9 | 0.016 | 1.115 | 0.265 | 0.054 | 1.507 | 0.132 | -0.027 | -0.414 | 0.679 |
| Baseline GAD-7 | -0.031 | -0.283 | 0.777 | 0.038 | 1.003 | 0.316 | -0.165 | -2.371 | 0.018 |
| TMS protocol *(SBL-DLPFC, R-LOFC/L-DLPFC)* | -0.012 | -0.742 | 0.458 | / | / | / | / | / | / |
| Baseline PHQ-9 item 1 (anhedonia) | 0.020 | 0.802 | 0.423 | 0.013 | 0.507 | 0.612 | 0.044 | 0.889 | 0.375 |
| Baseline PHQ-9 item 3 (sleep) | 0.004 | -0.451 | 0.652 | -0.016 | -0.695 | 0.487 | 0.012 | 0.291 | 0.771 |
| Baseline PHQ-9 item 9 (suicidality) | 0.011 | 0.246 | 0.805 | -0.002 | -0.102 | 0.919 | 0.028 | 0.627 | 0.531 |
| Baseline GAD-7 item 2 (rumination proxy) | -0.042 | -1.654 | 0.098 | -0.089 | -2.489 | 0.013 | 0.063 | 0.988 | 0.323 |

**Note.** For remitters, multiple linear regression revealed that overall sex (female), number of previously failed antidepressants (few), and baseline depression severity (PHQ-9; low score) are significant predictors. For the SBL-DLPFC-TMS group, the same variables were found to be significant in predicting remission. For the R-LOFC/L-DLPFC-TMS group, baseline anxiety severity (GAD-7; low score) was found to be a significant predictor of remission. For responders, multiple linear regression revealed that overall and in the bilateral DLPFC-TMS group sex (female) and number of previously failed antidepressants (few) are significant predictors. For the RLOFC/L-DLPFC-TMS group, no variable was found to be a significant predictor of response. DLPFC = dorsolateral prefrontal cortex; L-DLPFC = left DLPFC; GAD-7 = Generalized Anxiety Disorder-7 scale; PHQ-9 = Patient Health Questionnaire-9; R-LOFC = right lateral orbitofrontal cortex; SBL-DLPFC-TMS = sequential bilateral DLPFC transcranial magnetic stimulation; TMS = transcranial magnetic stimulation.

* Bonferroni-corrected p-value thresholds are 0.0045 for the overall analysis (0.05/11) and 0.005 for the SBL-DLPFC-TMS and R-LOFC/L-DLPFC-TMS analyses (0.05/10). **Bold** denotes statistically significant p-values.

*Table S2. Multiple linear regression results on predictors for percentage improvement x TMS protocol regarding baseline characteristics and treatment-related variables.*

| Correlation to Percentage improvement x TMS protocol | Overall ($n$ = 3202) | | |
|---|---|---|---|
| | *Standardized coefficients* | | |
| | $\beta$ | $t$ | $p$ |
| % improvement | --0.274 | --15.937 | **<.001** |
| Age | 0.055 | 2.621 | .009 |
| Sex | 0.011 | 0.632 | 0.527 |
| Illness duration | -0.047 | -2.220 | 0.027 |
| Number of previously failed antidepressants | -0.063 | -3.501 | **<.001** |
| Baseline PHQ-9 | -0.002 | -0.066 | 0.947 |
| Baseline GAD-7 | -0.009 | -0.267 | 0.790 |
| Baseline PHQ-9 item 1 (anhedonia) | 0.004 | 0.172 | 0.863 |
| Baseline PHQ-9 item 3 (sleep) | -0.020 | -1.014 | 0.311 |
| Baseline PHQ-9 item 9 (suicidality) | -0.009 | -0.456 | 0.648 |
| Baseline GAD-7 item 2 (rumination) | 0.013 | 0.414 | 0.679 |

**Note.** After Bonferroni correction, the analysis identified fewer previous failed antidepressant trials as correlated with differentially greater percentage improvement on the SBL-DLPFC-TMS versus the hybrid R-LOFC/L-DLPFC protocol. GAD-7 = Generalized Anxiety Disorder-7 scale; PHQ-9 = Patient Health Questionnaire-9.
* Bonferroni-corrected p-value thresholds are 0.0045 (0.05/11). **Bold** denotes statistically significant p-values.

# 6

# DISCUSSION

Depression, affecting over 280 million people worldwide, remains a leading cause of disability and a critical public health issue (Friedrich, 2017; World Health Organization, 2023). As a complex and multifaceted mental health disorder, its heterogeneity and intricate etiology pose significant challenges for both clinicians and researchers alike (Reiff & Feldman, 2014; World Health Organization, 2017), and underscore that no single treatment approach is universally effective. This is especially evident in cases of TRD, where a considerable proportion of patients fail to achieve response after two or more adequate antidepressant trials (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006). The failure of standard pharmacotherapy and psychotherapy in TRD raises important questions about the underlying neurobiological mechanisms driving the disorder and prompts the need to identify potential biomarkers that could enhance treatment personalization. Additionally, it emphasizes the importance of exploring novel interventions that can be tailored to patients who do not respond to conventional treatments. This thesis aimed to address some of these pressing questions. While limitations are acknowledged, the findings lay the groundwork for further research and offer promising directions for improving treatment outcomes in TRD.

## MECHANISMS OF TRD

Various hypotheses, such as the inflammatory and brain remodeling hypotheses (Drevets et al., 2008; Maes et al., 2009), attempt to explain the mechanisms of depression, yet the reasons why some patients fail to respond to conventional treatments remain unclear. While depression often manifests as a brain disorder, its origins are frequently tied to environmental factors or cognitive biases, which drive changes in brain physiology. Addressing these physiological changes through targeted interventions, while also tackling the underlying triggers, is essential for effective treatment and relapse prevention. Understanding these mechanisms in greater depth is critical to improving outcomes for treatment-resistant cases.

One key mechanism that may underlie TRD is the dysregulation of brain circuits, particularly the rACC and its connection to the frontoparietal network and salience network—regions crucial for mood regulation and emotional processing (Bruder et al., 2017; Dosenbach et al., 2008). The study in Chapter 2 revealed that patients undergoing second/third-line treatments (i.e., TMS and ECT) exhibited higher rACC-theta activity, while those receiving first-line treatments (i.e., psychotherapy and antidepressants) showed lower activity. These findings support the hypothesis that baseline rACC-theta activity increases with greater treatment-resistance, aligning with findings from the iSPOT-D study, where patients with more prior treatment failures exhibited a stronger relationship between elevated rACC-theta activity and poor treatment response (Arns et al., 2015). These results suggest that rACC-theta power may reflect neural changes associated with illness progression and treatment failures, possibly capturing a dynamic, state-related aspect of brain function influenced by neuroplasticity. Intriguingly, this raises the provocative hypothesis that multiple failed pharmacological trials may exacerbate treatment resistance by inducing brain changes that diminish the efficacy of subsequent interventions, including TMS.

Patients with MDD who have failed 2–3 treatments, classified as TRD, often respond more effectively to TMS protocols like 10 Hz stimulation of the L-DLPFC and iTBS compared to continued anti-

depressant therapy (Blumberger et al., 2018; Rush et al., 2006). The Dutch-Belgian consensus recommends the L-DLPFC as the primary target for first-line TMS in depression (Arns et al., 2019). However, TMS response is inconsistent, with one subgroup showing significant clinical improvement and another exhibiting only marginal changes in depression scores, reflecting a bimodal distribution (Bakker et al., 2015; Downar et al., 2014; Fitzgerald et al., 2016). This suggests that for the less responsive subgroup, targeting an alternative network, such as the non-reward network via the R-LOFC, may be more effective.

In the studies from chapters 3 and 4, an improvement in depression severity was found DLPFC-TMS non-responders when stimulating the R-LOFC. Specifically, in chapter 4's study, a significant and sharp decline in PHQ-9 scores was found among R-LOFC-TMS responders during the first 10 sessions following the switch to R-LOFC-TMS. This trajectory aligns with the exponential decay function described by Berlow and colleagues (2023), where early clinical responses are predictive of eventual treatment outcomes. The observed discontinuity suggests a causal therapeutic effect of the protocol switch (Marinescu et al., 2018) and indicates that targeting R-LOFC treats depression by stimulating a distinct neural circuit. In contrast, R-LOFC-TMS non-responders displayed a continuation of the previous curve, implying that their gradual, incremental improvement—despite undergoing 72 sessions—was likely due to cumulative residual benefits of non-specific factors common to both protocols (e.g., behavioral activation, social contact, daily routine, and other elements that are involved in attending TMS treatment aside from receiving the actual brain stimulation itself). This pattern resembles the "slowed response" group identified in a recent analysis of MDD patients treated with up to 51 sessions of TMS (Chen et al., 2024). These findings support the idea that improvements following R-LOFC-TMS are driven by a mechanism distinct from DLPFC-TMS, rather than by the nonspecific accumulative effects of additional TMS sessions. This aligns with the hypothesis that TRD involves disrupted connectivity across various neural circuits, which R-LOFC-TMS is particularly well-suited to address.

In keeping with this hypothesis, multiple case series from independent groups have shown that adding or switching to R-LOFC-TMS in patients unresponsive to DLPFC-TMS led to notable improvements (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023). Given the hypothesis that targeting the R-LOFC treats depression via a distinct neural circuit, this raises the question of whether offering all patients a combined R-LOFC/L-DLPFC-TMS strategy from the start could be advantageous. By simultaneously targeting both the salience and the non-reward networks, this approach may exploit potential synergistic or additive effects, ultimately leading to higher overall remission rates. However, as demonstrated in Chapter 5, no significant differences in clinical effectiveness across various clinical measures were found between SBL-DLPFC-TMS (1 Hz F4 + 20 Hz F3) and R-LOFC/L-DLPFC-TMS (1 Hz F8 + 20 Hz F3) in MDD patients, despite the large sample size (N > 3000). This suggests that administering the combination R-LOFC/L-DLPFC treatment from the first session does not provide additional benefits over standard bilateral DLPFC-TMS in TMS-naive MDD patients—at least not with the R-LOFC parameters used in this study.

One possible explanation for this null finding is that the 360 pulses of 1 Hz stimulation applied at F4 and F8 were insufficient to generate a meaningful therapeutic effect; in this interpretation, both groups effectively just received L-DLPFC treatment, and so the finding of no difference is somewhat trivial. However, 1 Hz stimulation with these parameters has previously been used successfully in past trials (Brunelin et al., 2014; Feffer et al., 2018; Fettes et al., 2017).

Another possible explanation is the specific R-LOFC target used. Recent research indicated that the F8 location is anatomically closer to the R-VLPFC rather than the R-LOFC, which has been linked to the salience network (Trambaiolli et al., 2022). Therefore, stimulating F8 may have led to overlapping network effects between the right-sided targets; turning the intended two-network (salience and non-reward) protocol into a one-network (salience-only) protocol. This interpretation aligns with recent research showing that SBL-DLPFC-TMS does not outperform left unilateral DLPFC-TMS (Aaronson et al., 2022), likely because L-DLPFC stimulation already activates the en-

tire salience network, including the R-DLPFC (Tik et al., 2023). Thus, SBL-DLPFC-TMS may simply deliver more pulses to the salience network without any additional therapeutic benefit, a theory supported by RCTs that showed no advantage to this approach (Fitzgerald et al., 2020). Therefore, the lack of added benefit from the combined R-LOFC/L-DLPFC protocol may be due to the R-LOFC stimulation re-engaging the salience network instead of the non-reward network as intended.

One final explanation on the lack of significant differences between the two TMS protocols could stem from a concept of "specificity" in neuroplasticity. Neuroplastic changes depend on consistent stimulation of specific neural circuits to strengthen connections through Hebbian plasticity, commonly phrased as "what fires together, wires together". In protocols using multiple targets, such as R-LOFC/L-DLPFC-TMS, this consistency may be disrupted, potentially overwhelming the brain's capacity to establish stable, long-lasting synaptic changes. Supporting this notion, a large cohort study found that patients undergoing unilateral DLPFC-TMS had superior treatment outcomes than those receiving SBL-DLPFC-TMS (Aaronson et al., 2022). This may be due to unilateral stimulation providing more focused engagement of neural pathways, enhancing the specificity of neuroplastic adaptation. Furthermore, this theory also aligns with chapter 3 and 4's findings, along with prior research, where positive treatment outcomes was reported for TRD patients treated with R-LOFC-TMS following an unsuccessful DLPFC-TMS course (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023). The preserved specificity of R-LOFC stimulation after DLPFC-TMS may allow the brain to integrate this targeted approach more effectively, supporting more enduring neuroplastic changes.

Further research on R-LOFC-TMS targeting different anatomical sites is needed to clarify which targets engage which networks most effectively, potentially improving the therapeutic precision of TMS for TRD.

## BIOMARKERS OF TRD AND FOR TREATMENT OUTCOME PREDICTION

Stratified psychiatry is moving beyond the traditional "one-size-fits-all" approach by tailoring psychiatric treatments for specific patient subgroups identified through biomarkers, clinical features, and other measurable data, with the goal of improving remission rates and treatment outcomes (Arns et al., 2023). Recent research has shown that stratifying treatments, such as TMS or ECT, using iAPF-based Brainmarker-I decile scores significantly enhances remission rates (Voetterl, Sack, et al., 2023). However, there remains a notable discrepancy in the literature regarding the role of theta power in predicting treatment outcomes. For example, the EMBARC study suggested that elevated baseline rACC-theta activity serves as a non-specific prognostic marker of treatment outcome (Pizzagalli et al., 2018). In contrast, the iSPOT-D study found that patients with high baseline rACC-theta activity had poorer responses to antidepressants, especially among those with a history of treatment failures (Arns et al., 2015). Additionally, bio-typing studies using neuroimaging are being conducted to explore differences between responders and non-responders to DMPFC-TMS (Drysdale et al., 2017). Two key questions emerge from the literature: First, does the degree of treatment-resistance correlate with baseline rACC-theta activity? Second, can biomarkers predict which depressed patients are likely to benefit from R-LOFC-TMS?

Chapter 2's findings suggest that rACC-theta activity may serve as an electrophysiological marker of treatment-resistance in MDD. Higher rACC-theta activity was observed in patients undergoing second/third-line treatments (i.e., TMS and ECT), whereas lower activity was seen in those undergoing first-line treatments (i.e., psychotherapy and antidepressants). These results align with findings from the iSPOT-D study, where patients with greater treatment resistance (i.e., more prior treatment failures) exhibited a stronger relationship between elevated rACC-theta activity and poor treatment response (Arns et al., 2015). Clinically, these results suggest that rACC-theta could potentially serve as a valuable biomarker for assessing treatment resistance, guiding prescribers to consider second- and third-

line interventions, like TMS or ECT, earlier in the treatment process. Furthermore, other frequency bands (delta, beta, gamma) could offer additional insights for refining treatment selection and improving outcomes, though further research is needed to integrate these bands into a comprehensive biomarker for treatment selection.

Chapters 3, 4, and 5 explored the predictive value of demographic and clinical features for TMS targeting the R-LOFC. Surprisingly, no significant predictive associations were found between clinical characteristics and treatment outcomes for patients undergoing R-LOFC-TMS after failing to respond to DLPFC-TMS. However, in TMS-naive patients, female sex and fewer previous failed antidepressant trials emerged as significant predictors of better outcomes. Specifically, within the SBL-DLPFC-TMS group, these predictors were joined by longer illness duration and lower baseline rumination proxy score, while in the R-LOFC/L-DLPFC-TMS group, only lower anxiety (GAD-7) scores significantly predicted greater improvement. These findings are somewhat consistent with previous research identifying various prognostic markers. For instance, a large open-label study by Sackeim and colleagues (2020) found that females were more likely to achieve positive outcomes with DLPFC-TMS, showing higher response and remission rates than males. Other studies have shown higher baseline anhedonia scores correlate with non-response to TMS (Downar et al., 2014; Krepel et al., 2020), while a case series suggested that patients with higher baseline rumination scores predicted greater mood and depression symptom improvement following R-LOFC-TMS (Tadayonnejad et al., 2023). Additionally, while baseline sleep dysfunction in MDD patients often improves with TMS treatment, it does not appear to predict the therapeutic response to TMS (Brakemeier et al., 2007; Dijkstra et al., 2024; Hines et al., 2021).

The mixed findings from our studies regarding significant predictive associations may stem from several factors. Variations in TMS protocols, such as differences in stimulation parameters and target locations, along with smaller sample sizes that reduce predictive power, could have contributed to inconsistent results. Additionally, demographic and clinical features alone may be insufficient to predict TMS efficacy for R-LOFC stimulation, suggesting the need

for multimodal approaches that integrate clinical, neurobiological, and other biomarkers. These findings highlight the importance of further investigating and combining diverse biomarkers and clinical characteristics to better tailor treatments to individual patients and optimize therapeutic outcomes in TRD.

## NOVEL INTERVENTIONS FOR PATIENTS WITH TRD

TRD is limited by existing therapies (i.e., psychotherapy and pharmacotherapy), which often fail to provide adequate relief to a significant subset of patients with TRD (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006). Non-invasive brain stimulation techniques, such as TMS, have continued to evolve over recent years to address these hurdles. The conventional TMS targets, including left and right unilateral DLPFC (Arns et al., 2019; George et al., 1995; O'Reardon et al., 2007), have proven effective for many patients. However, these targets do not work for all, with some patients showing marked clinical improvement, while others only marginal benefits, demonstrating a "bimodal distribution" in depression treatment outcomes (Bakker et al., 2015; Downar et al., 2014; Fitzgerald et al., 2016). This variability has led to the exploration of alternative TMS targets, such as the R-LOFC. Questions that were raised in the introduction were whether targeting the R-LOFC provides symptom relief in TRD patients unresponsive to conventional stimulation protocols? And whether adding R-LOFC stimulation to DLPFC-TMS offers better outcomes compared to traditional SBL-DLPFC-TMS, especially for TMS-naive patients?

In this thesis, the TMS case series presented in Chapter 3 and 4 further support the growing evidence that R-LOFC-TMS may be an effective treatment for MDD patients unresponsive to conventional DLPFC-TMS. Reviewing previous work on this theme by other groups, when switching to R-LOFC-TMS, Fettes et al (2016) documented remission in a case study (targeting Fp2), while Feffer et al. (2018) reported a 23.3% remission rate (targeting AF8). The remission rates found in the studies from Chapter 3 and 4 are comparable to the just cited studies, with Chapter 3 reporting a 24% remission rate

(targeting Fp2) and Chapter 4 finding 16.7% (targeting F8). Moreover, when R-LOFC-TMS was used as an add-on protocol, Chapter 3's study recorded a 31.3% remission rate (targeting AF8) while Tadayonnejad et al. (2023) reported a 24% response rate (targeting Fp2; remission rates were not reported). When consolidated, remission rates across studies targeting the R-LOFC range from 16.7% to 31.3%, depending on the protocol and specific site used. This consistent demonstration of efficacy across different studies and patient populations strengthens the case for considering R-LOFC-TMS as a first-choice off-label option in clinical guidelines for TRD, particularly for patients unresponsive to other interventions. Moreover, its remission rates are comparable to those reported for DLPFC-TMS in earlier studies (Aaronson et al., 2022; Carpenter et al., 2021; Sackeim et al., 2020).

Given that R-LOFC stimulation may target distinct neural circuits involved in depression, we hypothesized that combining R-LOFC and DLPFC stimulation throughout the course of treatment could produce synergistic effects, improving remission rates overall. However, as previously mentioned, the final study of this thesis, which compared outcomes for a conventional SBL-DLPFC-TMS protocol versus a "hybrid" R-LOFC/L-DLPFC-TMS protocol, found no significant differences in clinical effectiveness across multiple clinical measures. These findings suggest that, while R-LOFC stimulation may be a viable secondary target following DLPFC-TMS failure, in this study, incorporating this particular protocol for R-LOFC stimulation (360 pulses of 1 Hz treatment at F8) into the initial treatment course does not enhance overall treatment outcomes.

Notably, a recent fMRI study conducted a RCT comparing three groups: accelerated R-LOFC/L-DLPFC-TMS, accelerated L-DLPFC-TMS, and sham. Initially, responders to the R-LOFC/L-DLPFC protocol demonstrated greater improvement immediately following treatment than those receiving unilateral DLPFC-TMS. However, by one week post-treatment, depression levels among L-DLPFC-TMS responders had improved sufficiently, eliminating the significant difference between the two protocols (Cui et al., 2024). This outcome aligned with our findings, suggesting no difference in treatment ef-

fectiveness between standard DLPFC-TMS and R-LOFC/L-DLPFC-TMS. Therefore, while R-LOFC-TMS has shown promise as a rescue strategy for DLPFC-TMS non-responders, its utility as part of a combined first-line approach remains uncertain.

These findings highlight the complexity of depression as a neurobiological disorder and the ongoing need to refine and personalize neuromodulation techniques to enhance treatment outcomes for patients with TRD. Future developments of R-LOFC-TMS as a novel intervention for TRD will therefore need to focus on parameter optimization, with particular attention to target location and pulse intensity, to enhance therapeutic outcomes for TRD patients.

## LIMITATIONS

The study presented in Chapter 2 has several limitations that may have impacted the interpretation and generalizability of its findings. One major limitation is the lack of systematic collection of key demographic variables (e.g., premorbid IQ, socioeconomic status, ethnicity, and history of substance use), which may influence treatment resistance and thus the study's results. Additionally, the reliance on naturalistic, open-label datasets meant that treatment regimens were not standardized and were subject to clinical judgment, limiting the comparability with more controlled settings like RCTs. Another limitation is the study's focus on theta activity in the rACC and frontal regions, based on findings from the earlier 2015 iSPOT-D study (Arns et al., 2015). While this focus aimed to limit type-I error, it may have restricted the study's scope, potentially overlooking other regions of interest. The absence of post-treatment EEG data further limited the ability to assess longitudinal effects. Finally, the diverse range of antidepressant treatments employed in the naturalistic setting could not be thoroughly analyzed due to small sample sizes for each treatment type, adding another layer of complexity to the study's findings.

The study in Chapter 3, while revealing promising outcomes for R-LOFC-TMS, had several limitations. The small sample size (n = 41) across two cohorts (The Netherlands and US) reduced statisti-

cal power, limiting the detection of subtle predictors of treatment response. Differences between the Dutch and American samples—including R-LOFC stimulation sites (NL: Fp2 vs. US: AF8), TMS coils (NL: D-B80 coil vs. US: NeuroStar iron-core coil), patient demographics (females NL:48% vs US: 69%), and the number of prior DLPFC-TMS sessions before switching to R-LOFC-TMS (US: 20.4 sessions vs. NL: 42.4 sessions, due to differences in reimbursement policies)—may have influenced the findings. The absence of a sham control group complicated attributing the observed effects specifically to R-LOFC-TMS. Additionally, the absence of a randomized comparison between patients continuing L-DLPFC-TMS for an additional 36 sessions (72 total) and those switching to R-LOFC-TMS (36 sessions) after initial non-response prevented direct testing of the hypothesis that R-LOFC is more effective for DLPFC-TMS non-responders. Another limitation is the heterogeneity of the DLPFC protocols (10 Hz L-DLPFC, 1 Hz R-DLPFC, or bilateral DLPFC), which could have introduced variability in treatment outcomes, making it challenging to isolate the specific effects of R-LOFC-TMS from more consistent DLPFC protocols. Additionally, the study's focus on patients transitioning from DLPFC- to R-LOFC-TMS narrows its applicability, as it does not explore R-LOFC-TMS as a potential first-line treatment. Furthermore, despite examining various clinical and psychological characteristics, none significantly predicted remission, limiting patient stratification and treatment personalization. Finally, while the open-label design highlights the real-world potential of R-LOFC-TMS, it remains unclear whether the observed improvements are truly unique to this stimulation site or could be achieved with alternative TMS targets.

The study in Chapter 4 also has several limitations to be noted. Again, the small sample size (N=54) limits the generalizability of the results, and although the results suggest that females may respond better to R-LOFC-TMS, the study lacked sufficient statistical power to identify other potential predictors of treatment response or remission. Similarly, the absence of a control group, given that the study only included patients who did not respond to SBL-DLPFC-TMS, further limits the ability to conclusively determine the effectiveness of R-LOFC-TMS for MDD patients. Moreover, the use of a limited

set of clinical outcome scales prevented a thorough assessment of treatment effects on specific symptoms such as rumination, suicidal ideation, neuroticism, and other domains potentially relevant to the R-LOFC stimulation target. The lack of detailed psychometric evaluations and biomarkers also constrains the understanding of the therapeutic impact and underlying mechanisms of R-LOFC-TMS in this population.

The study in chapter 5 also has several limitations that affect the interpretation of its findings. Parameter choices may have influenced the results, as the 1 Hz protocol, possibly underdosed at 360 pulses, may have led to insufficient stimulation, effectively resulting in both groups receiving L-DLPFC stimulation. Also, as noted above, the F8 location may have inadvertently targeted the same network as F4 and F3, as it falls closer to the right VLPFC rather than the true R-LOFC, and the right VLPFC appears to participate in the salience network, similarly to the F3 and F4 regions (Trambaiolli et al., 2022). Additionally, the study used GAD-7 item 2 as a proxy for rumination, which did not predict beneficial outcomes, unlike previous studies where rumination measured by the RRS was a predictor of better R-LOFC-TMS response (Tadayonnejad et al., 2023). Lastly, as a non-RCT study relying on its large sample size to mitigate limitations inherent in its retrospective, naturalistic, open-label design, its findings require cautious interpretation.

Some general limitations also apply to each of the four studies presented here, reflecting broader challenges common in the literature on biomarkers and TMS. Notably, all of the studies were open-label, which limits the ability to control for placebo effects and introduces potential bias in the interpretation of treatment outcomes. In the context of biomarker studies, most research is retrospectively derived, with few biomarkers being prospectively validated in real-world clinical settings. Prospective testing, where treatment selection is guided by biomarkers, should be rigorously compared against standard sequential treatment algorithms to determine whether biomarker-driven approaches offer clinically significant improvements. Furthermore, the TMS field as a whole requires more large-scale RCTs to provide robust evidence for the efficacy of different TMS

protocols, as well as to identify reliable biomarkers for patient stratification and treatment optimization. These limitations underscore the significant knowledge gaps that remain and highlight the more general need for future work in this field to focus on prospective studies, larger sample sizes, and randomized designs, to strengthen the evidence base for TMS and its associated biomarkers.

## FUTURE RESEARCH DIRECTIONS FOR ENHANCING TREATMENT OUTCOMES IN TRD

While the study in Chapter 2 found that rACC-theta activity differs according to treatment resistance in patients with depression, it also identified key areas for further research. A major recommendation was to further refine the analyses by incorporating connectivity measures between the rACC and its association with TRD levels, particularly by comparing connectivity pre- and post-treatment to better understand intervention effects. A recent resting-state fMRI study addressed part of this objective, showing that patients with TRD exhibit hyperconnectivity within the default mode network—particularly between the rACC and posterior cingulate cortex—compared to individuals with treatment-sensitive depression and healthy controls (Barreiros et al., 2024). Chapter 2's exploratory analyses also revealed significant differences in other frequency bands—delta, beta, and gamma—across treatment groups. Given the limited literature on these bands in TRD, further exploration is suggested to determine their relevance in treatment selection or outcome prediction. While the use of large, naturalistic datasets allowed for generalization to real-world clinical practice, future research should also address potential confounding factors by collecting a broader range of demographic and clinical variables. Chapter 2's study also recommends focusing on markers that are specific to particular types of antidepressants, as the naturalistic setting limited detailed analyses of different medication classes or specific medications among the many available antidepressant treatments. Moreover, the specificity of the theta band versus other bands in predicting treatment outcomes should be further investigated to clarify the role of rACC-theta in particular as a treatment selection/treatment resistance biomarker.

Finally, longitudinal EEG studies in depressed patients are recommended to explore neuroplasticity in response to illness progression and successive treatment failures, providing deeper insights into the evolving nature of TRD.

The study in Chapter 3 highlights several key directions for future research on 1 Hz-R-LOFC-TMS in MDD. The small sample size and lack of a control group highlight the need for larger RCTs with well-matched control groups, including sham treatments, to confirm the specific efficacy of R-LOFC-TMS compared to other TMS targets. Additionally, exploring R-LOFC-TMS as a first-line treatment rather than a fallback after DLPFC-TMS failure could broaden its applicability. Investigating EEG biomarkers, like Brainmarker-I and OFC-theta band activity, and symptom-specific predictors, like rumination, could help stratify patients for more personalized interventions (Feffer et al., 2022; Tadayonnejad et al., 2023; Voetterl, Sack, et al., 2023). Multi-site studies with standardized protocols and more detailed, broad-spectrum assessment of patient symptoms and characteristics would clarify the potential impact that inter-site variations in protocol and patient selection had on this study, and aid in refining the clinical implementation of R-LOFC-TMS. Finally, expanding research to include more diverse populations of patients at earlier and later stages of treatment resistance, and exploring long-term effects, would further solidify R-LOFC-TMS's role in treating TRD, potentially reducing the need for more invasive treatments like ECT.

Similarly, the study in Chapter 4 outlines several future research directions for R-LOFC-TMS in MDD patients. Increasing the sample size is essential for enhancing generalizability of findings and to better identify predictors of treatment response, especially concerning sex differences. Expanding the use of psychometric assessments and clinical outcome scales would enable a more comprehensive evaluation R-LOFC-TMS effects on symptoms like rumination, suicidal ideation, and neuroticism, thereby helping to distinguish predictors of response to R-LOFC-TMS and DLPFC-TMS. Incorporating EEG (e.g., OFC-theta power) (Feffer et al., 2022) and fMRI biomarkers could refine patient stratification and optimize treatment protocol. Additionally, randomized sham-controlled trials are necessary to definitively

assess R-LOFC-TMS efficacy. Finally, and most crucially, conducting RCTs that compare outcomes from switching non-responders from DLPFC-TMS to R-LOFC-TMS, versus continuing DLPFC-TMS could provide valuable insights into optimal treatment strategies for TRD.

Chapter 5 identifies further research directions for establishing the efficacy of R-LOFC-TMS in MDD patients. Future RCTs should compare R-LOFC-TMS with sham stimulation, with DLPFC-TMS, and R-LOFC/L-DLPFC with bilateral DLPFC-TMS. Applying recent TMS-fMRI advancements, which have provided valuable insights into the neurophysiological effects of DLPFC stimulation (Tik et al., 2023), could help optimize R-LOFC stimulation parameters, including number of pulses, pulse sequence, and target location. Since clinical and demographic characteristics did not predict R-LOFC-TMS outcomes in the present work, incorporating EEG and fMRI biomarkers could offer a pathway toward a more personalized treatment approach. Using validated measures, like the RRS, could enhance outcome predictions, particularly for patients with high rumination levels. This comprehensive approach could lead to more tailored, effective TMS strategies, ultimately improving success rates for individuals with TRD.

Finally, an important consideration for any predictive biomarker for treatment selection is its practicality for real-world use. For example, fMRI-based predictors, which require complex acquisition sequences or analysis (e.g., Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), targeted functional network stimulation (TANS)) (Cole et al., 2020; Lynch et al., 2022), may be useful in advanced facilities such as general hospitals or tertiary care centers but may be harder to implement in smaller clinics or community mental health settings where access to advanced imaging technology and specialized expertise is limited. Conversely, other biomarkers offer simplicity and scalability. An example is the Heart-Brain Coupling (HBC) method, which requires only a 1-lead EKG and minimal training, making it deployable in almost any setting as a biomarker for TMS coil placement and treatment outcome prediction (Dijkstra et al., 2023). For R-LOFC treatment, it would be interesting to see whether a simple, scalable technique like HBC could be used to optimize

coil placement and predict treatment outcomes. This approach could enhance the precision of R-LOFC-TMS and broaden its applicability across various clinical environments. Additionally, for selecting R-LOFC vs DLPFC patients, a dedicated symptom scale (e.g., incorporating rumination, anhedonia, neuroticism, and other symptoms related to posited OFC functions) could be developed and validated in a prospective study. Simple, inexpensive, and widely scalable, clinical questionnaires may prove to be an essential tool alongside fMRI, EEG, and other more technically complex biomarkers in helping patients to receive more personalized treatments – particularly in settings where access to advanced neuroimaging or biomarker technology is limited.

## CONCLUSION

The central problem this thesis aimed to address is the longstanding challenge of TRD (or DTD), where a substantial proportion of patients fail to respond to conventional first-line treatments (i.e., antidepressants and psychotherapy). Despite decades of research, the neurobiological underpinnings of TRD remain elusive, leaving clinicians with limited tools to predict treatment outcomes or tailor interventions to individual patients. While TMS has proven effective for TRD, identifying the most effective brain targets and reliable biomarkers for guiding treatment remains a critical challenge in clinical practice. This thesis has made some progress in addressing these issues by identifying distinct neural markers (i.e., rACC-theta power) that could serve as a biomarker for assessing treatment resistance. Additionally, it has strengthened the case for alternative TMS targets (i.e., R-LOFC) in TRD patients unresponsive to conventional DLPFC-TMS. These findings align with broader advancements in the field, including work by Tadayonnejad and colleagues (2023), who similarly identified R-LOFC as a promising alternative TMS target, and Berlow and colleagues (2023), who demonstrated that depression improvement through TMS aligns better with an exponential decay model than a linear progression. This consistent demonstration of efficacy across different studies and patient populations further supports R-LOFC-TMS as a potential first-choice off-label option in clin-

ical guidelines for TRD, especially for patients unresponsive to other interventions. The development of accelerated TMS regimens (Cole et al., 2020, 2022) also opens exciting new directions for research into novel TMS targets in TRD. Nevertheless, much remains to be done. Future efforts should focus on large-scale RCTs to confirm the efficacy of R-LOFC-TMS, refine treatment protocols, and validate biomarkers like rACC-theta in prospective studies. Expanding research into EEG and fMRI biomarkers, coupled with the development of symptom-specific scales (e.g., for rumination or anhedonia), will be essential in personalizing treatment strategies. Pursuing these research avenues holds promise for substantial improvements in TRD patient outcomes, equipping clinicians with the tools to more effectively target the neural circuitry underlying depression. Such progress brings the potential for higher remission rates and renewed hope for those suffering from this debilitating disorder.

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## ENGLISH SUMMARY

Depression remains a major global health challenge, with a considerable number of individuals failing to respond to conventional therapies such as psychotherapy and pharmacotherapy. This persistent lack of efficacy underscores the need for innovative strategies and a deeper understanding of the mechanisms driving treatment resistance. TRD (or DTD) exemplifies the complexity of this condition, emphasizing the urgency for tailored interventions.

The first part of this thesis focused on enhancing the mechanistic understanding and diagnostic staging of TRD through g biomarkers, specifically rACC-theta activity. Analysis of oscillatory brain activity in large patient cohorts undergoing various treatments revealed distinct rACC-theta patterns across different levels of treatment-resistance. Higher rACC-theta activity was found in patients receiving second/third line care (i.e., rTMS and ECT), whereas lower activity was found in those undergoing first line care (i.e., psychotherapy and antidepressants). Notably, among antidepressant-treated patients, those who achieved remission exhibited higher rACC-theta activity than non-remitters. These findings suggest that rACC-theta may

hold promise as a biomarker for evaluating treatment resistance, guiding treatment selection and improving prognostic accuracy in clinical practice.

The second part of this thesis examined the therapeutic potential of R-LOFC-TMS as a rescue protocol for TRD patients unresponsive to standard DLPFC-TMS. The OFC, central to reward processing and emotional regulation, is implicated in depression through its role in the "non-reward" attractor state—a maladaptive neural mechanism associated with persistent depressive symptoms. The studies from chapters 3, 4, and 5 hypothesized that targeting the R-LOFC with TMS could modulate neural circuits distinct from those affected by conventional DLPFC-TMS, offering therapeutic benefits to a wider range of patients, in particular those with specific depressive subtypes or symptoms such as anhedonia or rumination.

Studies from chapters 3 and 4 demonstrated that 1 Hz-R-L-OFC-TMS, whether used as a standalone intervention or as an augmentation to DLPFC-TMS, significantly improved clinical outcomes for TRD patients. These studies revealed marked improvements in mood, anhedonia, rumination, and overall depressive severity among patients who had previously not responded to standard DLPFC-TMS, highlighting the efficacy of 1 Hz R-L-OFC-TMS and its value as an alternative target for brain stimulation. However, the study from chapter 5 showed unexpectedly that incorporating R-LOFC stimulation alongside DLPFC-TMS from the start of treatment did not provide additional therapeutic benefits compared to the conventional SBL-DLPFC-TMS protocol. Further study on parameter optimization for R-LOFC-TMS may therefore be required.

In summary, this thesis provides a dual contribution to the field of depression research: establishing rACC-theta activity as a robust biomarker reflecting treatment resistance and then validating R-LOFC-TMS as an effective intervention for patients unresponsive to traditional TMS protocols. These findings pave the way for more individualized, biomarker-driven treatments, addressing critical gaps in current mental health care. The findings also suggest directions for further parameter optimization in R-LOFC-TMS to improve out-

comes. This work underscores the importance of combining innovative therapeutic strategies with biomarker insights to advance the management of depression and improve the quality of life for those affected.

# NEDERLANDSE SAMENVATTING

Depressie blijft een grote mondiale gezondheidsuitdaging, waarbij een aanzienlijk aantal mensen niet reageert op conventionele therapieën zoals psychotherapie en farmacotherapie. Dit aanhoudende gebrek aan effectiviteit benadrukt de noodzaak van innovatieve strategieën en een dieper begrip van de mechanismen die behandelingsresistentie veroorzaken. TRD (of DTD) illustreert de complexiteit van deze aandoening en onderstreept de urgentie van op maat gemaakte interventies.

Het eerste deel van dit proefschrift richtte zich op het verbeteren van het mechanistisch begrip en de diagnostische classificatie van TRD door middel van biomarkers, specifiek rACC-theta-activiteit. Analyse van oscillerende hersenactiviteit bij grote patiëntcohorten die verschillende behandelingen ondergingen, onthulde specifieke rACC-theta-patronen bij verschillende niveaus van behandelingsresistentie. Hogere rACC-theta-activiteit werd waargenomen bij patiënten in de tweede/derde lijnszorg (d.w.z. rTMS en ECT), terwijl lagere activiteit werd gevonden bij patiënten in de eerstelijnszorg (d.w.z. psychotherapie en antidepressiva). Opmerkelijk was dat anti-

depressivumgebruikers die remissie bereikten, een hogere rACC-theta-activiteit vertoonden dan degenen die geen remissie bereikten. Deze bevindingen suggereren dat rACC-theta potentie heeft als biomarker voor het evalueren van behandelingsresistentie, waardoor de behandeling beter kan worden afgestemd en de prognostische nauwkeurigheid in de klinische praktijk kan worden verbeterd.

Het tweede deel van dit proefschrift onderzocht het therapeutische potentieel van R-LOFC-TMS als reddingsprotocol voor TRD-patiënten die niet reageren op standaard DLPFC-TMS. De OFC, die centraal staat in beloningsverwerking en emotieregulatie, speelt een rol bij depressie via de "non-reward" attractortoestand—een maladaptief neuronaal mechanisme dat wordt geassocieerd met aanhoudende depressieve symptomen. De studies in hoofdstukken 3, 4 en 5 stelden de hypothese dat TMS toegepast op de R-LOFC neurale circuits kan moduleren die anders zijn dan die welke worden beïnvloed door conventionele DLPFC-TMS, en daarmee therapeutische voordelen kan bieden aan een bredere groep patiënten, met name aan die met specifieke depressieve subtypes of symptomen zoals anhedonie of rumineren.

De studies in hoofdstukken 3 en 4 toonden aan dat 1 Hz-R-LOFC-TMS, zowel als zelfstandige interventie als in combinatie met DLPFC-TMS, significante klinische verbeteringen opleverde voor TRD-patiënten. Deze studies rapporteerden duidelijke verbeteringen in stemming, anhedonie, rumineren en algehele depressieve ernst bij patiënten die eerder niet reageerden op standaard DLPFC-TMS, wat de effectiviteit van 1 Hz-R-LOFC-TMS benadrukt en de waarde ervan als alternatieve doellocatie voor hersenstimulatie aantoont. Echter, de studie in hoofdstuk 5 toonde onverwacht aan dat het combineren van R-LOFC-stimulatie met DLPFC-TMS vanaf het begin van de behandeling geen extra therapeutische voordelen opleverde ten opzichte van het conventionele SBL-DLPFC-TMS-protocol. Verder onderzoek naar parameteroptimalisatie voor R-LOFC-TMS is daarom mogelijk nodig.

Samenvattend levert dit proefschrift een dubbele bijdrage aan het onderzoek naar depressie: het vaststellen van rACC-theta-activite-

it als een robuuste biomarker behandelingsresistentie en het valideren van R-LOFC-TMS als een effectieve interventie voor sommige patiënten die niet reageren op traditionele TMS-protocollen. Deze bevindingen banen de weg voor meer gepersonaliseerde, biomarker-gestuurde behandelingen, waarmee kritieke hiaten in de huidige geestelijke gezondheidszorg worden aangepakt. Daarnaast wijzen de resultaten op de noodzaak van verdere parameteroptimalisatie in R-LOFC-TMS om de behandelresultaten te verbeteren. Dit werk benadrukt het belang van het combineren van innovatieve therapeutische strategieën met biomarkerinzichten om het beheer van depressie te verbeteren en de levenskwaliteit van de getroffen personen te verhogen.

## IMPACT PARAGRAPH

Depression, a condition affecting over 280 million individuals worldwide, is the leading cause of disability globally and poses a significant public health challenge (Friedrich, 2017; World Health Organization, 2023). TRD, characterized by the failure of patients to achieve response after two or more adequate antidepressant trials, represents one of its most severe and debilitating forms (McAllister-Williams et al., 2021; McIntyre et al., 2023; Rush et al., 2006). This thesis makes substantial contributions to advancing our understanding of TRD, providing novel insights into its neurobiological underpinnings and exploring innovative interventions aimed at improving treatment outcomes for this challenging patient population.

A key contribution of this thesis is the finding that rACC-theta power may reflect neural changes associated with illness progression and treatment failures, capturing a dynamic, state-dependent aspect of brain function shaped by neuroplasticity. The study from chapter 2 demonstrated that patients undergoing second/third-line treatments (i.e., TMS and ECT) exhibited higher rACC-theta activity, relative to those receiving first-line treatments (i.e., psychotherapy and anti-

depressants) showing lower activity. These findings build on prior research, such as the iSPOT-D study, which reported a stronger association between elevated rACC-theta activity and poor treatment response in patients with more prior treatment failures (Arns et al., 2015). This work provides a deeper understanding of the role of the rACC in mood regulation and offers valuable implications for personalized treatment strategies. For example, rACC-theta activity could serve as a stratification tool for assessing treatment resistance, enabling clinicians to identify patients who might benefit from an early initiation of second- or third-line treatments such as TMS or ECT. By tailoring treatment pathways based on biomarkers, this approach has the potential to improve care efficiency and improve clinical outcomes for individuals with TRD.

This thesis also makes a significant contribution to the field of neuromodulation by exploring the therapeutic potential of targeting the R-LOFC with TMS. While conventional TMS protocols have predominantly focused on the DLPFC (Arns et al., 2019; George et al., 1995; O'Reardon et al., 2007), a considerable proportion of patients fail to respond (Bakker et al., 2015; Downar et al., 2014; Fitzgerald et al., 2016), highlighting the need for alternative targets. The findings from the studies of chapters 3 and 4 revealed that switching to or augmenting DLPFC-TMS with R-LOFC-TMS (targets Fp2, AF8, F8) following treatment failure can achieve treatment response in a sizeable subgroup of patients. An explanation laid forward is that R-LOFC-TMS engages distinct neural circuits involved in the pathophysiology of depression, particularly those involved in reward, non-reward, and rumination. The findings from the studies of chapters 3 and 4 align with previous research on R-LOFC-TMS as an effective rescue strategy for DLPFC-TMS non-responders, with consistent efficacy demonstrated across different R-LOFC targets (Feffer et al., 2018; Fettes et al., 2017; Tadayonnejad et al., 2023). This consistent demonstration of efficacy across multiple studies and diverse patient populations reinforces the potential of R-LOFC-TMS as a leading off-label option in clinical guidelines for TRD, particularly for patients unresponsive to other interventions. This work highlights R-LOFC-TMS as a powerful addition to the therapeutic toolkit, providing new hope for patients with TRD who have exhausted conventional treatment options.

Finally, this thesis also underscores the intricate consideration involved in combining TMS targets to optimize treatment outcomes. The study from Chapter 5 compared a hybrid R-LOFC/L-DLPFC-TMS protocol to a conventional SBL-DLPFC-TMS protocol in a large sample of over 3000 TMS-naive patients. While, unexpectedly, no significant difference in clinical effectiveness was found between the protocols, this finding provides valuable insights into the complexities of designing multi-network stimulation strategies, and suggests directions for future optimization of the R-LOFC protocol, to fully harness the therapeutic potential of multi-target TMS approaches. For instance, the 360 pulses of 1 Hz stimulation delivered to F8 (R-LOFC) may not have been optimized to generate robust therapeutic effects. Furthermore, anatomical factors, such as the proximity of F8 to the R-VLPFC rather than the R-LOFC (Trambaiolli et al., 2022), suggest that refining target localization could enhance network specific engagement. This consideration is particularly relevant for protocols aiming to engage both the salience and non-reward networks. A final important perspective arises from the concept of "specificity" in neuroplasticity. Unilateral DLPFC-TMS, shown to outperform SBL-DLPFC-TMS (Aaronson et al., 2022), may enhance neuroplastic adaptation through focused neural engagement. Building on this principle, only targeting the R-LOFC following DLPFC-TMS failure may have a focused and specific effect, helping the brain adapt to this new stimulation more efficiently and resulting in durable changes in brain connectivity. These findings highlight exciting opportunities for future research to refine R-LOFC-TMS protocols. By optimizing stimulation parameters and exploring alternative anatomical targets, future work could significantly advance the therapeutic precision and efficacy of TMS for TRD.

While this thesis illustrates how both biomarkers and novel treatment approaches can enhance overall outcomes, it also underscores the complexities involved in developing effective new therapies and biomarkers. Specifically, even treatments (or biomarkers) with promising initial results often require extensive parameter optimization before they can succeed on a larger scale. The potential for failure of new treatments and biomarkers when applied at scale emphasizes the continuing need to deepen our understanding of the funda-

mental neural processes that give rise to depression and perpetuate treatment-resistance. By advancing this knowledge, future efforts to develop biomarkers and interventions will be better positioned to translate into improved outcomes for the millions of patients with depression still seeking a path to remission.

In summary, this thesis makes important contributions to the scientific understanding and practical treatment of TRD. By elucidating the role of rACC-theta activity, demonstrating the promise of R-LOFC-TMS, and identifying challenges in optimizing combination protocols, it provides a foundation for future innovation. The findings emphasize the need for continued research into biomarkers, targeted neuromodulation, and personalized approaches to improve treatment outcomes for individuals with TRD, ultimately enhancing their quality of life.

## CURRICULUM VITAE

Amourie Prentice was born on the 2nd of October 1993 in London, United Kingdom. She obtained her Bachelor's degree in Psychology from the Université Libre de Bruxelles (Belgium) in 2019, and her Master's degree in Neuropsychology from Maastricht University (The Netherlands) in 2020. During this education, she undertook a summer internship with Dr. Randy McIntosh and a master's internship with Dr. Donna Rose Addis at the Rotman Research Institute in Toronto (Canada).

In October 2020, she commenced the PhD program in collaboration with Research Institute Brainclinics Research Institute and Synaeda Psycho Medisch Centrum with Dr. Martijn Arns and Dr. Nikita van der Vinne serving as co-supervisors, and officially started the PhD program in September 2021 at Maastricht University, with Dr. Alexander Sack as her supervisor, resulting in the completion of this thesis.

During her time as a PhD student, Amourie attended international conferences, showcasing her work through poster and oral presentations. In addition to her published manuscripts, her record of productivity also includes giving birth to her son (Keffran) on 8th of September 2023, following a challenging pregnancy marked by hyperemesis gravidarum.

## LIST OF PUBLICATIONS

### PUBLISHED

Prentice, A., Arns, M., Middleton, V., Bowman, J., Donachie, N., Kriske, J., ... & Downar, J. (2025). Sequential bilateral dorsolateral prefrontal versus right lateral orbitofrontal/left dorsolateral prefrontal TMS for major depression: a large naturalistic case series. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*.

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## CONFERENCE PROCEEDINGS

### ORAL PRESENTATIONS

A comparison of clinical outcomes using sequential right lateral orbitofrontal cortex/left DLPFC-TMS, versus conventional sequential bilateral DLPFC-TMS for major depressive disorder, in a large naturalistic patient sample. *6th International Brain Stimulation Conference*, 2025, Kobe, Japan.

Clinical effectiveness of switching to right lateral orbitofrontal-TMS after a failure of sequential bilateral dorsolateral prefrontal-TMS in major depression. *3rd BeNe Brain Stimulation Symposium*, 2024, Gent, Belgium

Clinical effectiveness of OFC-TMS. *TMS Certification Course & Masterclass, 2024,* Nijmegen, The Netherlands.

EEG-biomarkers gericht op de predictie van behandelsucces en op het meten van hardnekkigheid van depressie. *Symposium RGOC: Netwerk Stemming en Angst*, 2022, Groningen, The Netherlands.

### POSTER PRESENTATIONS

Evaluating Right Lateral Orbitofrontal Cortex (R-LOFC)-TMS: A Rescue Option for DLPFC-TMS Non-Responders and Insights Into Its Role in Initial Combination Protocols. *Society of Biological Psychiatry Annual Meeting*, 2025, Toronto, Canada.

Rostral anterior cingulate cortex as an antidepressant treatment predictor or for indexing treatment resistance? *BeNe Brain Stimulation Conference*, 2022, Hasselt, Belgium

Investigating EEG biomarker specificity to combined rTMS with psychotherapy: Psychotherapy, rTMS or sham? A blinded prediction study. *4th International Brain Stimulation Conference*, 2021, Charleston, SC, US.

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