Deep Transcranial Magnetic Stimulation for Geriatric Depression

Applications of Deep Transcranial Magnetic Stimulation in Older Adults with Treatment-Resistant Depression

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Lay abstract

Brain stimulation therapies, such as deep transcranial magnetic stimulation (dTMS), show promising results for treatment-resistant depression (TRD). However, the applications of dTMS remain overlooked in geriatric populations with TRD, limiting the generalizability of such treatments to older adults. This dissertation aimed to examine current evidence supporting the use of dTMS in older adults with depression. In Study 1, we conducted a systematic review of available evidence on the clinical efficacy of dTMS across psychiatric and cognitive disorders. We found most evidence supporting the clinical efficacy of dTMS for the treatment of depressive episodes. However, the underrepresentation of older adults in such research was highly prevalent, with only one study being focused on older adults. In Study 2, we explored the effectiveness of diverse recruitment methods used in an ongoing dTMS trial for older adults with depression. Additionally, we identified potential facilitators and barriers to recruitment. Overall, the most effective recruitment strategies were (1) health provider outreach within the affiliated inpatient and outpatient mental health clinics and (2) Facebook advertising. Furthermore, social support from research staff and high time commitment of dTMS treatments were identified as facilitators and barriers to recruitment, respectively. These findings highlight the importance of conducting dTMS research in older adults to address the issue of underrepresentation and to improve evidence-based care in this special population.

Abstract

Objectives: To examine current evidence of clinical efficacy and applications of deep transcranial magnetic stimulation (dTMS) among older adults with treatment-resistant depression (TRD).

Methods: In Study 1, we conducted a systematic review of existing literature on the clinical efficacy of dTMS across psychiatric and cognitive disorders. Studies eligible for inclusion were clinical trials which were required to have a sham/control condition to mitigate confounding variables and to strengthen our assessment of efficacy. This dissertation specifically aimed to discuss these findings in the context of older adults with depression, as a means to investigate whether available evidence supporting the clinical efficacy of dTMS for depression is generalizable to older populations. In Study 2, we analyzed recruitment data from a pilot study investigating the effects of dTMS in older adults with TRD. Specifically, we aimed to evaluate the effectiveness of various recruitment strategies by using an enrollment-cost analysis, as well as comparing enrollment rates (i.e., enrolled participants/referrals received) for each recruitment method. Moreover, we identified potential facilitators and barriers to recruitment following a verbal thematic analysis of qualitative interview data.

Results: In Study 1, most substantial evidence (n = 6 studies) within the literature supports the clinical efficacy of the dTMS H1-coil for the treatment of depressive episodes in patients with bipolar disorder (BD) or major depressive disorder (MDD). Only one randomized controlled trial was conducted in older adults with TRD. This trial reported higher remission rates in the active dTMS arm compared to the sham dTMS arm

following treatment with the H1-coil. In study 2, we found (1) health provider outreach within the affiliated inpatient and outpatient mental health clinics and (2) Facebook, to be the most effective recruitment strategies. Lastly, social support from research staff (n = 15; 88.24%) and the time-intensiveness aspect of dTMS treatments (n = 6; 35.29%) were the most frequently identified facilitators and barriers to recruitment, respectively.

Conclusions: While there is notable evidence supporting the clinical efficacy of the dTMS H1-coil for the treatment of depressive episodes, the majority of such evidence is based on findings from younger-to-middle aged groups. Thus, the generalizability of dTMS treatment efficacy to older adults remains less understood. Further sham-controlled studies are needed to determine the clinical efficacy of dTMS in older adults and to improve evidence-based care in the field of geriatric psychiatry. Importantly, we aimed to address this underrepresentation of older adults in clinical research by analyzing recruitment strategies and examining facilitators and barriers to recruitment. Future research is warranted to examine facilitators and barriers to recruitment in older adults with depression, particularly the importance of social support, which may offer valuable insights on how to overcome the issue of underrepresentation.

Keywords: Brain stimulation, Clinical trials, Clinical research, Deep transcranial magnetic stimulation, Depression, Elderly, Geriatrics, Geriatric depression, Geriatric psychiatry, Older adults, Recruitment, Seniors, Treatment-resistant depression.

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These two years of research have flown by, but not without substance. I have grown as an individual within this short period of time. I have developed so many meaningful friendships, when I never imagined I would, conducted fascinating research with prestigious members in my field, a position in which I never thought I would be, and developed self-resilience in times of self-doubt.

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List of Abbreviations

ACC: Anterior cingulate cortex

ADHD: Attention-deficit/hyperactivity disorder

ASD: Autism spectrum disorder

AUD: Alcohol use disorder

BD: Bipolar disorder

BHS: Beck Hopelessness Scale

CAARS: Conners' Adult ADHD Rating Scales scores

CAPS: Clinician-Administered *PTSD* Scale

CUD: Cocaine use disorder

DBS: Deep brain stimulation

DLPFC: Dorsolateral prefrontal cortex

dmPFC: dorsomedial prefrontal cortex

DSM-IV/5: Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth edition

dTMS: Deep transcranial magnetic stimulation

FDA: The Food and Drug Administration

fMRI: functional magnetic resonance imaging

FTND: The Fagerström Test for Nicotine Dependence

GI: Gastro-intestinal

H-coil: Hesed-coil

HDRS: Hamilton Depression Rating Scale

HF: High frequency stimulation

ICD-11: International Classification of Diseases, Eleventh edition

ITT: Intention-to-treat

LF: Low frequency stimulation

MCI: Mild cognitive impairment

MDD: Major depressive disorder

mPFC: Medial prefrontal cortex

MT: Motor threshold

NUD: Nicotine use disorder

OCD: Obsessive-compulsive disorder

PANSS: Positive and Negative Syndrome Scale scores

PFC: Prefrontal cortex

PP: Per-protocol

PTSD: Posttraumatic stress disorder

RAADS: Ritvo Autism Asperger Diagnostic Scale

RCT: Randomized controlled trial

rTMS: Repetitive transcranial magnetic stimulation

SNRIs: Serotonin and norepinephrine reuptake inhibitors

SSRIs: Selective serotonin reuptake inhibitors

SUD: Substance use disorder

TCAs: Tricyclic antidepressants

TMS: Transcranial magnetic stimulation

TRD: Treatment-resistant depression

VLPFC: Ventrolateral prefrontal cortex

VNS: Vagus nerve stimulation

TPJ: Tempo parietal junction

ECR: Enrollment-cost ratio

Declaration of Academic Achievement

As the first author of the two studies included in this sandwich thesis, I was responsible for data collection, synthesizing the methodology, and writing the manuscript. My co-authors edited and proofread the final drafts. I conceptualized all figures and tables in each study.

Study 1: Dr. Dante Duarte conceptualized the manuscript and provided constructive feedback to assist with the manuscript's completion. As the first author, I extracted data from the literature, conducted data analyses, and produced the manuscript. The remaining co-authors gave feedback and edited the final draft of the manuscript.

Study 2: Dr. Dante Duarte and I conceptualized the study's objectives. Moreover, I determined the appropriate statistical analyses to be performed. I produced the manuscript in its entirety, including data collection, data analyses, and the final write-up. The remaining co-authors provided guidance and feedback on the final draft of the manuscript.

Chapter 1. Background

1.1. Geriatric Depression

Depression is a leading cause of disability worldwide, contributing to significant global burden (Liu et al., 2020; Proudman et al., 2021) and financial strain on the healthcare system (Greenberg et al., 2023; Tanner et al., 2020). For the affected, it is a dark cloud bearing no relief. Depression can lead to emotional dysregulation (Ebneabbasi et al., 2021), social impairment (Saris et al., 2017), and cognitive disturbances (Perini et al., 2019), collectively impacting an individual's daily functioning and quality of life. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of major depressive disorder (MDD) must constitute a depressed mood and/or a loss of interest or pleasure for a minimum two-week period, as well a minimum of five symptoms related to sleep difficulties, fatigue, feelings of worthlessness, and concentration difficulties, among other symptoms (American Psychiatric Association, 2022). In the elderly, symptom presentation can be difficult to interpret, as depressive symptoms often manifest as physical complaints which may be attributed to dementia or other medical comorbidities (Devita et al., 2022). Considering this difficulty, diagnosing depression in the elderly remains a prevalent challenge in healthcare system, as it often is misdiagnosed or underdiagnosed due to its complicated and atypical presentation (Allan et al., 2014; Devita et al., 2022). Therefore, there is an urgent need for healthcare practitioners to strategically identify and diagnosis depression in older adults.

Older adults face an increased risk of depression due to various factors associated with the progression of age. For example, older adults are more likely to suffer from age-

related conditions and illnesses (i.e., vascular diseases, neurological conditions, cardiovascular complications, diabetes, etc.), elevating their risk for depression (Allan et al., 2014; N. G. Choi et al., 2014; Jellinger, 2021). The "vascular depression" hypothesis suggests that older adults may have an increased risk of depression or experience worsening depressive symptoms due to cerebrovascular conditions (Alexopoulos et al., 1997; Taylor et al., 2013), which are more prevalent with age (J. Y. Choi et al., 1998). Poor social activity may be another significant risk factor for depression. Older adults who report experiencing loneliness and social isolation are more likely to report feeling depressed and have a lower quality of life (Barnes et al., 2022; Czaja et al., 2021).

1.2. Limitations of Conventional Antidepressant Treatments in Geriatric Depression

In the field of psychiatry, antidepressants remain a first line treatment for depressive disorders and are commonly prescribed due to their tolerability and safety (Gautam et al., 2017). While approximately two-thirds of older adults respond to antidepressant therapies, the remaining one third encounter treatment-resistance (Blaszczyk et al., 2023). Though an objective definition of treatment-resistance is lacking consensus within the current literature (McIntyre et al., 2023), individuals with treatment resistance typically do not respond well to one or more antidepressant medications, with the duration of treatment and number of antidepressants changing depending on the given definition of treatment resistance. Older adults who experience treatment-resistant depression (TRD) frequently present with medical comorbidities, reducing the likelihood of adequate treatment response (Wang et al., 2023).

Beyond the challenges of treatment resistance, further complications may arise in older adults who are taking antidepressants. The high rate of medical comorbidities in older adult populations presents a challenge for healthcare providers, who must consider potential negative drug interactions. Though an elderly patient may benefit from improvements in depressive symptoms following a course of antidepressant therapy, other medical risks must be considered. For example, adverse drug-to-drug interactions may occur between antidepressants and other medications, possibly worsening a patient's condition (Mark et al., 2011). Therefore, clinicians must be aware of and well-informed about an elderly patient's medical history, as certain antidepressants may increase the risk of serious medical conditions. For instance, serotonergic antidepressants have been known to increase the risk of upper gastro-intestinal (GI) bleeding in the elderly due to the disruption of proper platelet aggregation (Avasthi & Grover, 2018; van Walraven et al., 2001). In older adults with previous serious GI conditions, such as ulcers, cancers, and gastritis, the risk of upper GI bleeding is elevated. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), also increase the risk of falls in the elderly. These medications can cause sedation, sleep changes (e.g., hypersomnia), and disturbances in postural reflexes, thus increasing the likelihood of falls (Darowski et al., 2009). In the elderly, falls can lead to serious head injuries and bone fractures (Vaishya & Vaish, 2020), demonstrating the necessary precautions for geriatric psychiatrists when choosing the optimal treatment regimen. Hyponatremia – or borderline low sodium levels – is another serious ramification of antidepressant use (Viramontes et al., 2016), occurring in approximately 9% of older adults taking

antidepressants (Mannesse et al., 2013). In a review of antidepressant-induced hyponatremia cases among older adults, serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine (i.e., an atypical antidepressant), and SSRIs were the most commonly cited medications (Viramontes et al., 2016).

Considering the potential adverse drug interactions associated with antidepressant use in the elderly, non-pharmacological treatment options may help expand treatment options for elderly patients who are at an increased risk of adverse drug-to-drug effects. Moreover, individuals with TRD may benefit from non-invasive, non-pharmacological treatment options.

1.3. Deep Transcranial Magnetic Stimulation: Current Applications in Depression

Deep repetitive transcranial magnetic stimulation (dTMS) is a relatively novel, non-pharmacological, and non-invasive brain stimulation technique utilizing magnetic pulses to alter the cortical excitability and neural plasticity within specific regions of the brain. Derived from its predecessor, repetitive transcranial magnetic stimulation (rTMS), the dTMS "H-coil" offers an alternative form of rTMS by targeting deeper and broader regions of the brain (Roth et al., 2007, 2014). Both rTMS and dTMS enhance cortical and subcortical excitability and functioning by delivering repeated magnetic pulses to their target region(s) of interest (Chen, 2000). With the potential to broadly modulate cortical activity across deeper regions of the brain, dTMS shows promise for various psychiatric disorders. Furthermore, while the traditional rTMS "figure-8 coil" can stimulate approximately 1 to 2 cm below the scalp, dTMS H-coils can target 2 to 6 cm in depth

(Roth et al., 2007, 2014). The mechanisms of dTMS, along with rTMS, are discussed in further detail in the Introduction section of Study 1 (Chapter 2).

The effects of dTMS have been explored across numerous psychiatric disorders, including major depressive disorder (MDD; Levkovitz et al., 2007, 2015; Rosenberg et al., 2010) obsessive-compulsive disorder (OCD; Carmi et al., 2018, 2019), posttraumatic stress disorder (Isserles et al., 2013, 2021), and substance use disorders (Addolorato et al., 2017; Ceccanti et al., 2015; Dinur-Klein et al., 2014; Girardi et al., 2015; Harel et al., 2022). Currently, three H-coils that have been approved by Health Canada and the Food and Drug Administration (FDA) for clinical applications. The H1-coil was approved in 2008 for TRD, with its target stimulation site being the left dorsolateral prefrontal cortex (DLPFC; Tendler et al., 2017). The dTMS device by BrainsWay™ is depicted in Figure 1, along with the H1-coil arm attachment. The H7-coil, targeting the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC), was approved in 2018 for the treatment of OCD, and in 2020, for the treatment of anxious depression (Harmelech et al., 2021). Lastly, the H4-coil was approved for short-term smoking cessation in 2020 (Zangen et al., 2005). This coil strategically targets the bilateral insula, ventrolateral prefrontal cortex (VLPFC), and the DLPFC.

Figure 1. The deep transcranial magnetic stimulation (dTMS) device produced by BrainsWay.™

1.4. Target Brain Areas of dTMS H4 and H7 coils and Depression Pathophysiology

While the H1-coil role has been clinically approved for TRD and is supported by the considerable literature on the DLPFC's role in depression, the primary target regions of the H4 and H7 coils have also been implicated in the pathophysiology of depression.

For instance, the insula — a target region of the H4-coil — has a distinguished role in socio-emotional processing and pain perception (Uddin et al., 2017) and has garnered attention for its potential contribution in the pathophysiology of depression. Disturbed functional connectivity has been observed in patients with MDD (Avery et al., 2014; Hamilton et al., 2011; Veer et al., 2010). Reduced functional connectivity between

the insula and DLPFC/midcingulate cortex has been reported as a neural marker of poorer treatment response (Oberlin et al., 2022). Interestingly, fMRI study by Avery et al., (2014) found abnormal insula activity in unmedicated MDD patients during an interoceptive attention task. Specifically, insular activity was negatively associated with both the severity of somatic complaints and depression severity. Regarding structural abnormalities, asymmetrical thickness of the bilateral insula has been shown to increase one's risk of MDD (Jones et al., 2019). Moreover, cortical thickness of the insula has been positively correlated with depression symptom severity in patients with depression (Schnellbächer et al., 2022).

Furthermore, the anterior cingulate cortex (ACC) — a primary target region of the H7-coil — is known for its role in emotion and high-order cognitive processes (Stevens et al., 2011). Functional abnormalities of the ACC have frequently been observed in individuals with depression (Connolly et al., 2013; Peng et al., 2021; Rolls et al., 2019). For example, older adults with MDD who experience apathy have been characterized by reduced functional connectivity between the dorsal ACC, DLFPC, and VLPFC (Alexopoulos et al., 2013). Other research has demonstrated how the severity of apathy is correlated with decreased grey matter volumes in the right ACC among older adults with MDD (Lavretsky et al., 2007). Notably, ACC volume has been found to be an important marker of antidepressant response. In a clinical trial exploring ACC volumes and treatment response to escitalopram, non-remitters were found to have smaller ACC volumes compared to remitters (Gunning et al., 2009). Considering the substantial evidence supporting the insula and ACC as a potential neural markers of depression

symptomatology, pathophysiology, and treatment response, these brain regions warrant further attention as target sites for dTMS interventions.

While the H1-coil is well-examined in depression (Kaster et al., 2018; Levkovitz et al., 2015; Rosenberg et al., 2011; Tendler et al., 2023), there is limited research examining the potential therapeutic benefits of stimulating other brain regions using different H-coils. In addition to broadly targeting the prefrontal cortices, the H4 and H7 coils target important regions implicated in depression pathophysiology: the insula and ACC, respectively. It is possible that stimulating different areas may provide differential effects on subsets of depressive symptoms, thereby expanding treatment options for clinicians and their patients. To date, only one study (Zangen et al., 2023) has examined the effects of the H7-coil for MDD, in comparison to the well-established H1-coil. Interestingly, both H-coils had clinically comparable response rates. Therefore, future clinical research should examine the differential effects of diverse H-coils in MDD.

1.5. Challenges of Recruiting Older Adults with Depression for Clinical Research on Deep Transcranial Magnetic Stimulation

Recruitment challenges are a leading cause of early trial termination, posing a major barrier to clinical research (Bernardez-Pereira et al., 2014; Williams et al., 2015). Additional barriers to recruitment must be considered in older populations. For example, older adults with psychiatric conditions are less inclined to consult with healthcare professionals compared to their younger counterparts (Elshaikh et al., 2023; Lavingia et al., 2020). Deterrents to seeking professional help may include the fear of worsening

one's health, underlying medical comorbidities, and a negative view towards mental health care (Bloch & Charasz, 2014; Lavingia et al., 2020). More importantly, given the relative novelty, and therefore unfamiliarity, of neurostimulation interventions, like dTMS, researchers may face added challenges recruiting older adults. The current literature lacks insights on how to address such challenges and enhance dTMS research in older adults with depression. Additional information on recruitment challenges in older adults with respect to dTMS interventions are discussed in greater depth in the Introduction section of Chapter 3.

1.6. Objectives of the Current Thesis

With the substantial rise of dTMS research within the past two decades, a comprehensive analysis of controlled dTMS studies is needed to appraise the clinical efficacy of dTMS across psychiatric and cognitive disorders. An analysis of controlled dTMS studies (i.e., studies with an active dTMS condition vs. a sham/control condition) is lacking within the current literature. A detailed summary of controlled clinical trials is necessary to provide clinicians with data regarding the strength of evidence supporting dTMS as an efficacious treatment for the given disorder of interest. Importantly, this knowledge is crucial for clinical decision-making and promoting patient autonomy regarding available treatment options (Gold et al., 2017). Study 1 addresses this notable gap in the literature. Though study 1 provides an overview of dTMS clinical efficacy across all psychiatric and cognitive disorders, the current thesis aims to discuss the findings of Study 1 in the context of depression and older adults. Provided that dTMS shows promise in the

treatment of depression, this dissertation aims to address the following questions: (1) What evidence is there supporting the clinical efficacy of dTMS for the treatment of depression? and (2) Is such evidence applicable to older adults with depression?

Another considerable limitation of the current literature is the paucity of dTMS research in older adults with depression. To date, a limited number of trials (Kaster et al., 2018; Roth et al., 2024) have investigated the effects of dTMS interventions specifically in older adults with depression. Due to the complicated clinical presentation of depression in senior populations, dTMS research in older adults is highly warranted. By tailoring dTMS interventions to accommodate the needs of older populations, clinicians will be able to offer empirically supported and customized dTMS interventions for their older patients. Thus, the next logical step is to recruit older adults with depression for a clinical trial on dTMS, which presents a challenge in and of itself.

The current literature lacks insights into recruitment strategies used in clinical trials for older adults. Existing research exploring recruitment methods for older adults with depression is limited to psychotherapy interventions (Tegeler et al., 2022) and wellness interventions (Albert et al., 2016). Considering the relative novelty of neurostimulation interventions, like dTMS, further research is needed to understand the possible impact of this novel treatment on clinical trial recruitment in older adults. Examining the effectiveness of different recruitment strategies is an essential step to conducting dTMS research in older adults, with the final goal of improving psychiatric care. Therefore, an additional objective of the present dissertation is to examine recruitment data in older adults with depression — as part of the DIVINE study

(ClinicalTrials.gov identifier: NCT05855850**)**. This is a feasibility study examining dTMS (i.e., the H4 and H7 coils) in older adults with depression. In study 2, we aimed to address the literature's shortcomings by analyzing the effectiveness of various recruitment strategies, as well as identifying potential facilitators and barriers to recruitment for dTMS trials, from the DIVINE study.

Chapter 2. Clinical efficacy of deep transcranial magnetic stimulation (dTMS) in psychiatric and cognitive disorders: A systematic review (Study 1)

In the present systematic review, we examined evidence supporting the clinical efficacy of dTMS across psychiatric and cognitive disorders. Notably, only studies containing a sham (or another control) condition against an active dTMS condition were included to minimize potential confounding variables and strengthen our assessment of efficacy under controlled conditions. Following a systematic search of the APA PsycINFO, Cochrane, Embase, Medline, and PubMed databases, 28 eligible articles were identified. The findings of this review point to the large body of evidence supporting the clinical efficacy of dTMS in patients with obsessive-compulsive disorder (OCD; $n = 2$), substance use disorders (SUDs; $n = 8$), and in those experiencing depressive episodes with major depressive disorder (MDD) or bipolar disorder (BD; $n = 6$). However, the efficacy of dTMS in attention-deficit/hyperactivity disorder, posttraumatic stress disorder, and schizophrenia, consisted of mixed findings. A single study explored the effects of dTMS in older adults with depression, which revealed positive findings. This systematic review highlights dTMS as a valuable addition to psychiatric care. However, future

research should determine the durability of treatment effects and moderators of dTMS efficacy. Of importance, this dissertation discusses the implications from Study 1's findings in the context of older adults with depression in Chapter 4.

Chapter 3. Recruitment for Clinical Research in Older Populations with Depression: A Retrospective Longitudinal Study (Study 2)

In this study, we explored the effectiveness of diverse recruitment methods utilized in our pilot study investigating the effects of dTMS in older adults with depression. To examine effectiveness, we conducted an enrollment-cost analysis to provide insights into recruitment-associated costs. Moreover, we explored potential facilitators and barriers to recruitment, as addressing this knowledge gap may help expand clinical research in older adults with depression. The study results highlighted the effectiveness of healthcare provider outreach within affiliated inpatient and outpatient mental health clinics ($537.63 CAD/person enrolled). The second most effective recruitment method was Facebook advertising ($925.93 CAD/person enrolled). Social support from research personnel was noted as a potential facilitator of recruitment, while time-intensiveness and accessibility challenges were noted as potential barriers.

In summary, the most robust evidence supports the clinical efficacy of dTMS for depressive episodes, showing promise for the treatment of MDD and TRD. Despite the lack of dTMS research in older adults with depression, we found evidence supporting the effectiveness of diverse recruitment efforts to target this special population. Furthermore, the identification of facilitators and barriers to recruitment aims to enhance dTMS clinical research in older adults with depression.

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Chapter 2

Study 1: Clinical efficacy of deep transcranial magnetic stimulation (dTMS) in psychiatric and cognitive disorders: A systematic review

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Context and implications: This systematic review provides a comprehensive overview of research examining the clinical efficacy of deep transcranial magnetic stimulation (dTMS) for psychiatric and cognitive disorders. We found significant evidence supporting the clinical efficacy of dTMS for the treatment of depressive episodes, obsessive-compulsive disorder, and substance use disorders. While dTMS appears to be a promising asset to psychiatry, further investigation is required to determine the durability of dTMS efficacy as well as moderators of treatment outcomes.

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Abstract

Deep transcranial magnetic stimulation (dTMS) has gained attention as an enhanced form of traditional TMS, targeting broader and deeper regions of the brain. However, a fulsome synthesis of dTMS efficacy across psychiatric and cognitive disorders using sham-controlled trials is lacking. We systematically reviewed 28 clinical trials comparing active dTMS to a sham/controlled condition to characterize dTMS efficacy across diverse psychiatric and cognitive disorders. A comprehensive search of APA PsycINFO, Cochrane, Embase, Medline, and PubMed databases was conducted. Predominant evidence supports dTMS efficacy in patients with obsessive-compulsive disorder (OCD; $n = 2$), substance use disorders (SUDs; $n = 8$), and in those experiencing depressive episodes with major depressive disorder (MDD) or bipolar disorder (BD; $n = 6$). However, the clinical efficacy of dTMS in psychiatric disorders characterized by hyperactivity or hyperarousal (i.e., attention-deficit/hyperactivity disorder, posttraumatic stress disorder, and schizophrenia) was heterogeneous. Common side effects included headaches and pain/discomfort, with rare but serious adverse events such as seizures and suicidal ideation/attempts. Risk of bias ratings indicated a collectively low risk according to the Grading of Recommendations, Assessment, Development, and Evaluations checklist (Meader et al., 2014). Literature suggests promise for dTMS as a beneficial alternative or add-on treatment for patients who do not respond well to traditional treatment, particularly for depressive episodes, OCD, and SUDs. Mixed evidence and limited clinical trials for other psychiatric and cognitive disorders suggest more extensive

research is warranted. Future research should examine the durability of dTMS interventions and identify moderators of clinical efficacy.

Keywords: Brain stimulation; deep rTMS; deep TMS; deep transcranial magnetic stimulation; dTMS; H-coil.

Introduction

Psychiatric and cognitive disorders are leading causes of disability and burden worldwide (Antunes et al., 2018; GBD 2019 Mental Disorders Collaborators, 2022; Moon et al., 2021) and are associated with poorer quality of life (Bárrios et al., 2013; Berghöfer et al., 2020; Saarni et al., 2010; Sagayadevan et al., 2018). From 1990 to 2019, the number of disability-adjusted life-years due to psychiatric disorders has increased globally from 80.8 million to 125.3 million (GBD 2019 Mental Disorders Collaborators, 2022). Currently, an estimated 20-60% of patients with psychiatric disorders are treatment-resistant to first-line medications (Howes et al., 2022). In particular, treatment-resistance occurs in approximately one-third of patients with major depressive disorder (MDD; Gaynes et al., 2018; Zhdanava et al., 2021), 30 -60% of patients with schizophrenia (Beck et al., 2019; Lally et al., 2016; Samara et al., 2019), and 40-60% of patients with obsessive-compulsive disorder (OCD; Bloch et al., 2013; Pallanti and Quercioli, 2006). As for cognitive disorders, dementia is on the rise as a leading cause of global mortality (GBD 2019 Collaborators, 2021). Further, older adults with mild cognitive impairment (MCI) show an increased risk of mortality (Bae et al., 2018; Sachs et al., 2011). Currently, while there are interventions to manage the symptoms, there are no effective treatment options to delay the progression of mild cognitive impairment and dementia (Sanford, 2017), nor are there effective interventions to manage the behavioural and psychological burdens of such conditions at the advanced stages (Blair et al., 2020; Chen et al., 2021; Madhusoodanan and Ting, 2014; Magierski et al., 2020). Given the prevalence of treatment-resistance in response to first-line pharmacological interventions

in psychiatric disorders, as well as the limited treatment options to effectively treat and manage cognitive disorders, new effective treatments are urgently needed. One technique is brain stimulation.

Brain stimulation methods have shown increasing promise and widespread acceptance as non-pharmacological interventions to treat various psychiatric (Cimpianu et al., 2017; Mishra et al., 2011) and cognitive disorders (Teselink et al., 2021; Zhang et al., 2021). Electroconvulsive therapy (ECT; Deng et al., 2022) and transcranial magnetic stimulation (TMS; Lorentzen et al., 2022; Sigrist et al., 2022) are the most commonly used treatments, involving the stimulation of the brain through electrical currents and magnetic pulses, respectively. Traditional single-pulse TMS is used to explore brain functioning, whereas repetitive TMS (rTMS) is administered to induce changes in brain activity lasting beyond the stimulation period (Chail et al., 2018). These non-invasive stimulation techniques offer potentially efficacious therapies for neurological and psychiatric disorders (Janicak and Dokucu, 2015). Research on other therapy options, such as vagus nerve stimulation (VNS; George et al., 2008; Rush et al., 2000) and deep brain stimulation (DBS; Dandekar et al., 2018; Mar-Barrutia et al., 2021; Sheth et al., 2022) have continued to accumulate, offering further insight into these treatment options for psychiatric disorders.

Another promising method is deep transcranial magnetic stimulation (dTMS) — a non-invasive technique allowing for stimulation of deeper cortical areas and neural networks (Lu and Ueno, 2017; Roth et al., 2002). Since the approval of dTMS in 2013 by the US Food and Drug Administration (FDA) for MDD (Gellersen and Kedzior, 2018),

this method of intervention has gained popularity for the treatment of diverse psychiatric disorders. The aim of dTMS is to modulate brain activity by applying an electrical current over the scalp using magnetic fields. Brief magnetic pulses are used to induce targeted neuronal depolarization in deeper regions of the brain with less focal distribution of the electric field (Fadini et al., 2009). Trains of pulses can be delivered with high frequency (HF) stimulation (>5 Hz) to increase neuronal excitability, or at low frequency (LF) stimulation (~1 Hz) to reduce neural excitability (Pell et al., 2011). The use of a Hesed-coil (H-coil) dTMS system is a relatively novel, non-invasive method that stimulates deeper regions of the brain in comparison to traditional rTMS (Roth et al., 2014, 2007). While traditional TMS figure-8 coils generally stimulate subdural cortical targets up to 0.7 cm (Roth et al., 2007), dTMS target areas are up to ~4 cm beneath the surface depending on the chosen H-coil (Zangen et al., 2005). More than twenty different types of H-coils have been developed with the goal of effectively stimulating various brain structures (Deng et al., 2014). The H-coil configuration received clearance from FDA for the treatment of major depression (H1-coil), obsessive-compulsive disorder (H7-coil), smoking cessation (H4-coil), and anxious-depression, in 2013, 2018, 2020, and 2021, respectively. Various H-coil designs have been shown to be safe and efficacious in the treatment of various neuropsychiatric conditions (Isserles et al., 2013; Levkovitz et al., 2011; Rosenberg et al., 2010).

H-coils have complex winding designs and broad dimensions to encompass a larger surface area for stimulation of the electric field (Deng et al., 2014). The different types of H-coil designs reflect the subdural depth and volume of stimulation, as well as

the region of stimulation. The H1-coil was designed to stimulate the bilateral prefrontal cortex (PFC) with preference to the left dorsolateral prefrontal cortex (DLPFC) of approximately 1.8 cm subdurally (Tendler et al., 2017). The volume of stimulation for the H1-coil configuration typically encompasses 18 cm^3 (Harmelech et al., 2021). Contrarily, the H7-coil design primarily stimulates 3 cm of subdural depth and a volume of 40.3 cm^3 in the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC; Harmelech et al., 2021). The H4-coil targets the bilateral insula and ventrolateral and dorsolateral PFC with a depth of 1.5 cm and a volume of 15.2 cm^3 (Harmelech et al., 2021). In comparison, the traditional figure-8 coil used in rTMS stimulates 0.7 cm below the scalp with a volume of 3 cm^3 (Harmelech et al., 2021). The most utilized dTMS protocol involves high-frequency (18- 20 Hz) and high intensity (120% of the resting motor threshold [MT]) stimulation delivered for 20 days (Tendler et al., 2016).

Given the increasing interest in the application of dTMS in psychiatry (Tendler et al., 2016), it is critical that its clinical effects be systematically appraised. As dTMS is a relatively novel form of therapy for psychiatric disorders, assessments of its clinical efficacy are largely limited to individual trials within the current body of literature. One previous systematic review (Hung et al., 2020) examined the clinical efficacy of dTMS for treatment-resistant depression but was restricted to that condition. Another previous systematic review (McGirr et al., 2021) explored the effects of rTMS in patients with posttraumatic stress disorder (PTSD), but only one sham-controlled dTMS study (Isserles et al., 2013) was included. A third systematic review by Kedzior et al. (2018) examined the effects of dTMS for substance use disorders (SUDs). However, clinical efficacy was

not appraised due to the limited number of sham-controlled trials. Most recently, a fourth systematic review by Cheng et al. (2023) summarized the effects of dTMS for psychiatric and neurological conditions but did not incorporate several important RCTs included in the current review. Notably, the latter review (Cheng et al., 2023) did not investigate the clinical efficacy of dTMS as it contained studies lacking a control/sham condition.

A review exclusive to sham/controlled conditions is warranted to inform future researchers and clinicians of available evidence supporting dTMS clinical efficacy. The presence of a sham or controlled arm carries several advantages when evaluating the clinical efficacy of a treatment. The clinical efficacy of a novel treatment is analyzed most effectively under controlled conditions— that is, the potential benefits or disadvantages of a particular intervention can be evaluated while controlling for other potential confounding variables. Selecting dTMS trials with a sham/control condition enhances the internal validity of their findings by controlling for confounding effects (Gold et al., 2017). Moreover, comprehensive analyses of controlled clinical trials are integral to clinician decision-making and informed treatment options (Gold et al., 2017). Thus, the current systematic review aims to examine dTMS clinical trials with a sham/control condition to determine the clinical efficacy of dTMS for psychiatric and cognitive disorders.

Methods

Literature Search

A systematic search of the APA PsycINFO, Embase, and MEDLINE databases was completed via OVID on October 10, 2023. An additional search of the Cochrane and PubMed databases was conducted for active dTMS vs. sham/controlled trials on October 15, 2023. The complete search strategy can be found in Supplementary material. Two authors (A.D and M.D) independently conducted the searches and primary screening of articles. The keywords used in the searches included "dTMS," "deep rTMS," "deep TMS," "deep transcranial magnetic stimulation," and "H-coil." Automatic filters were applied to limit search results to clinical trials and RCTs. No date limits were applied. A manual search of existing literature on dTMS for psychiatric disorders and cognitive disorders was conducted to identify other potential articles from the reference sections of relevant reviews and articles.

Study Selection: Inclusion and Exclusion Criteria

Articles were independently screened and assessed for eligibility by two authors (A.D and M.D) according to the inclusion criteria. We included clinical trials (both open-label and randomized controlled trials) reporting the clinical effects of dTMS interventions for psychiatric or cognitive disorders compared to a sham/control arm (i.e., active vs. sham/control dTMS interventions). Non-inferiority trials comparing two or more active treatments without a control or sham arm were not included due to their inability to mitigate the placebo effect and confounding variables. Non-inferiority trials are typically conducted in situations where using a placebo arm is not feasible or ethical (Stefanos et al., 2020). Due to the complexity, interpretational challenges, and distinct methodological hypothesis testing of non-inferiority trials compared to superiority trials (Kishore and Mahajan, 2020),

we prioritized clinical trials examining treatment superiority. Therefore, the current review only incorporated studies with a sham/control arm to assess clinical efficacy and enhance the results' internal validity by mitigating confounding factors.

Articles written in English were eligible for inclusion. Participants were required to have a valid diagnosis of a recognized psychiatric or cognitive disorder according to a recognized diagnostic manual (i.e., the Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth edition [DSM-IV, DSM-5], or the International Classification of Diseases, Eleventh edition [ICD-11]). Articles of any publication year were accepted. Articles comparing active dTMS to a sham/control arm had to include patients with a psychiatric or cognitive disorder. Therefore, we excluded articles in which healthy participants were assigned to either of these conditions. Exclusion criteria also included conference abstracts, letters to the editor, books, reviews, and case reports.

Data extraction

We extracted data from articles pertaining to the country of publication, study type, comparison type (i.e., active dTMS vs. sham, or standard pharmacotherapy, or another control type), participant sample size (i.e., intention-to-treat [ITT] and per-protocol [PP] analyses), participant sex, and mean age. The psychiatric or cognitive disorder diagnosis was recorded. Regarding treatment procedures, we reported the treatment duration, number of treatment sessions, H-coil type, and the brain region of interest (i.e., target regions of stimulation). Additionally, we reported dTMS parameters, including frequency (Hz) and intensity (% of the MT) of stimulation, pulses per session,

time per session, trains per session, and inter-train interval duration. Post-treatment comparisons between active vs. sham groups were extracted, including data on remission and response rates following treatment. Remission and response criteria were reported. Lastly, we collected data on adverse events following treatment and dropout rates.

Quality of Assessment

All articles were assessed according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) checklist (Meader et al., 2014) to evaluate the quality of data and determine risk of bias. Eligible studies were assessed for risk of bias using the following six domains: (1) selection bias, (2) performance bias, (3) detection bias (4) attrition bias (5) and reporting bias. We classified studies as having a low, low-to-moderate, moderate, moderate-to-high, or a high risk of bias based on meeting or failing to meet a select number of items on the GRADE checklist. Please refer to the Supplementary material (Table S1 and Table S2) for more details on how we conducted evaluations for risk of bias.

Results

Studies Retrieved

The search rendered a total of 28 eligible articles following the article screening and full-text assessment of eligibility as depicted in the PRISMA Flow Chart (Figure 1). A search of the APA PsycINFO, Embase, and MEDLINE databases yielded 7717 articles. A total of 7095 articles were removed by OVID automation tools, which limited articles to English, human participants, clinical trials, and RCTs. Additionally, 59 duplicate

records were removed by automation tools. After screening the abstracts of the remaining 563 articles, 499 were excluded. The full texts of the remaining 64 articles were then screened for eligibility. Following the full-text screening, 40 articles were excluded for the following reasons: not having a sham or control condition (n = 17); the control group was not a psychiatric population (n = 2); no new data were reported (n = 8); intervention was with TMS, not dTMS (n = 1); participants were healthy volunteers (n = 1); did not assess psychiatric or cognitive outcomes in a population with a neurological disorder (n = 3); and were not clinical trials (n = 8). In total, 24 articles were deemed eligible for inclusion. Following a manual search, an additional four clinical trials (Alyagon et al., 2020; Bolloni et al., 2016; Ibrahim et al., 2023; Zangen et al., 2021) were identified. For additional information regarding how these articles were retrieved, please refer to the Supplementary materials. No additional articles were retrieved from PubMed or the Cochrane database. In total, 28 clinical trials were included in our review, which are summarized in Tables 1-5.

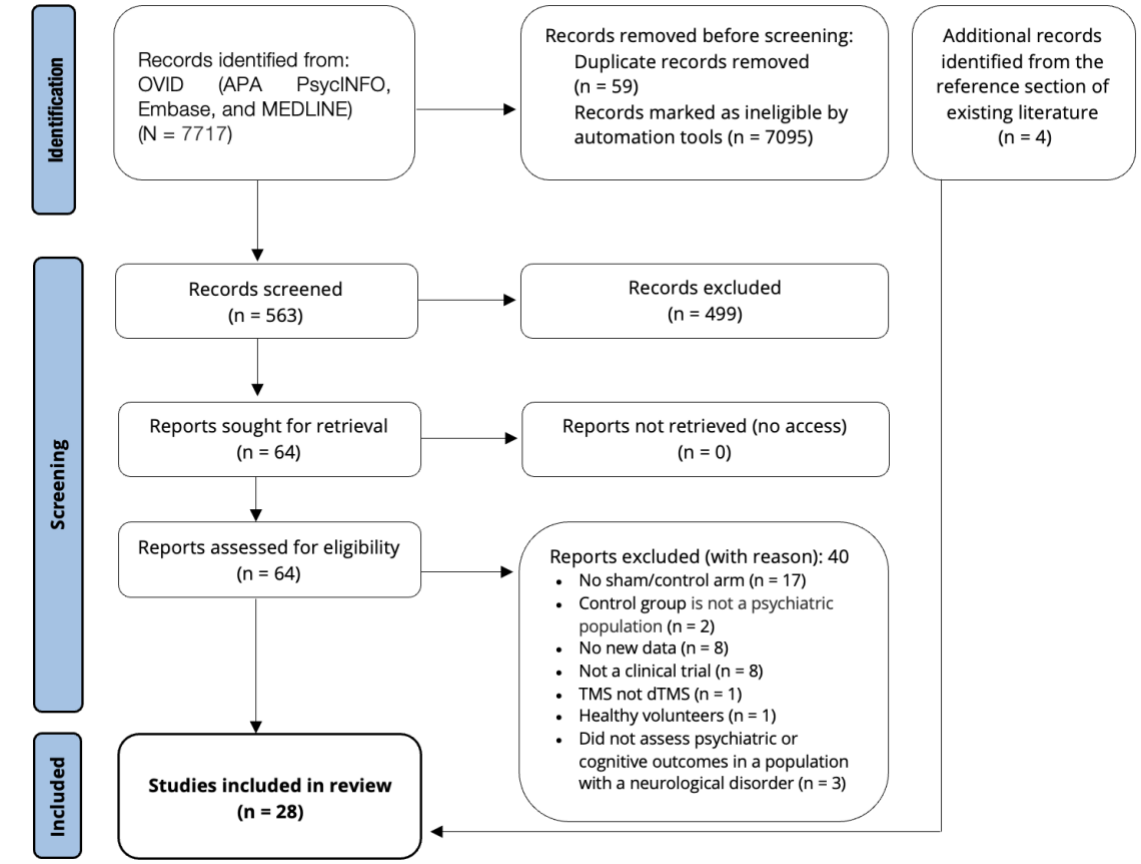


Figure 1. PRISMA flowchart. The title-abstract and full-text screenings of potentially eligible reports were performed. Articles were excluded at each stage of the screening process according to the inclusion and exclusion criteria.

Quality Assessment Results

After examining the quality of the evidence, most studies were appraised as having a low risk of bias. All studies were assessed as having a low risk of reporting bias, inferring that data outcomes were reported consistently. Most studies implemented random sequence generation allocation concealment, which may lower the risk of selection bias. Six out of 28 (21.43%) clinical trials (Alyagon et al., 2020; Enticott et al.,

2014; Filipčić et al., 2019; Gajšak et al., 2023; Girardi et al., 2015; Martinez et al., 2018) did not blind participants and research personnel, resulting in an increased risk of bias. Moreover, 15 (53.57%) trials (Addolorato et al., 2017; Alyagon et al., 2020; Bolloni et al., 2016; Ceccanti et al., 2015; Dinur-Klein et al., 2014; Gajšak et al., 2023; Girardi et al., 2015; Ibrahim et al., 2023; Leocani et al., 2021; Martinez et al., 2018; Matsuda et al., 2020; Moeller et al., 2022; Paz et al., 2018; Perini et al., 2020; Rabany et al., 2014) did not report any blinding of outcome assessors, leading to a higher risk of detection bias. Most trials were appraised as having a low risk of attrition bias, with only six (21.43%) trials (Addolorato et al., 2017; Bolloni et al., 2016; Dinur-Klein et al., 2014; Moeller et al., 2022; Rosenberg et al., 2012; Zangen et al., 2021) failing to include at least 80% of enrolled participants in the final analyses. Altogether, most studies were evaluated as having an overall very low (n = 9; Bleich-Cohen et al., 2021; Carmi et al., 2019, 2018; Harel et al., 2022; Isserles et al., 2021, 2013; Kaster et al., 2018; Levkovitz et al., 2015; Tavares et al., 2017) low (n = 10; Ceccanti et al., 2015; Enticott et al., 2014; Ibrahim et al., 2023; Leocani et al., 2021; Matsuda et al., 2020; Paz et al., 2018; Perini et al., 2020; Rabany et al., 2014; Rosenberg et al., 2012; Zangen et al., 2021) or low-to-moderate (n = 6) risk of bias (Addolorato et al., 2017; Alyagon et al., 2020; Bolloni et al., 2016; Dinur-Klein et al., 2014; Filipčić et al., 2019; Gajšak et al., 2023). Fewer studies had a moderate (n = 2; Martinez et al., 2018; Moeller et al., 2022) or moderate-to-high (n = 1; Girardi et al., 2015) risk of bias.

Country of Origin, Year of Publication, and Study Design

The majority of studies were conducted in Israel (*n* = 13; Alyagon et al., 2020; Bleich-Cohen et al., 2021; Carmi et al., 2018, 2019; Dinur-Klein et al., 2014; Harel et al., 2022; Isserles et al., 2013, 2021; Levkovitz et al., 2015; Paz et al., 2018; Rabany et al., 2014; Rosenberg et al., 2012; Zangen et al., 2021), followed by Canada (*n* = 6; Carmi et al., 2019; Ibrahim et al., 2023; Isserles et al., 2021; Kaster et al., 2018; Levkovitz et al., 2015; Zangen et al., 2021), the United States (*n* = 5; Isserles et al., 2021; Levkovitz et al., 2015; Martinez et al., 2018; Moeller et al., 2022; Zangen et al., 2021), Italy (*n* = 5; Addolorato et al., 2017; Bolloni et al., 2016; Ceccanti et al., 2015; Girardi et al., 2015; Leocani et al., 2021), and Croatia (*n* = 3; Filipčić et al., 2019; Gajšak et al., 2023; Isserles et al., 2021). Other study sites included Australia (Enticott et al., 2014), Brazil (Tavares et al., 2017), Germany (Levkovitz et al., 2015), Japan (Matsuda et al., 2020) and Sweden (Perini et al., 2020). Four identified as multicenter studies (Carmi et al., 2019; Isserles et al., 2021; Levkovitz et al., 2015; Zangen et al., 2021). Studies ranged in publication from 2012 to 2023 (Figure 2).

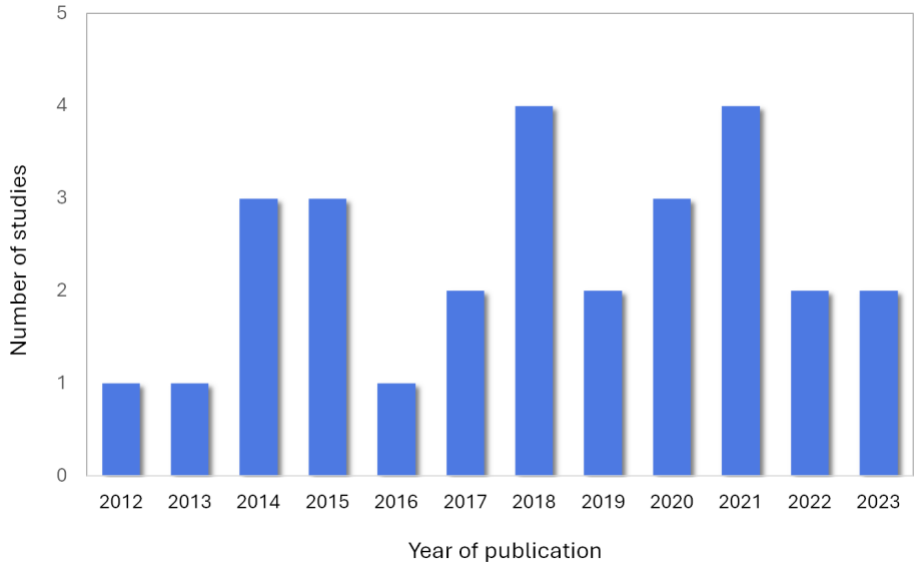


Figure 2. Number of studies by year of publication.

Figure 3 provides a visual representation of comparison type (e.g., LF vs. HF stimulation, and active dTMS vs. sham, etc.) across studies. Studies varied in stimulation frequency, number of treatment arms, and treatment arm procedures. A detailed outline of such variations is described in Figure 3. The most common treatment comparison type used among studies was HF (10 - 20 Hz) active dTMS vs. sham dTMS paradigm, whereby participants were randomized to either of these conditions.

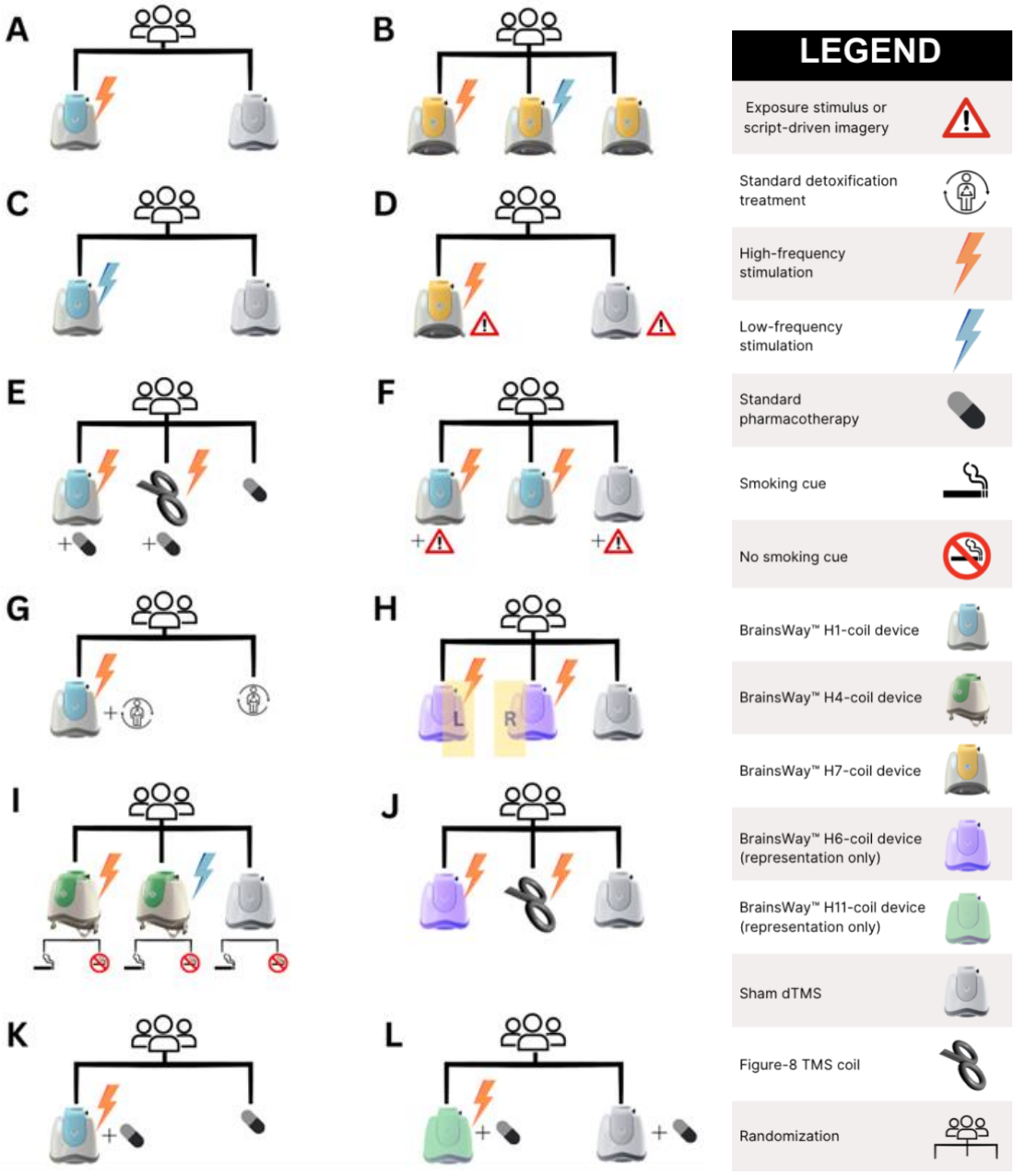


Figure 3. **Study design by comparison type**. **(A)** 15 studies (Addolorato et al., 2017; Bolloni et al., 2016; Carmi et al., 2019; Ceccanti et al., 2015; Harel et al., 2022; Kaster et al., 2018; Leocani et al., 2020; Levkovitz et al., 2015; Matsuda et al., 2020; Moeller et al., 2022; Paz et al., 2018; Perini et al., 2020; Rabany et al., 2014; Tavares et al., 2017; Zangen et al., 2021) compared high-frequency (HF; 10-20 Hz) active dTMS (i.e., H1, H2, H4, H5, H7, and H8 coils) to sham dTMS. Two studies (Addolorato et al., 2017; Ceccanti et al., 2015) did not specify the H-coil design. Figure 3A shows the BrainsWay™ H1-coil device. The other H-coils used in each clinical trial

are not depicted. **(B)** Two trials (Carmi et al., 2018; Martinez et al., 2018) randomized participants to receive HF (10-20 Hz), low-frequency (LF; 1 Hz), or sham dTMS using the H7-coil. **(C)** Two studies compared LF vs. sham dTMS using the H1-coil (Rosenberg et al., 2012) and the HAUT-coil (Enticott et al., 2014) using 1 Hz and 5 Hz, respectively. Figure 3C shows the BrainsWay™ H1-coil device. The HAUT-coil is not shown. **(D)** One trial (Isserles et al., 2021) randomized participants to undergo HF (18-20 Hz) or sham dTMS with the H7-coil and added script-driven imagery exposures to both conditions. **(E)** One study (Filipčić et al., 2019) randomly allocated participants to receive either HF dTMS (18 Hz) with the H1-coil, HF TMS (10 Hz) with the Figure-8 coil, or standard of care pharmacotherapy (all three conditions had pharmacotherapy). **(F)** One clinical trial (Isserles et al., 2013) compared HF dTMS (20 Hz) + stimulus exposure vs. HF dTMS (20 Hz) + non-exposure vs. sham dTMS + stimulus exposure. The H1-coil was used. **(G)** One trial (Girardi et al., 2015) randomized participants to receive HF dTMS (20 Hz) with the H1-coil as an add-on to standard detoxification treatment (SDT) vs. SDT alone. **(H)** One trial (Bleich-Cohen et al., 2021) compared HF dTMS (18 Hz) to the left prefrontal cortex (PFC) vs. HF dTMS to the right PFC vs. sham dTMS using the H6-coil. **(I)** One trial (Dinur-Klein et al., 2014) had participants randomized to six experimental arms, consisting of three dTMS conditions (i.e., HF [10 Hz], LF [1 Hz], vs. sham with H4-coil) and two smoking cue conditions (i.e., cue vs. no cue). **(J)** One trial (Alyagon et al., 2020) compared HF dTMS (18 Hz) with the H6-coil, HF TMS (18 Hz) using the F8-coil, and sham dTMS. **K)** One trial (Gajšak et al., 2023) compared HF dTMS (18 Hz) with the H1-coil vs. standard pharmacotherapy alone (both conditions had pharmacotherapy). **L)** One trial (Ibrahim et al., 2023) compared active HF dTMS (10 Hz) vs. sham dTMS with the H11-coil. Both conditions were given adjunctive pharmacotherapy (i.e., varenicline).

NOTE*:* The H1, H4, and H7 coils presented in Figure 3 are accurate depictions of the colour design manufactured by BrainsWay.™ Given that images of the other H-coils have not been made available by BrainsWay™, a random colour scheme was used to represent the H6 and H11 coils. It should also be noted that the colour of the "Sham dTMS" coil is only representative.

Demographics

Table 1 displays the demographic and clinical information of patients across included studies. The following data was extracted from each study: psychiatric/cognitive diagnosis, sample size, percentage of females, and mean age at baseline. The percentage of female participants varied across studies, ranging from 0% (Ceccanti et al., 2015) to 79% (Alyagon et al., 2020) within treatment arms. ITT analysis sample sizes ranged from

14 (Addolorato et al., 2017) to 228 participants (Filipčić et al., 2019). Most studies (26; 92.86%) had younger adult or middle-aged subjects, with a mean age range of approximately 26 to 53 years. Two studies (Kaster et al., 2018; Leocani et al., 2021) investigated the effect of dTMS in older adults (i.e., 65 years old or greater).

Table 1. **Study Demographics and Clinical information by Disorder**

Author; Origin	Sample size (ITT analysis)	Sample size (PP analysis)	Female (%)	Mean age at baseline
Alzheimer's disease				
(Leocani et al., 2021) Italy	N = 30*	N = 28 Active dTMS (n = 16) Sham dTMS (n = 12)	Active dTMS: 7 (43.8) Sham dTMS: 6 (50) **PP analysis*	Active dTMS: 69.6 ± 7.9 Sham dTMS: 72.6 ± 8.3 **PP analysis*
Attention deficit/ hyperactivity disorder				
(Bleich-Cohen et al., 2021) Israel	N = 73 lPFC active dTMS (n = 28) rPFC active dTMS (n = 26) Sham dTMS (n = 19)	N = 62 lPFC active dTMS (n = 22) rPFC active dTMS (n = 24) Sham dTMS (n = 16)	lPFC: 7 (31.82) rPFC: 7 (29.17) Sham dTMS: 8 (50) **PP analysis*	lPFC dTMS: 35.1± 10 rPFC dTMS: 35.6 ± 8.7 Sham dTMS: 34.7 ± 9.2 **PP analysis*
(Alyagon et al., 2020) Israel	N = 52 H6-coil (n = 20) F8-coil (n = 16) Sham dTMS (n = 16)	N = 43 H6-coil (n = 15) F8-coil (n = 14) Sham dTMS (n = 14)	H6-coil: 13 (86.67) F8-coil: 10 (71.43) Sham dTMS: 11 (78.57) **PP analysis*	H6-coil: 26.62 ± 0.66 F8-coil: 26.13 ± 0.59 Sham dTMS: 27.64 ±1.58 **PP analysis*
(Paz et al., 2018) Israel	N = 26 Active dTMS (n = 12) Sham dTMS (n = 14)	N = 22 Active dTMS (n = 9) Sham dTMS (n = 13)	Active dTMS: 3 (33.33) Sham dTMS: 5 (38.46) **PP analysis*	Active dTMS: 32.11 ± 6.47 Sham dTMS: 30.85 ± 6.82 **PP analysis*
Autism spectrum disorder				
(Enticott et al., 2014) Australia	N = 30 Active dTMS (n = 16) Sham dTMS (n = 14)	N= 28 Active dTMS (n = 15) Sham dTMS (n = 13)	Active dTMS: 2 (13.33%) Sham dTMS: 3 (23.08%) **PP analysis*	Active dTMS: 33.87 ± 13.07 (18–59) Sham dTMS: 30.54 ± 9.83 (19–54) **PP analysis*
Bipolar disorder				

(Tavares et al., 2017) Brazil	N = 50 Active dTMS (n = 25) Sham dTMS (n = 25)	N = 43 Active dTMS (n = 20) Sham dTMS (n = 23)	Active dTMS: 17 (68) Sham dTMS: 18 (72) **ITT analysis*	Active dTMS: 43.5 ± 12 Sham dTMS: 41.2 ± 8.9 **ITT analysis*
Bipolar disorder/ Major depressive disorder				
(Matsuda et al., 2020) Japan	N = 40 Active dTMS (n = 20) Sham dTMS (n = 20)	N = 38 Active dTMS (n = 18) Sham dTMS (n = 20)	Active dTMS: 2 (10) Sham: dTMS 1 (5) **ITT analysis*	Active dTMS: 43.4 ± 5.5 Sham dTMS: 45.2 ± 7.0 **ITT analysis*
Major depressive disorder				
(Gajšak et al., 2023) Croatia	N = 103 Active dTMS (n = 51) Control group (n = 52)	N = 98 Active dTMS (n = 48) Control group (n = 50)	Active dTMS: 27 (53) Control group: 25 (48) **ITT analysis*	Active dTMS: 50 ± 12.3 Control group: 50 ± 10.4 **ITT analysis*
(Filipčić et al., 2019) Croatia	N = 228 H1-coil (n = 72) F8 coil (n = 75) SOC pharmacotherapy (n = 81)	N = 209 H1-coil (n = 65) F8 coil (n = 72) SOC pharmacotherapy (n = 72)	H1-coil: 41 (56.9) F8 coil: 34 (45.3) SOC pharmacotherapy: 45 (55.66) **ITT analysis*	H1-coil: 50 (44-60) F8 coil: 51 (42-59) SOC pharmacotherapy : 53 (48-61) **ITT analysis*
(Kaster et al., 2018) Canada	N = 58 Active dTMS (n = 30) Sham dTMS (n = 28)	N = 47 Active dTMS (n = 20) Sham dTMS (n = 27)	Active dTMS: 8 (32) Sham dTMS: 12 (44.44) **PP analysis*	Active dTMS: 65.0 ± 5.5 (60- 80) Sham dTMS: 65.4 ± 5.5 (60-79) **PP analysis*
(Levkovitz et al., 2015) Canada, Germany, Israel, USA	N = 212 Active dTMS (n = 101) Sham dTMS (n = 111)	N = 181 Active dTMS (n = 89) Sham dTMS (n = 92)	Active dTMS: 48 (47.52) Sham: 53 (47.75) **ITT analysis*	Active dTMS: 45.1 ± 11.7 Sham dTMS: 47.6 ± 11.6 **ITT analysis*
Obsessive-compulsive disorder				
(Carmi et al., 2019) Canada & Israel	N = 94 Active dTMS (n = 47) Sham dTMS (n = 47) **Modified ITT sample*	N = 87 Active dTMS (n = 42) Sham dTMS (n = 45)	Active dTMS: 27 (57.4) Sham dTMS: 28 (59.6) **Modified ITT analysis*	Active dTMS: 41.1 ± 11.97 Sham dTMS: 36.5 ± 11.38 **Modified ITT analysis*
(Carmi et al., 2018) Israel	N = 41 HF dTMS (n = 18) LF dTMS (n = 8) Sham dTMS (n = 15)	N = 38 HF dTMS (n = 16) LF dTMS (n = 8) Sham dTMS (n = 14)	HF dTMS: 7 (43.75) LF dTMS: 4 (50) Sham dTMS: 7 (50) **PP analysis*	HF dTMS: 36 ± 2.1 LF dTMS: 28 ± 3.1 Sham dTMS 35 ± 3.5 **PP analysis*
Posttraumatic stress disorder				

(Isserles et al., 2021) Canada, Croatia, Israel, & USA	N = 109 dTMS + SDI (n = 53) Sham dTMS + SDI (n = 56)	N = 91 dTMS + SDI (n = 40) Sham dTMS + SDI (n = 51)	dTMS + SDI: 39 (65) Sham dTMS + SDI: 44 (67.69) **ITT analysis*	dTMS + SDI: 44.8 ± 13.19 Sham dTMS + SDI: 43.7 ± 12.25 **ITT analysis*
(Isserles et al., 2013) Israel	N = 30 Active dTMS + EXP (n = 10) Active dTMS + no EXP (n = 10) Sham dTMS + EXP (n = 10)	N = 26 Active dTMS + EXP (n = 9) Active dTMS + no EXP (n = 8) Sham dTMS + EXP (n = 9)	Active dTMS + EXP: 2 (22.22) Active dTMS + no EXP: 3 (37.50) Sham dTMS + EXP: 1 (11.11) **PP analysis*	Active dTMS + EXP: 49 ± 12.5 Active dTMS + no EXP: 40.5 ± 9.8 Sham dTMS + EXP: 40.4 ± 10.5 **PP analysis*
Schizophrenia / schizoaffective disorder				
(Rabany et al., 2014) Israel	N = 30 Active dTMS (n = 20) Sham dTMS (n = 10)	N = 25 Active dTMS (n = 16) Sham dTMS (n = 9)	Active dTMS: 7 (35) Sham dTMS: 2 (20) **ITT analysis*	Active dTMS: 33.1 ± 11.31 Sham dTMS: 35.9 ± 11.00 **ITT analysis*
Schizophrenia				
(Rosenberg et al., 2012) Israel	N = 18 Active dTMS (n = 9) Sham dTMS (n = 9)	N = 10 Active dTMS (n = 5) Sham dTMS (n = 5)	Active dTMS: 2 (22.22) Sham dTMS: 1 (11.11) **ITT analysis*	Active dTMS: 40.8 ± 16.6 (19 – 63) Sham dTMS: 38.4 ± 12.6 (22 – 63) **ITT analysis*
Substance use disorders				
Alcohol use disorder/ Alcohol dependence				
(Harel et al., 2022) Israel	N = 51 Active dTMS (n = 27) Sham dTMS (n = 24)	N = 46 Active dTMS (n = 23) Sham dTMS (n = 23)	Active dTMS: 8 (34.78) Sham dTMS: 8 (34.78) **PP analysis*	Active dTMS: 43.7 ± 8.7 Sham dTMS: 42.5 ± 9.8 **PP analysis*
(Perini et al., 2020) Sweden	N = 56 Active dTMS (n = 29) Sham dTMS (n = 27)	N = 45 Active dTMS (n = 23) Sham dTMS (n = 22)	Active dTMS: 4 (17.39%) Sham dTMS: 4 (18.18%) **PP analysis*	Active dTMS: 50.6 ± 10.4 Sham dTMS: 53.5 ± 7.5 **PP analysis*
(Addolorato et al., 2017) Italy	N = 14*	N = 11 Active dTMS (n = 5) Sham dTMS (n = 6)	Active dTMS: 1 (20) Sham dTMS: 1 (16.67) **PP analysis*	48.6 ± 9.9* **ITT analysis*
(Ceccanti et al., 2015) Italy	N = 18 Active dTMS (n = 9) Sham dTMS (n = 9)	N = 18 Active dTMS (n = 9) Sham dTMS (n = 9)	0 (0)	Active dTMS: 43.22 ± 11.10 Sham dTMS: 47.29 ± 11.46

Cocaine use disorder				
(Martinez et al., 2018) USA	NR	N = 18 HF dTMS (n = 6) LF dTMS (n = 6) Sham dTMS (n = 6)	HF dTMS: 0 (0) LF dTMS: 0 (0) Sham: 1 (16.67) **PP analysis*	HF dTMS: 42 ± 7 LF dTMS: 44 ± 5 Sham dTMS: 44 ± 6 **PP analysis*
(Bolloni et al., 2016) Italy	N = 18 Active dTMS (n = 10) Sham dTMS (n = 8)	N = 10 Active dTMS (n = 6) Sham dTMS (n = 4)	Active dTMS: 1 (10) Sham dTMS: 1 (12.5)	Active dTMS: 33.9 ± 6.5 (27–48) Sham dTMS: 32.4 ± 10.6 (23–50)
Nicotine/ tobacco use disorder (dependence)				
(Ibrahim et al., 2023) Canada	N = 42 Active dTMS (n = 24) Sham dTMS (n = 18)	N = 42 Active dTMS (n = 24) Sham dTMS (n = 18)	Active dTMS: 4 (16.7) Sham dTMS: 8 (44.4)	Active dTMS: 43.8 ± 12.5 Sham dTMS: 46.2 ± 12.9
(Zangen et al., 2021) Canada, Israel & USA	N = 262 Active dTMS (n = 123) Sham dTMS (n = 139)	N = 169 Active dTMS (n = 75) Sham dTMS (n = 94)	Active dTMS: 60 (48.8) Sham dTMS: 66 (47.5) **ITT analysis*	Active dTMS: 45 ± 13 Sham dTMS: 44.8 ± 13.4 **ITT analysis*
(Dinur-Klein et al., 2014) Israel	N = 115 HF dTMS (n = 50) LF dTMS (n = 24) Sham dTMS (n = 41)	N = 77 HF dTMS + cue (n = 16) HF dTMS no cue (n = 16) LF dTMS + cue (n = 7) LF dTMS no cue (n = 7) Sham dTMS + cue (n = 15) Sham dTMS no cue (n = 16)	HF dTMS + cue: 5 (31.25) HF dTMS no cue: 4 (25) LF dTMS + cue: 3 (42.89) LF dTMS no cue: 4 (57.14) Sham dTMS + cue: 5 (33.3) Sham dTMS no cue: 8 (50)	HF dTMS + cue: 49.9 ± 12.0 HF dTMS no cue: 50.3 ± 9.3 LF dTMS+ cue : 48.3 ± 10.8 LF dTMS no cue : 50.1 ± 12.1 Sham dTMS + cue: 51.6 ± 10.9 Sham dTMS no cue: 50.2 ± 7.5
Comorbid conditions				
Comorbid schizophrenia/ schizoaffective disorder & tobacco dependence				
(Moeller et al., 2022) USA	N = 32*	N = 20 Active dTMS (n = 10) Sham dTMS (n = 10)	Active dTMS: 3 (30) Sham TMS: 3 (30) **PP analysis*	Active dTMS: 50.2 ± 6.8 Sham TMS: 47.4 ± 9.9 **PP analysis*
Comorbid alcohol use disorder & dysthymic disorder				
(Girardi et al., 2015)	N = 20 dTMS-AO (n = 10)	N = 20 dTMS-AO (n = 10)	dTMS-AO: 5 (50) SDT: 3 (30)	dTMS-AO: 52.6 ± 7.7 SDT: 54.1 ± 11.4

Italy	SDT (n = 10)	SDT (n = 10)

Abbreviations. ADHD= attention-deficit hyperactivity disorder, AO= add-on, ASD= autism spectrum disorder, AUD= alcohol-use disorder, CUD= cocaine use disorder, DD= dysthymic disorder, dTMS= deep transcranial magnetic stimulation, EXP= exposure, HD= high distress, HF= high frequency, ITT= Intention-to-treat, LD= low distress, LF= low frequency, lPFC= left prefrontal cortex, MDD= major depressive disorder, OCD= obsessive-compulsive disorder, PFC= prefrontal cortex, PP= per-protocol, PTSD= posttraumatic stress disorder, rPFC= right prefrontal cortex, SDI= script-driven imagery, SDT= standard detoxification treatment, SOC= standard of care, TUD = tobacco use disorder.

* Indicates the number of participants in each treatment arm were not specified.

Patient Characteristics: Psychiatric and Cognitive Disorder Diagnoses

Table 2 displays psychiatric and cognitive disorders by number of studies. Most clinical trials (9; 32.14%) were conducted in patients with SUDs, specifically in individuals with alcohol dependence or alcohol use disorder (AUD; Addolorato et al., 2017; Ceccanti et al., 2015; Girardi et al., 2015; Harel et al., 2022), cocaine use disorder (CUD; Bolloni et al., 2016; Martinez et al., 2018) and nicotine dependence or nicotine use disorder (NUD; Dinur-Klein et al., 2014; Ibrahim et al., 2023; Zangen et al., 2021). Moeller et al. (2022) studied patients with comorbid tobacco dependence and schizophrenia or schizoaffective disorder, and Girardi et al. (2015) explored dTMS in patients with comorbid AUD and dysthymic disorder. The remaining clinical trials explored dTMS in the following psychiatric disorders: attention-deficit/hyperactivity disorder (ADHD; Alyagon et al., 2020; Bleich-Cohen et al., 2021; Paz et al., 2018), autism spectrum disorder (ASD; Enticott et al., 2014), bipolar disorder (BD; Tavares et al., 2017), BD or MDD with an active depressive episode (Matsuda et al., 2020), MDD (Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015), OCD (Carmi et al., 2019, 2018), PTSD (Isserles et al., 2021, 2013), and schizophrenia or

schizoaffective disorder (Rabany et al., 2014; Rosenberg et al., 2012). As for cognitive disorders, one clinical trial (Leocani et al., 2021) was conducted in patients with Alzheimer's disease.

Table 2. Psychiatric and cognitive disorders by number of studies.

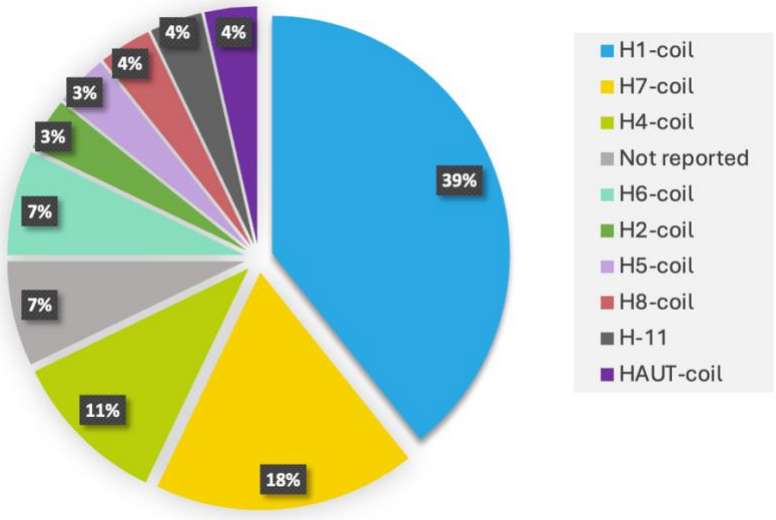
Psychiatric or cognitive disorder	No. of clinical trials	Percentage of clinical trials (%)
Alzheimer's disease	1	3.57
Attention-deficit/hyperactivity disorder	3	10.71
Autism spectrum disorder	1	3.57
Bipolar disorder	1	3.57
Bipolar disorder/ Major depressive disorder	1	3.57
Major depressive disorder	4	14.29
Obsessive-compulsive disorder	2	7.14
Posttraumatic stress disorder	2	7.14
Schizophrenia and related disorders	2	7.14
Substance use disorders		
Alcohol use disorder/Alcohol dependence	4	14.29
Cocaine use disorder	2	7.14
Nicotine dependence	3	10.71
Comorbid conditions		
Comorbid schizophrenia/ schizoaffective disorder and tobacco dependence	1	3.57
Comorbid alcohol use disorder and dysthymic disorder	1	3.57
Total	28	100

H-coil Design and Target Brain Regions

The included studies examined the following H-coil designs: the H1, H2, H4, H5, H6, H7, H8, H11, and HAUT coils (Figure 4). Kaster et al. (2018) originally used the H1L-coil for the first six enrolled participants. However, due to negative side effects (e.g., one seizure in the active group) and tolerability issues, the protocol was changed to the H1-coil instead. Therefore, the H1L-coil was not included in Figure 4. More than one-third of studies (11; 39.29%) used the H1-coil, followed by the H7 (5; 17.86%), and H4 coils (3; 10.71%). Two studies (Addolorato et al., 2017; Ceccanti et al., 2015) did not report the specific H-coil design.

Common target regions using the H1-coil included various structures of the PFC, including the dorsolateral PFC (DLPFC), the ventromedial PFC (vmPFC), and the ventrolateral PFC (VLPFC). Target regions for the H7-coil were the ACC and mPFC. The remaining H-coils mainly targeted various substructures of the PFC. In patients with SUDs disorders, several H-coils were used to stimulate the various regions, including the ACC (H7-coil), bilateral or lateral PFC (H1 and H4 coils), mPFC (H7-coil), DLPFC (H1-coil), and insula (H4, H8, and H11 coils).

Figure 4. **Percentage of H-coil designs used across *n = 28* clinical trials.**



dTMS stimulation parameters

dTMS stimulation parameters (i.e., stimulation frequency, intensity [%MT], total pulses, inter-train intervals, etc.) can be summarized in Table 3. Across the 28 included clinical trials, dTMS was most often applied using HF at 100 –120% of the resting MT. Fewer studies employed a LF dTMS condition in which participants received 1-5 Hz of stimulation. To examine which is more or equally effective, three studies (Carmi et al., 2018; Dinur-Klein et al., 2014; Martinez et al., 2018) introduced a HF and LF condition in addition to sham.

Treatment Duration

dTMS interventions varied in length, with the number of treatment sessions ranging from 10 to 30 days. Mean (SD) number of sessions for the treatment phase across studies was 16.43 (4.78). Maintenance, follow-up, or additional sessions (beyond the treatment phase) were not included in this calculation. Overall, studies in patients with OCD had the longest duration (mean number of sessions: 27; range: 25-29 days). All four studies (Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015) in patients with MDD consisted of 20 treatment sessions. One study (Matsuda et al., 2020) in patients with MDD or BD administered 20 sessions during the treatment phase, with the option of an additional 10 sessions if remission was not achieved. In patients with SUDs, the average duration was lower (mean number of sessions: 14.55; range: 10-20 sessions). Other studies varied regarding the number of treatment sessions.

Side Effects and Adverse Events

The most reported side effects across included clinical trials were headaches and stimulation site pain/discomfort. Side effects and adverse events among the 28 clinical trials are summarized in detail in Table 4. Four studies (Addolorato et al., 2017; Ceccanti et al., 2015; Girardi et al., 2015; Rabany et al., 2014) did not comment on side effects or adverse events.

Headaches. Nineteen (67.86%) clinical trials reported headaches (Table 4). Ten studies reported headaches in both active and sham dTMS conditions (Carmi et al., 2018; Dinur-Klein et al., 2014; Isserles et al., 2021; Levkovitz et al., 2015; Perini et al., 2020; Zangen et al., 2021), four of which explicitly reported no significant group differences in their occurrence (Carmi et al., 2019; Harel et al., 2022; Ibrahim et al., 2023; Tavares et

al., 2017). Interestingly, several studies reported headaches exclusively in the sham dTMS group. For instance, one study (Leocani et al., 2021) reported a transient headache from a participant in the sham group. Moreover, another study (Dinur-Klein et al., 2014) reported greater headaches and/or nausea in the sham condition compared to the LF and HF dTMS groups.

Pain and Discomfort. Twelve studies (42.86%; Alyagon et al., 2020; Carmi et al., 2019; Dinur-Klein et al., 2014; Enticott et al., 2014; Filipčić et al., 2019; Gajšak et al., 2023; Isserles et al., 2013; Kaster et al., 2018; Levkovitz et al., 2015; Moeller et al., 2022; Tavares et al., 2017; Zangen et al., 2021) reported pain or discomfort among participants. One study (Kaster et al., 2018) observed significant differences in reports of pain between the active (16%) and sham (0%) groups ($p < 0.05$). Another study (Tavares et al., 2017) reported greater scalp pain in the active (20%) versus sham (0%) group ($p = 0.05$). Filipčić et al. (2019) observed application site discomfort in the active group, but not in the sham group. Gajšak et al. (2023) reported higher pain in the active dTMS group (neck pain: 24%; back pain or acute mood change: 10%) compared to the standard pharmacotherapy control group (neck pain: 0%; back pain: 2%). Another study (Zangen et al., 2021) found significantly more active group participants compared to sham reporting adverse events ($p = 0.004$), including application site pain/discomfort, as well as muscle, facial, jaw, and neck pain.

Discomfort was another commonly reported side effect of dTMS. One study (Isserles et al., 2013) had two patients withdraw from the active ($n = 1$) and sham ($n = 1$) groups due to discomfort. Another study (Moeller et al., 2022) reported head/facial

discomfort in the active dTMS group (n = 3), with a single report (n = 1) of neck and chest discomfort in the sham group. Three studies (Filipčić et al., 2019; Levkovitz et al., 2015; Zangen et al., 2021) reported application site pain/discomfort and three reported scalp pain/discomfort (Alyagon et al., 2020; Gajšak et al., 2023; Tavares et al., 2017). One trial (Gajšak et al., 2023) observed scalp discomfort in nearly a third of participants in the active dTMS group, whereas this side effect was not present in the pharmacotherapy control group. Zangen et al. (2021) noted that application site discomfort was the only side effect that was significantly more frequently reported in the active dTMS group compared to the sham group. In terms of dTMS tolerability, one study (Martinez et al., 2018) reported that participants found it difficult to handle the increase from 100% to 120% of their MT. Notably, one participant (1/47; 2.13%) in the active group of Carmi et al. (2019) dropped out during treatment due to dTMS-related discomfort. Kaster et al. (2018) also reported one dropout (1/30) from a participant in the active dTMS group who experienced discomfort from the pulses. Dinur-Klein et al. (2014) reported discomfort-related dropouts from two participants in the LF dTMS group. Of importance, one study (Zangen et al., 2021) noted pain and discomfort decreased for most participants after receiving several sessions of dTMS.

Muscle spasms or twitching. Six studies (21.43%) reported twitching/muscle spasms (Filipčić et al., 2019; Gajšak et al., 2023; Levkovitz et al., 2015; Moeller et al., 2022; Perini et al., 2020; Zangen et al., 2021) and tingling (Moeller et al., 2022) in patients receiving active dTMS treatments. One study (Perini et al., 2020) reported facial twitches in both active dTMS and sham groups. Another study (Gajšak et al., 2023) noted

three active dTMS participants and one control participant reporting spasms or twitching of the facial muscles. Moeller et al. (2022) reported three participants in the active condition who experienced tingling or twitching in their hands. In the study by Filipčić et al. (2019), 8 (12%) dTMS participants experienced muscle twitching/spasms or jaw pain, whereas there were no reports of muscle twitching in the traditional F8-coil TMS group. Levkovitz et al. (2015) reported muscle twitching in the active dTMS group, but not in the sham group. Contrarily, Zangen et al. (2021) did not find any significant differences in reports of muscle spasms or twitching between the active and sham groups.

Anxiety. A less common reported side effect was anxiety. One study (Filipčić et al., 2019) reported anxiety among patients within the control group (n = 2; 3%) and the F8-coil TMS group (n = 1; 1%), while this was not found in the H1-coil group. Another study (Isserles et al., 2013) reported increased anxiety in a single patient receiving active dTMS who eventually withdrew from treatment. Moreover, Isserles et al. (2021) reported seven participants in the dTMS (n = 3) and sham groups (n = 4) who experienced moderate-to-severe anxiety. Interestingly, one study (Levkovitz et al., 2015) reported anxiety in the sham group (1.8%), but not in the active group.

Nausea and Dizziness. Fewer studies reported nausea and/or dizziness as a side effect. Three studies (Filipčić et al., 2019; Gajšak et al., 2023; Ibrahim et al., 2023) reported dizziness/light-headedness in both the active dTMS and sham/control groups. Dinur-Klein et al. (2014) reported nausea for three participants in the sham group, one in the LF dTMS condition and two in the HF dTMS condition. Another study (Gajšak et al., 2023) reported nausea/itching and nausea/dizziness in the active (n = 8; 16%) and control

groups (n = 2; 4%), respectively. Ibrahim et al. (2023) observed similar rates of nausea among the active dTMS (33.3%) and sham (16.7%) conditions (p = 0.30). Filipčić et al. (2019) reported a single case of nausea in the pharmacotherapy control group, but not in the active TMS conditions. Regarding more serious cases, Levkovitz et al. (2015) reported nausea and vomiting from a participant in the sham condition.

Table 3. Study Design and dTMS parameters.

Author	Comparison type	Treatment duration	Total sessions	Coil type	Target regions	Frequency (Hz)	Intensity (% MT)	Pulses/ session	Time/ session (min)	Trains per session	Inter-train interval (s)
Alzheimer's disease											
(Leocani et al., 2021)	Active dTMS vs. sham dTMS	3 sessions per week for 4 weeks + 4 weeks of maintenance (1 session/week)	12 (16 including maintenance phase)	H2	Bilateral fronto-temporo-parietal regions	10	120	840	NR	42	22
Attention-deficit/ hyperactivity disorder											
(Bleich-Cohen et al., 2021)	rPFC dTMS vs. lPFC dTMS vs. sham dTMS	5 days a week for 3 weeks	15	H6	rPFC or lPFC, including the DLPFC & VLPFC	18	120	1440	NR	40	20
(Alyagon et al., 2020)	Active dTMS vs. TMS (F8-coil) vs. sham dTMS	15 sessions over 3 weeks (+ 1 maintenance session at 1-month FU visit)	15 (16 including maintenance phase)	H6 & F8	right PFC, including the DLPFC & VLPFC	H6: 18 F8: 18	H6: 120 F8: 120	H6: 1440 F8: 1440	NR	H6: 40 F8: 40	H6: 20 F8: 20
(Paz et al., 2018)	Active dTMS vs. sham dTMS	5 days per week for 4 weeks	20	H5	Bilateral PFC	18	120	1980	NR	55	20
Autism Spectrum Disorder											

(Enticott et al., 2014)	Active dTMS vs. sham dTMS	5 days per week for 2 weeks	10	HAUT	Bilateral dmPFC	5	110	1500	15	30	20
Bipolar disorder											
(Tavares et al., 2017)	Active dTMS vs. sham dTMS	5 days per week for 4 weeks	20	H1	Left DLPFC	18	120	1980	NR	55	20
Bipolar disorder/ Major depressive disorder											
(Matsuda et al., 2020)	Active dTMS vs sham dTMS	5 days per week for 4 weeks **If remission was not met by the week 4, additional treatment would be administered up to 2 weeks*	20 (max. 30 with additional treatment)	H1	Left DLPFC	18	120	1980	NR	55	20
Major depressive disorder											
(Gajšak et al., 2023)	H1 coil vs. standard pharmacotherapy. **Both conditions had standard pharmacotherapy*	5 days per week for 4 weeks	20	H1	Left DLPFC	18	120	1980	20	55	20
(Filipčić et al., 2019)	H1-coil vs. F8 coil vs. standard pharmacotherapy. **All conditions had standard pharmacotherapy*	5 days per week for 4 weeks	20	H1 & F8	Left DLPFC	H1: 18 F8: 10	120 (H1 & F8)	H1: 1980 F8: 3000	H1: 20 F8: 40	H1: 55 F8: 75	H1: 20 F8: 26

(Kaster et al., 2018)	Active dTMS vs. sham dTMS	5 days per week for 4 weeks	20	H1	Dorsolateral & ventrolateral PFC, with greater intensity over the left-hemisphere	18	120	6012	61	167	20
(Levkovitz et al., 2015)	Active dTMS vs. sham dTMS	5 days per week for 4 weeks + 12-week maintenance phase (twice per week)	20 (44 total with maintenance phase)	H1	DLPFC & VLPFC, medial prefrontal structures (subgenual cingulate gyrus)	18	120	1980	30	55	20
Obsessive-compulsive disorder											
(Carmi et al., 2019)	Active dTMS vs. sham dTMS	5 days per week for 5 weeks + 4 sessions during week 6	29	H7	Dorsal mPFC & ACC bilaterally	20	100	2000	NR	50	20
(Carmi et al., 2018)	Active HF dTMS vs. active LF dTMS vs. sham dTMS	5 sessions per week for 5 weeks	25	H7	mPFC & ACC	HF: 20 LF: 1	HF: 100 LF: 110	HF: 2000 LF: 900	NR	HF: 50 LF: NR	HF: 20 LF: NR
Posttraumatic stress disorder											
(Isserles et al., 2021)	Active dTMS vs. sham dTMS (both with SDI)	3 days per week for 4 weeks	12	H7	mPFC & ACC	18	100	NR	NR	80	20
(Isserles et al., 2013)	EXP-STIM dTMS, NOEXP-STIM dTMS vs. EXP-SHAM dTMS	3 sessions weekly for 4 weeks	12	H1	mPFC	20	120	1680	20	42	20
Schizophrenia / schizoaffective disorder											
(Rabany et al., 2014)	Active dTMS vs. sham dTMS	Daily for 4 weeks	20	H1	Left DLPFC	20	120	NR	NR	42	20
Schizophrenia											

(Rosenberg et al., 2012)	Active dTMS vs. sham dTMS	10 days (one session per day)	10	H1	Left temporoparietal cortex	1	110	NR	10	NR	NR
Substance use disorders											
Alcohol use disorder/ Alcohol dependence											
(Harel et al., 2022)	Active dTMS vs sham dTMS	5 days per week for 3 weeks (+maintenance phase including 5 sessions over 3 months)	15 (20 including maintenance phase)	H7	mPFC & ACC	10	100	3000	30	100	15
(Perini et al., 2020)	Active dTMS vs sham dTMS	5 days per week for 3 weeks	15	H8	Bilateral insula	10	120	1500	NR	50	20
(Addolorato et al., 2017)	Active dTMS vs. sham dTMS	3 sessions per week for 4 weeks	12	NR	Bilateral DLPFC	10	100	NR	NR	20	15
(Ceccanti et al., 2015)	Active dTMS vs. sham dTMS	5 sessions per week for 2 weeks	10	NR	mPFC	20	120	NR	NR	30	30
Cocaine use disorder											
(Martinez et al., 2018)	HF dTMS vs. LF dTMS vs. sham dTMS	On weekdays for 3 weeks	13	H7	mPFC & dACC	HF: 10 LF: 1	Initial intensity: 90%. ↑ to 110% over 2-3 days	HF: 1200 LF: 900	NR	HF: 40 LF: NR	HF: 20 LF: NR
(Bolloni et al., 2016)	Active dTMS vs. sham dTMS	3 sessions per week for 4 weeks	12	H1	Bilateral PFC	10	100	1000	~10	20	15
Nicotine/ tobacco use disorder (dependence)											

(Ibrahim et al., 2023)	Active dTMS vs. sham dTMS (4 weeks) + varenicline (12 weeks; both arms)	5 sessions per week for 4 weeks	20	H11	Bilateral insula	10	110 - 120	1020	16	34	26
(Zangen et al., 2021)	Active dTMS vs. sham dTMS	3 weeks of daily treatment (treatment phase) + 1 session/week for 3 weeks (follow-up phase)	18 (15 treatment phase + 3 follow-up phase)	H4	Lateral PFC & insula	10	120	1800	NR	60	15
(Dinur-Klein et al., 2014)	Active dTMS (HF vs LF) vs. sham; smoking cue (+ cue, - no cue)	10 daily treatments within 2 weeks + 3 treatments during week 3	13	H4	Lateral PFC & bilateral insula	HF: 10 LF: 1	120	HF: 990 LF: 600	HF :12.7 LF: NR	HF: 33 LF: NR	HF: 20 LF: NR
Comorbid conditions											
Comorbid schizophrenia / schizoaffective disorder & tobacco dependence											
(Moeller et al., 2022)	Active dTMS vs sham dTMS	5 days per week for 3 weeks	15	H4	Bilateral insula	10	120 *visit 1: 100%* *visit 2: 110%* *visit 3+: 120%*	NR	20	60	15
Comorbid alcohol use disorder & dysthymic disorder											
(Girardi et al., 2015)	Active dTMS-AO vs. SDT alone (control group)	5 sessions per week for 4 weeks	20	H1	DLPFC	20	120	NR	NR	55	20

Abbreviations: ACC = anterior cingulate cortex, AO= add-on, dACC = dorsal anterior cingulate cortex, DLPFC= dorsolateral prefrontal cortex, dmPFC= dorsomedial prefrontal cortex, dTMS= deep transcranial magnetic stimulation, EXP-SHAM dTMS= exposure + sham dTMS, EXP-STIM dTMS= exposure + active stimulus (dTMS), F8= figure-8 coil, HF= high frequency, LF= low frequency, lPFC= left prefrontal cortex, mPFC= medial prefrontal cortex, NOEXP-STIM dTMS= no exposure + active stimulus (dTMS), NR= not reported, PFC= right prefrontal cortex, rPFC= right prefrontal cortex, SDI= Script-driven imagery, SDT= standard detoxification treatment, TD = tobacco dependence, TMS= transcranial magnetic stimulation, VLPFC= ventrolateral prefrontal cortex.

Serious Adverse Events (SAEs)

Suicidal ideation or attempts. One study (Carmi et al., 2019) reported that a patient in the active dTMS experienced severe suicidal thoughts, though this was attributed to family issues and not the treatment itself. Another study (Levkovitz et al., 2015) documented two cases of suicidal ideation (n = 2) in the sham condition. The authors also reported a suicide attempt in a participant who had not yet been randomized to a treatment arm (Levkovitz et al., 2015). Lastly, Isserles et al. (2021) reported two participants (n = 2) in the active condition as having suicidal ideation possibly due to worsening chronic suicidal ideation and a suicide attempt under alcohol intoxication.

Seizures. Across 28 clinical trials, three cases of seizures were reported (N = 1636, Σ ITT participants) during dTMS treatment. Isserles et al. (2013) reported that a patient in the H1-coil condition suffered from a seizure. Levkovitz et al. (2015) reported one seizure in the H1-coil group that was appraised device-related. Kaster et al. (2018) reported a seizure from a participant in the active H1L-coil condition. Due to tolerability issues, the H1L-coil was replaced by the H1-coil for subsequent participants. Although not dTMS, one study (Alyagon et al., 2020) reported a seizure in the F8-coil condition (i.e., traditional TMS) and the participant was subsequently withdrawn from the study. For more details regarding cases of seizures, please refer to the Supplementary Table S3.

Other SAEs. One study (Levkovitz et al., 2015) identified a case of nephrolithiasis (n = 1) from a participant in the sham group. Another SAE from this study (Levkovitz et al., 2015) was a case of nausea and vomiting (n = 1) from a participant in the sham group. In the active dTMS group, an elbow fracture (n = 1) and a cluster headache (n = 1) were reported (Levkovitz et al., 2015). Another study (Zangen et al.,

2021) reported a sole case of tinnitus from a participant in the active dTMS arm, which was appraised as "possibly related to treatment."

Dropout rates

Dropout rates across studies and reasons for dropouts are summarized in detail in Table 4. Dropout rates were calculated according to the cumulative number of dropouts reported during the treatment phase and follow-up/maintenance phases (i.e., not prior to treatment). Participants withdrawn from analysis due to protocol deviations were not included in this calculation. Of the 25 studies that reported participant dropouts, the cumulative mean (SD) dropout rate during the treatment phase and follow-up/maintenance phases was 24.82% (20.33%), with a range of 3.51% to 88.89%. Four trials (Addolorato et al., 2017; Girardi et al., 2015; Martinez et al., 2018; Rabany et al., 2014) did not report dropout rates during the treatment phase or follow-up/maintenance phases and therefore were excluded from this calculation.

Table 4. Adverse Events and Dropout Rates

Author	Adverse events	Dropout rates*			Reasons for dropouts
		Active group (s)	Sham/control group (s)	Total	

(Gajšak et al., 2023)	▪ dTMS group: 16 (32%) patients reported mild headaches, 15 (30%) drowsiness, 14 (28%) scalp discomfort, 12 (24%) neck pain, 9 (18%) difficulty concentrating, 8 (16%) itching or nausea, 5 (10%) back pain or acute mood swings, 3 (6%) spasms or twitching of facial muscles, 2 (4%) sleep disturbances, and 1 (2%) dizziness. ▪ Control group: 6 (12%) patients reported drowsiness or difficulty concentrating, 3 (6%) headache, 2 (4%) nausea or dizziness, and 1 (2%) back pain, facial twitching or spasm, sleep disturbances and hearing loss. ▪ No serious adverse events were reported	Active dTMS: 3/51 (5.88%)	Control: 2/52 (3.85%)	5/103 (4.85 %)	<u>Dropouts during treatment phase:</u> Active dTMS: no reason provided (n = 1); COVID-19 (n = 1) Control: no reason provided (n = 1) <u>Dropouts during follow-up phase:</u> Active dTMS: lost to follow-up (n = 1) Control: lost to follow-up (n = 1)
(Ibrahim et al., 2023)	▪ No serious adverse events observed ▪ No significant differences in side effects between active vs sham groups were found. ▪ Most common side effects were nausea (1 headaches (16.7% active vs. 33.3% sham), and vivid dreams (16.7% active vs. 11.1% sham).	Active dTMS: 8/24 (33.33%)	Sham dTMS: 3/18 (16.67%)	11/42 (26.19 %)	<u>Dropouts during follow-up phase</u> Active dTMS: Time commitment (n = 3); nausea (n = 1); COVID-19 (n = 2); Unknown (n = 1); no longer in Toronto (n = 1) Sham dTMS: Time commitment (n = 2); nausea (n = 1
(Harel et al., 2022)	▪ Moderate-to-severe headaches (no group differences in occurrence or intensity). ▪ No serious adverse events observed.	Active dTMS: 7/27 (25.93%)	Sham dTMS: 3/24 (12.5%)	10/51 (19.61 %)	<u>Dropouts during treatment phase</u>: Active dTMS: relapse (n = 4) Sham dTMS: relapse (n = 1) <u>Dropouts during follow-up phase</u>: Active dTMS: relapse or noncompliance with study scheduling (n = 3) Sham dTMS: relapse or noncompliance with

					study scheduling (n = 2)
(Moeller et al., 2022)	▪ Active dTMS group: head and facial discomfort (n = 3), tingling/twitching in the hands (n = 3), back pain (n = 2), feeling that the stimulation was too powerful (n = 2); and one minor fall outside of the lab. ▪ Sham dTMS group: neck/chest discomfort at the end of a session (n = 1) ▪ No participant withdrawals due to side effects.	N/A	N/A	4/32 (12.50%)	Withdrawal of consent (n = 4) **Note. Study did not explicitly report dropouts, when dropouts occurred (i.e., treatment vs follow-up phase), or treatment group.*
(Bleich-Cohen et al., 2021)	8 patients reported dTMS-related headaches and toothaches after week 1 (leading to withdrawal of consent)	lPFC dTMS: 6/28 (21.43%) rPFC dTMS: 2/26 (7.69%)	3/19 (15.79%)	11/73 (15.07%)	<u>Dropouts during treatment phase:</u> lPFC dTMS: discomfort from treatment (n = 4) rPFC dTMS: discomfort from treatment (n = 2) Sham dTMS: discomfort from treatment (n = 2) & pathology from MRI finding (n = 1) <u>Dropouts during follow-up phase:</u> lPFC dTMS: lost to follow-up (n = 2)

(Isserles et al., 2021)	▪ The most common adverse event was headaches (33 in the active and 31 in the sham). ▪ 46 (76.70%) and 41(63.10%) participants in the dTMS and sham groups, respectively, (χ^2 p = 0.099), experienced adverse events. ▪ 7 participants (3 in the active dTMS and 4 in the sham) reported moderate or severe anxiety. ▪ 2 participants in the active dTMS group reported suicidal ideation (one made a suicide attempt under alcohol intoxication and the other had chronic suicidal ideation).	Active dTMS + SDI: 13/53 (24.53%)	Sham dTMS + SDI: 5/56 (8.93%)	18/109 (16.51%)	<u>Dropouts during treatment phase:</u> Active dTMS + SDI: withdrew consent (n = 5), lost during follow-up (n = 2), suicidal attempt/ideation (n = 2), non-compliance (n = 1), more than 2 treatments missed (n = 2). Sham dTMS + SDI: consent withdrawn (N = 4). <u>Dropouts during follow-up phase</u>: Active treatment: lost to follow-up (N = 1). Sham treatment: lost to follow-up (N = 1).
(Leocani et al., 2021)	▪ No serious side effects. ▪ One report of a transient headache (sham group). The same participant had an acute myocardial infarction after 2 weeks of treatment (not involving dTMS sessions), which was deemed unrelated to treatment. ▪ One patient (active group) could not tolerate high intensity (120% MT), which was lowered to 95-110% MT.	NR	NR	NR	*No dropouts reported during or after treatment.* *Two participants assigned to sham dTMS were excluded (prior to treatment) after having a diagnosis of SCA17 (n = 1) and an acute myocardial infarction (n = 1).*

(Zangen et al., 2021)	▪ Headaches were reported in active (24.4%) and sham (18%) groups. ▪ Reports of transient and mild-to-moderate pain or discomfort: specifically, application site pain/discomfort, spasms, twitching and or pain within the muscle, jaw pain, facial pain, and neck pain (group not specified). ▪ Reports of transient and mild-to-moderate muscle pain/spasm/twitching (group not specified). ▪ Discomfort/pain decreased after several sessions for most participants ▪ Significantly more active group participants (relative to sham) reported adverse events (53.7% vs. 36.0%, X2 = 8.274, p = 0.004) ▪ No significant differences between conditions were found, apart from application site discomfort which was reported more frequently in the active group ▪ 1 serious adverse event of tinnitus reported in the active condition (possibly related to treatment)	Active dTMS: 48/123 (39.02%)	Sham dTMS: 45/139 (32.4%)	93/262 (35.5 %)	<u>Dropouts during treatment phase + short follow-up</u>: Active dTMS: missed treatments (n = 40); did not attend assessment at the sixth week (n = 8) Sham dTMS: missed treatments (n = 33); did not attend assessment at the sixth week (n = 12).
(Alyagon et al., 2020)	▪ 1 seizure in the F8-coil group at session 3 (patient withdrawn). ▪ Reports of transient headaches and scalp discomfort (group not specified).	Active dTMS: 9/20 (45.0%) F8-coil: 4/16 (25.0%)	Sham dTMS: 4/16 (25.0%)	17/52 (32.69 %)	<u>Dropouts during treatment phase:</u> Active dTMS (H6-coil): scheduling (n = 2) & consent withdrawn (n = 3) F8-coil group: scheduling problems (n = 1) & seizure (n = 1) Sham dTMS: scheduling problems (n = 1) & non-compliance (n = 2)

					<u>Dropouts during follow-up phase:</u> Real group: scheduling problems (n = 4) F8-coil group: scheduling problems (n = 1) & moved away (n = 1) Sham dTMS: scheduling problems (n = 1)
(Matsuda et al., 2020)	No adverse events occurred in either the active or sham group.	Active dTMS: 2/20 (10 %)	Sham dTMS: 0/20 (0%)	2/40 (5.0%)	<u>Dropouts during treatment phase:</u> Active dTMS: Application site pain (n = 1); vertigo (n =1)
(Perini et al., 2020)	▪ Facial twitches reported in both the active dTMS and sham groups. ▪ Both conditions reported moderate to strong headaches (n = 23)	Active dTMS: 8/29 (27.59%)	Sham dTMS: 9/27 (33.33%)	17/56 (30.36 %)	<u>Dropouts during treatment phase:</u> Active dTMS: dropout (n = 2) & did not complete (n = 4) Sham dTMS: dropout (n = 2) & did not complete (n = 3) <u>Dropouts during follow-up phase:</u> Active dTMS: follow-up was not completed (n = 2) Sham dTMS: follow-up was not completed (n = 4) **The authors were not explicit as to why participants dropped out or did not complete the study*

(Filipčić et al., 2019)	▪ No serious adverse events were observed. ▪ H1-coil group: 20 (29%) patients reported headaches; 8 (12%) muscle twitching/spasms or jaw pain; 5 (7%) reported application site pain; 5 (7%) reported insomnia; 4 (6%) had light-headedness/dizziness; and 3 (4%) patients reported application site discomfort. ▪ F8-coil group: 15 (20%) reported headaches, 5 (7%) patients reported insomnia; 2 (3%) reported light-headedness/dizziness; 1 (1%) reported anxiety; 1 (1%) reported application site discomfort; no reports of application site pain or muscle twitching. ▪ Control group: 4 (5%) of patients reported insomnia, 3(4%) reported headaches, 2(3%) anxiety, 2(3%) fatigue, 1 (1%) dizziness, and 1(1%) nausea.	H1-coil: 2/72 (2.78%) F8 coil: 1/75 (1.33%)	5/81 (6.17%)	8/228 (3.51 %)	<u>Dropout during treatment phase:</u> H1-coil: dropout (n = 2) F8-coil: dropout (n = 1) SOC pharmacotherapy: dropout (n = 5) **Authors did not disclose reasons for dropouts.*
(Carmi et al., 2019)	▪ 35 (73%) participants in the active dTMS group and 35 (69%) in the sham group reported adverse events (no significant group differences: $p = 0.639$). ▪ 37.5% and 35.3% in the active dTMS and sham groups reported headaches, respectively (nonsignificant). ▪ One patient in active group developed severe suicidal thoughts. Patient believed that such thoughts were brought on by family issues, and not the dTMS treatment itself.	7/47 (14.89%)	3/47 (6.38%)	10/94 (10.64 %)	<u>Dropouts during treatment phase:</u> Active dTMS: suicidal ideation (N = 1), discomfort (N = 1) & scheduling (N = 3). Sham dTMS: scheduling (N = 2) <u>Dropouts during follow-up phase:</u> Active dTMS: lost to follow-up (N = 2) Sham dTMS: lost to follow-up (N = 1)

(Carmi et al., 2018)	▪ No severe adverse events reported. ▪ Headache and fatigue were reported in the HF dTMS group (n = 3) and sham group (n = 1).	HF dTMS: 9/50 (18%) LF dTMS: 4/24 (16.7%)	Sham dTMS: 6/15 (40%)	19/41 (46.0 %)	<u>Dropouts during treatment phase:</u> HF dTMS: discontinued (n = 2) LF dTMS: discontinued (n = 0) Sham dTMS: (n = 1) <u>Dropout during follow-up phase:</u> HF dTMS: lost during follow-up (n = 7) LF dTMS: lost during follow-up (n = 4) Sham dTMS: lost during follow-up (n = 5)
(Kaster et al., 2018)	▪ One report of a seizure in the active H1L-coil condition. ▪ Only significant difference between active dTMS and sham groups was reports of pain (16.0% vs. 0%; $p<0.05$).	Active dTMS H1-coil: 5/25 (20.0%) Active dTMS H1L-coil: 2/5 (40.0%)	Sham dTMS H1-coil: 0/27 (0%) Sham dTMS H1L-coil: 1/1 (100%)	8/58 (13.79 %)	<u>Dropouts during treatment phase</u> Active dTMS H1-coil: corneal tear requiring surgery (n = 1) and a renal colic (n =1); felt worse after treatment (n =1); discomfort from the pulses (n = 1); did not wish to continue despite showing clinical improvements (n = 1). Active dTMS H1L-coil: seizure (n = 1); tolerability issues (n = 1) Sham dTMS H1L-coil: tolerability issues (n = 1)
(Martinez et al., 2018)	▪ Participants had difficulty tolerating the increase from 100 to 120% MT. Protocol was changed to have participants start at 90% MT and increase gradually over 2 to 3 days to 110% MT.	N/A	N/A	N/A	<u>Dropouts during treatment phase</u> 4 participants dropped out during the first 3 days of dTMS due to the uncomfortable sensation of increasing the % MT from 100 to 120%.

	▪ Authors did not report side effects or adverse events.				**Could not calculate dropout rate (authors did not report original sample size)*
(Paz et al., 2018)	▪ No major side effects reported. ▪ 1 participant withdrew after 5 sessions due to headaches (did not specify treatment condition).	NR	NR	4/26 (15.38 %)	<u>Dropouts during treatment phase:</u> 1 patient did not attend any treatment sessions; 2 patients withdrew due to inconvenience; and 1 patient withdrew due to headaches. *Study did not report dropouts by treatment group.*
(Addolorato et al., 2017)	NR	NR	NR	NR	*No dropouts were reported during the treatment phase*
(Tavares et al., 2017)	▪ Scalp pain was present in the active dTMS group (20%) but not in the sham (0%) group (p = 0.05). ▪ No significant group differences in headaches, neck pain, burning sensations, hearing complaints and concentration difficulties were found.	5/25 (20%)	2/25 (8.0%)	7/50 (14.0 %)	<u>Dropouts during treatment phase:</u> Active dTMS: missed visits (n = 2), severity of depressive symptoms (n = 1), and headaches/scalp irritation (n = 1) Sham dTMS: missed visits (n = 2)
(Bolloni et al., 2016)	No discomfort observed, apart from 1 report of a mild headache in the active group.	1/10 (10%)	3/8 (37.5%)	4/18 (22.22 %)	<u>Dropouts during treatment phase:</u> Active dTMS: n = 1 Sham dTMS: n = 3 *Reason for dropouts were not reported by the authors*
(Ceccanti et al., 2015)	NR	7/9 (77.77%)	9/9 (100%)	16/18 (88.89 %)	*No dropouts were reported during the treatment phase* <u>Dropouts during maintenance phase:</u> Active dTMS group: n = 7 dropped out by the

					6th month (reasons not provided) Sham group: n = 9 dropped out by the 6th month (reasons not provided).
(Girardi et al., 2015)	NR. Treatment was well-tolerated by all patients.	NR	NR	NR	*No dropouts were reported*
(Levkovitz et al., 2015)	▪ There was a significant difference in reports of application site pain (p = 0.02) between the active and sham conditions. ▪ <u>Sham condition</u>: 21 participants (18.9%) experienced headaches, 4 (3.6%) insomnia, 3 (2.7%) back pain, 2 (1.8%) application site discomfort, and 2 (1.8%) anxiety. No application site pain was reported. ▪ More serious adverse events included accounts of suicidal ideation (n = 2), nausea and vomiting (n = 1), and nephrolithiasis (n = 1). ▪ <u>Active dTMS condition</u>: 27 participants (26.7%) reported headaches, 5 (5.0%) application site pain, 3 (3.0%) application site discomfort, 2 (2.0%) muscle twitching, 2 (2.0%) back pain, and 2 (2.0%) insomnia. ▪ More serious adverse events included an elbow fractures (n = 1), a cluster headache (n = 1), and a seizure (n = 1).The seizure was appraised as device related. ▪ There was a suicide attempt (n = 1) from subject who was not randomized to the study.	Active dTMS: 46/89 (51.69%)	Sham group: 64/92 (69.57%)	110/181 (60.77 %)	<u>Dropouts during treatment phase</u> Active dTMS group: lost to follow-up (n = 1), missed treatments (n = 1), a seizure (n = 1), self-reports of no improvement (n = 3), and withdrawal of consent (n = 1). Sham dTMS group**:** safety concerns (n = 3), non-compliance (n = 2), suicidal ideation (n = 1), intolerability of abstaining from medications (n = 1), self-reports of no improvement (n = 3), worsening symptoms (n = 1), withdrawal of consent (n = 2), and other (n = 2). <u>Dropouts during maintenance phase:</u> Active dTMS group**:** no significant improvement (n = 24), safety concerns (n = 2), missed treatments (n = 1), non-compliance (n = 2), and withdrawal of consent (n = 10).

					Sham dTMS group: no significant improvement (n = 27), safety concerns (n = 1), missed treatments (n = 2), non-compliance (n = 1), and withdrawal of consent (n = 18).
(Dinur-Klein et al., 2014)	▪ Headaches and nausea were reported by 3 participants in the sham condition, 1 in the LF condition and 2 in the HF condition. ▪ 2 participants in the LF condition reported discomfort with the treatment.	HF group: 21/50 (42%) LF group: 12/24 (50%)	Sham group: 14/41 (34.15%)	38/115 (33.04 %)	<u>Dropouts during treatment phase</u> HF group: lack of time (n = 5); personal reasons unrelated to treatment (n = 2) headaches/nausea (n = 2); treatment discomfort (n = 0); reason not provided (n = 9). LF group: lack of time (n = 1); personal reasons unrelated to treatment (n = 1) headaches/nausea (n = 1); treatment discomfort (n = 2); reason not provided (n = 5). Sham group: lack of time (n = 2); personal reasons unrelated to treatment (n = 1) headaches/nausea (n = 3); reason not provided (n = 4). <u>Dropouts during follow-up phase</u> HF group: loss to follow-up (n = 3)

					LF group: loss to follow-up (n = 2) Sham group: loss to follow-up (n = 4)
(Enticott et al., 2014)	▪ No serious adverse events reported. ▪ 1 participant reported transient light-headedness following treatment ▪ 2 participants reported mild facial discomfort during treatment.	1/16 (6.25%)	1/14 (7.14%)	2/30 (6.67 %)	<u>Dropouts during treatment phase</u> Active group: unrelated ongoing health problems (n = 1) <u>Dropouts during follow-up phase</u> Sham group: refused to complete assessments (n = 1)
(Rabany et al., 2014)	NR	NR	NR	NR	NR
(Isserles et al., 2013)	▪ Most patients did not experience any side effects and treatment was well tolerated. ▪ Mild headaches were reported at the beginning of the treatment period in some patients. ▪ 1 patient experienced increased anxiety and withdrew after the 4th session (EXP-STIM group) ▪ Another withdrew at after the 2nd session due to feeling uncomfortable with treatment (EXP-STIM group) ▪ 1 patient in the EXP-SHAM group reported discomfort with the treatment and study requirements and withdrew after the 4th session. ▪ 1 patient (EXP-STIM group) had a transient generalized seizure at the end of the 8th session	EXP-stim group: 1/10 (10%) NOEX-STIM group: 2/10 (20%)	EXP-sham group: 1/10 (10%)	4/30 (13.33 %)	<u>Dropouts during treatment phase</u> EXP-STIM group: seizure (n = 1). NOEX-STIM group: significant discomfort (n = 1); increased anxiety (n = 1). EXP-SHAM group: significant discomfort (n = 1)

(Rosenberg et al., 2012)	▪ One patient reported mild headaches after 2 treatments (treatment group not specified). ▪ No other side effects were observed.	4/9 (44%)	4/9 (44%)	8/18 (44.44 %)	<u>Dropouts during treatment phase</u> Active dTMS group: delusions about magnet (n = 1), inability to tolerate treatment (n = 1), worsening psychotic symptoms (n = 1), and psychotic exacerbation (n = 1). Sham group: self-harm ideation/obsessive thoughts (n = 1), inability to tolerate sensation of pulse (n = 1), delusions about coil (n = 1) and no reason provided (n = 1).

Clinical outcomes

The clinical outcomes across studies by psychiatric or cognitive disorder are summarized in detail in Table 5. A meta-analysis was not feasible for the purposes of our review due to the heterogeneity in study design in studies examining the clinical efficacy of dTMS for a given psychiatric/cognitive disorder. Current evidence largely supports the clinical efficacy of dTMS for depressive episodes in BD or MDD. Six clinical trials (*n* = 6; 100%; Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) utilizing the H1-coil for the treatment depressive episodes in patients with MDD or BD noted significant improvements in depressive symptoms, outperforming sham dTMS (Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) and standard pharmacotherapy (Filipčić et al., 2019; Gajšak et al., 2023). Of the two clinical trials investigating dTMS in patients

with OCD, both trials (Carmi et al., 2019, 2018) produced positive findings (*n* = 2; 100%), with active dTMS demonstrating superiority over sham. Moreover, several trials showed evidence supporting dTMS clinical efficacy in patients with SUDs. Four out of five trials (*n* = 4; 80%; Addolorato et al., 2017; Ceccanti et al., 2015; Girardi et al., 2015; Harel et al., 2022) had positive findings in patients with AUD. Moreover, all four trials (*n* = 4; 100%) in patients with nicotine dependence (Dinur-Klein et al., 2014; Ibrahim et al., 2023; Moeller et al., 2022; Zangen et al., 2021) showed active dTMS as superior to sham. Of the two trials investigating dTMS for CUD (Bolloni et al., 2016; Martinez et al., 2018), authors reported no effect of treatment condition (i.e., active vs sham dTMS) on cocaine craving levels (Martinez et al., 2018) or cocaine intake (Bolloni et al., 2016), though improvements were noted in the active dTMS groups relative to the other conditions. Furthermore, one study (Leocani et al., 2021) reported dTMS as superior to sham in patients with Alzheimer's disease, though this effect was only trend-level and no longer present at the two-month follow-up. Another clinical trial (Enticott et al., 2014) found significant social functional improvements in patients with ASD who received a course of active dTMS (as compared to sham). Lastly, the clinical efficacy of dTMS was heterogeneous in psychiatric disorders characterized by hyperactivity or hyperarousal, specifically, in patients with ADHD, BD, PTSD, and schizophrenia. Here, we provide a detailed analysis of the clinical efficacy of dTMS by psychiatric or cognitive disorder.

Alzheimer's Disease

In the clinical trial by (Leocani et al., 2021), dTMS was found to be superior to sham (trend-level) for the treatment of Alzheimer's disease. However, such effects were short-term and were no longer evident two months posttreatment, suggesting that the efficacy cannot be assumed to be robust across time. This aligns with a recent meta-analysis (Chou et al., 2020) reporting rTMS effects could last between 4 -12 weeks in patients with Alzheimer's disease. Notably, the present review of dTMS on Alzheimer's disorder was limited to one study and only found trend-level significance.

Attention-deficit/hyperactivity disorder

In patients with ADHD, three clinical trials used the H5 (Paz et al., 2018) and H6 (Alyagon et al., 2020; Bleich-Cohen et al., 2021) coils to target the bilateral, left, or right PFC. The results were heterogeneous. One study (Alyagon et al., 2020) reported that dTMS was superior to sham according to changes in the Conners' Adult ADHD Rating Scales (CAARS) scores. Contrarily, another study (Bleich-Cohen et al., 2021) found that this group effect was dependent on the scale (or subscale) used, as well as the given timepoint. A previous meta-analysis (Westwood et al., 2021) found that traditional rTMS produced little to no significant clinical improvements in patients with ADHD. A sham-controlled RCT (Bloch et al., 2010) reviewed by Westwood et al. (2021) found that traditional rTMS of the right PFC improved attention in ADHD participants but had no effect on mood or hyperactivity symptoms. It is possible that stimulation of the PFC may only mitigate a subset of ADHD symptoms, such as attention deficits or memory problems. In line with this idea, the included trial by Bleich-Cohen et al. (2021) found

that participants who underwent rPFC stimulation compared to sham stimulation had greater improvements on the CAARS self-report Inattention/Memory Problems subscale. Further investigation is required to determine the optimal target sites for stimulation in individuals with ADHD to encompass and target a diverse range of ADHD symptoms. A previous open-label trial (Gómez et al., 2014) found that rTMS of the left DLPFC reduced hyperactivity, inattention, and impulsivity in children with ADHD. It is possible, therefore, that unilateral stimulation of the DLPFC may produce effects on a specific subset of ADHD symptoms. Sham conditions are also necessary for future clinical trials to rule out the possibility of a placebo effect.

Autism Spectrum Disorder

One clinical trial (Enticott et al., 2014) reported significant improvements in social functioning in members of the active group compared to the sham group, as measured by the the Ritvo Autism Asperger Diagnostic Scale (RAADS) social relatedness scale and self-oriented anxiety regarding emotional social situations. Treatment had no effect on communication, language, or sensorimotor functioning. Ten sessions of stimulation using the HAUT-coil targeted the dorsomedial PFC (dmPFC) in participants with ASD. The dmPFC is a central region involved in processing social interactions and social cognition (Wagner et al., 2016). Reduced activity in the dmPFC, among other regions of the PFC, have been associated with social deficits when making social judgments toward others (Watanabe et al., 2012). It is possible that stimulation of the dmPFC could revert dysfunction to these areas, thus leading to improvements in

social functioning. However, due to the limited number of studies on ASD, future research is warranted to corroborate the findings of this study (Enticott et al., 2014). It is also worth exploring if targeting other brain regions using various H-coils could be beneficial for other symptoms of ASD, such as common impairments in communication, language, or sensorimotor functioning. Given the high co-morbidity of ASD and ADHD, further research is warranted to determine if the therapeutic effects of dTMS for ADHD may be similar to those for ASD.

Bipolar disorder

One sham-controlled clinical trial (Tavares et al., 2017) examined the efficacy of dTMS in patients with bipolar disorder experiencing an active depressive episode. Tavares et al. (2017) found that applying dTMS to the left DLPFC produced short-term, clinically superior results compared to sham treatment. Specifically, active dTMS was superior to sham in the HDRS change from baseline to week 4 ($p = 0.03$) and week 6 ($p = 0.02$), but not at later timepoints. Moreover, there was a trend for greater response rates in the active (48%) vs. sham condition (24%) at week 4 ($p = 0.08$).

Corroborating these findings, rTMS of the right DLFPC using the traditional figure-8 coil has shown greater clinical efficacy in patients with acute bipolar depression compared to sham (McGirr et al., 2016). Previous studies have produced contrasting results. For instance, a former pilot study (Nahas et al., 2003) found that rTMS of the left PFC using the figure-8 coil did not produce significant clinical effects compared to sham in patients with bipolar affective disorder. Likewise, findings from another sham-

controlled trial (Fitzgerald et al., 2016), which applied rTMS to the bilateral DLPFC using the figure-8 coil, did not demonstrate the superiority of rTMS over sham in patients with BD. Given these heterogenous findings and the limited number of trials investigating dTMS for BD, further investigation is warranted to examine the clinical effects of dTMS in bipolar disorder— specifically, whether DLPFC stimulation induced by the H1-coil produces superior clinical efficacy compared to sham.

Bipolar disorder/ Major depressive disorder

The study by Matsuda et al. (2020) examined the use of active dTMS over the left DLPFC compared to sham dTMS in patients with MDD or BD with a current major depressive episode. From baseline to week 6, the authors noted larger and superior reductions in HDRS-21 scores of the active group relative to sham ($p = 0.045$). Although at week 6, there were no significant group differences in response ($p = 1.0$) and remission rates ($p = 0.677$) or cognitive functioning. Consistent with these results, Tavares et al. (2017) observed clinically superior reductions in depressive scores in patients with BD. Both trials (Matsuda et al., 2020; Tavares et al., 2017) targeted the left DLPFC using the H1-coil and found that active dTMS was clinically superior to sham. Therefore, the left DLPFC may be a valuable stimulation site for patients experiencing depressive episodes and who have diagnosis of BD or MDD. Further evidence supporting the clinical efficacy of DLPFC stimulation for patients with MDD is discussed below.

Major depressive disorder

In patients with MDD, dTMS of the left DLPFC using the H1-coil produced significant clinical effects. Three clinical trials (Filipčić et al., 2019; Kaster et al., 2018; Levkovitz et al., 2015) in MDD patients demonstrated superior response and remission rates in the active dTMS groups compared to the sham/control groups. In addition, one trial (Gajšak et al., 2023) found greater reductions in the Beck Hopelessness Scale (BHS) scores in MDD patients assigned to the active dTMS arm (10.8%; 95% CI: −17.8% to −3.9%) compared to the standard of care pharmacotherapy control arm (0.7%; 95% CI: 7.5% −6.1%; $p = 0.037$; FDR < 5%).

In total, six trials (Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) targeted the left DLPFC using the H1-coil in patients experiencing major depressive episodes, all of which produced clinically significant results compared to the sham/control arm. In a recent meta-analysis (Kan et al., 2023), rTMS of the left DLPFC relative to sham stimulation was found to have a medium effect size on depressive symptoms (Hedges' g -0.725, 95% CI = –0.889 to –0.561; $p < 0.0001$). Hypoactivity of the DLPFC has been observed in MDD patients (Akiyama et al., 2018; Fales et al., 2008), which is thought to mediate emotion dysregulation. HF dTMS has been shown to induce excitatory effects and promote long-term potentiation of neural synapses (Fitzgerald et al., 2006). Thus, stimulation of the hypoactive DLPFC in MDD patients could restore neural activity levels and enhance neural plasticity, thereby producing significant therapeutic effects compared to sham. The longevity of such clinical effects is needed to determine how often patients should undergo dTMS maintenance sessions to prevent relapse.

Obsessive-compulsive disorder

Two clinical trials (Carmi et al., 2019, 2018) supported dTMS as a clinically effective OCD treatment compared to sham. In a recent meta-analysis of sham-controlled trials (Fitzsimmons et al., 2022), rTMS of the DLPFC and mPFC were found to be efficacious for OCD. With the H7-coil targeting the mPFC, this may explain the observed significant clinical effects in the aforementioned trials (Carmi et al., 2019, 2018). However, the durability or long-term sustainability of dTMS remains uncertain. Significance between groups was lost at the 1-month follow-up in the study by Carmi et al. (2018). In contrast, a long-term analysis (Harmelech et al., 2022) of the more recent study (Carmi et al., 2019) reported an average dTMS durability of ≥ 1.98 (± 0.13) years post-treatment. However, long-term outcomes between active dTMS vs. sham were not explored. Further research is required to examine the long-term outcomes of dTMS treatment, and whether dTMS treatment effects are sustainable. Furthermore, the level of perceived distress during exposure treatments in combination with dTMS may be another important factor to consider. A post-hoc analysis (Guzick et al., 2022) of the large multi-center trial (Carmi et al., 2019) found that participants' level of perceived distress following exposures played a key role in dTMS treatment efficacy. Specifically, higher distress during provocations was associated with an increased active versus sham response, while this difference was less pronounced among patients who reported lower levels of distress.

Posttraumatic stress disorder

For patients with PTSD, two clinical trials (Isserles et al., 2021, 2013) applied stimulation using the H1 (Isserles et al., 2013) and H7 (Isserles et al., 2021) coils. The efficacy of active dTMS compared to sham showed varying degrees of superiority. The first study (Isserles et al., 2013) found that improvements in the Clinician-Administered *PTSD* Scale (CAPS) scores were only significant in the exposure + dTMS group compared to the exposure + sham group and dTMS alone. It is possible that exposure processes play an important role as potential moderators of treatment success, requiring further investigation. In line with these findings, a longitudinal fMRI study (Zhu et al., 2018) found that exposure therapy in PTSD patients led to enhanced resting-state FC between the amygdala and the hippocampus-mPFC, indicating that exposure therapy may help to restore normal levels of mPFC-to-amygdala inhibition as well as moderate threat-appraisal. More replication on exposure therapy for PTSD in concurrence with dTMS is required, given that sham-controlled dTMS studies in PTSD populations are limited and findings to date have been equivocal. Furthermore, existing research (Boggio et al., 2010; Cohen et al., 2004; Leong et al., 2020) has found rTMS of the right DLPFC has produced greater improvements in PTSD symptoms compared to the left DLPFC. A clinical trial by Rosenberg et al. (2002) found that rTMS of the left frontal cortex using the F8-coil only marginally improved core PTSD symptoms. Therefore, hemispheric targeting may be an important factor to consider when customizing dTMS for patients with PTSD.

The study by Isserles et al. (2021) found greater improvements favouring the sham condition compared to the active dTMS condition. Participants received stimulation

targeting the ACC and mPFC using the H7-coil, with both conditions receiving a traumatic exposure. The mPFC has been highly implicated in emotion dysregulation processes observed in PTSD (Koenigs and Grafman, 2009). Moreover, hypoactivation of the ACC and ventromedial PFC is highly associated with emotional regulation difficulties in individuals suffering from PTSD (Etkin and Wager, 2007). It is unclear why sham dTMS was more favourable than active dTMS, given that the brain regions targeted (i.e., ACC and mPFC) are known to be underactive in PTSD. It is possible that the different brain structures stimulated by the two coils in the former (Isserles et al., 2013; H1 coil) and later study (Isserles et al., 2021; H7 coil) may explain the contrasting results in the two studies. Further research is warranted to evaluate the efficacy of the different H-coils for the treatment PTSD.

Schizophrenia and related disorders

Positive symptoms. Evidence supporting the clinical efficacy of dTMS for positive symptoms of schizophrenia was heterogeneous. LF rTMS to the left temporoparietal junction (TPJ) has been previously associated with improvements in auditory hallucinations in patients with schizophrenia (Xie et al., 2021). One clinical trial (Rosenberg et al., 2012) included in our review aimed to target this region using the H1-coil in patients with schizophrenia. Though improvements in auditory hallucinations were found in both groups, active dTMS was not superior to sham (Rosenberg et al., 2012). The H1-coil primarily targets the bilateral DLPFC, and thus, it is possible that such coil may not result in adequate stimulation of the left TPJ to produce significant improvements in auditory hallucinations relative to sham. Using the H1-coil, another trial

(Rabany et al., 2014) noted trend-level improvements in Positive and Negative Syndrome Scale (PANSS) scores in the active treatment group, but not the sham group. However, group differences were nonsignificant. Another trial (Moeller et al., 2022) noted significant reductions in positive symptoms in the active dTMS group following stimulation of the PFC and insula ($p = 0.011$), but not in the sham group ($p = 0.84$). Interestingly, a meta-analysis (Kennedy et al., 2018) reported that rTMS of the TPJ or PFC significantly ameliorated hallucinations (Hedge's g = -0.51, $p < 0.001$) relative to sham, but was associated with poorer outcomes for other positive symptoms (Hedge's g = 0.28, $p = 0.13$). Therefore, further research is warranted to evaluate the efficacy of dTMS in targeting specific positive symptoms of schizophrenia.

Negative symptoms. Evidence supporting the clinical efficacy of dTMS for negative symptoms of schizophrenia was limited. Findings from the meta-analysis by Kennedy et al. (2018) highlighted significant improvements in negative symptoms following active rTMS of the TPJ or PFC (Hedge's g = -0.49, $p = 0.01$) relative to sham treatment. Moreover, previous research in the absence of a sham condition have noted significant improvements in negative symptoms following dTMS stimulation of the left DLPFC (Levkovitz et al., 2011; H1-coil) and bilateral PFC (Linsambarth et al., 2019; H2-coil). By contrast, Rosenberg et al. (2012) did not observe any reduction in negative symptoms in either the active (H1-coil) or sham condition. Moeller et al. (2022) also failed to observe any reduction in negative symptoms following dTMS of the PFC and insula (using the H4-coil) in either the active or sham conditions. Although, Rabany et al. (2014) observed significant reductions in negative symptoms in the H1-coil dTMS group

but not in the sham condition. However, group differences were not statistically significant. It is important to consider this study's (Rabany et al., 2014) small sample size (N = 30), which may have limited its ability detect significant differences between treatment groups. Subsequent research employing double-blind sham-controlled studies with larger sample sizes is necessary to explore the efficacy of dTMS in alleviating negative symptoms in schizophrenia. Moreover, sham-controlled trials are needed to determine if dTMS can offer clinical improvements in patients with schizophrenia, as well as if various brain regions targeted by diverse H-coils may produce differential effects on subsets of symptoms (i.e., positive vs. negative schizophrenia symptoms).

Substance use disorders

Across studies in patients with SUDs, stimulation varied across regions within the PFC – including the mPFC, DLPFC, and lateral PFC – and the insula. Previous research has identified the PFC as a critical region thought to mediate impulsivity and destructive behaviours associated with substance use (Goldstein and Volkow, 2011). The PFC has regulatory connections to the brain's reward circuits (Chau et al., 2018) and higher-order cortical regions (Kim et al., 2020; St Onge and Floresco, 2010) which are involved in self-control, executive functioning, and decision-making. Thus, it is posited that stimulation of the PFC could potentially enhance neural plasticity, restore regulatory functioning, and produce therapeutic benefits in patients with SUDs.

Alcohol use disorder/alcohol dependence. The majority of clinical trials examining dTMS for alcohol dependence found favourable results. Four clinical trials (Addolorato et al., 2017; Ceccanti et al., 2015; Girardi et al., 2015; Harel et al., 2022)

reported dTMS as superior to sham in patients with alcohol dependence (*Note.* One of these trials [Girardi et al., 2015] was in patients with comorbid AUD and dysthymic disorder). In contrast, one clinical trial (Perini et al., 2020) reported no effect of group on alcohol consumption or self-reported use at any timepoint ($p > 0.3$). Interestingly, the four clinical trials that reported dTMS as superior to sham targeted various regions of the PFC— which is heavily innervated with the brain's reward circuits (Chau et al., 2018) and higher-order cortical regions thought to mediate substance use behaviors (Kim et al., 2020; St Onge and Floresco, 2010). Contrarily, Perini et al. (2020) solely targeted the insula. The current literature's insights on the insula's role in AUD is conflicting, with studies showing reduced insular activity during abstinence, but increased activity in response to alcohol cues or during alcohol consumption (Campbell and Lawrence, 2021). As dTMS aims to enhance neural activity within the target region(s), it is still unclear whether stimulation of the insula would be an effective treatment for alcohol dependence given that this region shows increased activity in AUD patients who are not abstaining from alcohol.

Collectively, dTMS of the PFC appears to be effective in treating patients with alcohol dependence or AUD. However, the sustainability of treatment gains has not yet been addressed sufficiently by current clinical trials, with follow-ups being short-term in duration (< 6 months). One study (Ceccanti et al., 2015) found significant improvements in daily alcohol consumption favouring active dTMS to sham for up to three months post-stimulation, although at later follow-ups significance was lost. Likewise, another study (Girardi et al., 2015) reported significant differences in HDRS scores between active and

sham groups at the end of treatment. However, such differences were lost at the 6-month follow-up. A recent systematic review (Kedzior et al., 2018) examining dTMS for the treatment of SUDs suggests that the effects of dTMS may last up to 12 months, without the need for further follow-up sessions. Future clinical trials should assess the long-term effects (> 6 months) of dTMS to determine the average durability of intervention effects.

Nicotine/tobacco use disorder (dependence). In patients with nicotine dependence, Dinur-Klein et al. (2014) reported that HF dTMS of the insula using the H4-coil was superior to sham for reducing abstinence rates and cigarette consumption. There were no group differences between the LF and sham groups, suggesting that HF stimulation is more effective at producing significant clinical improvements compared to LF stimulation. Another study (Moeller et al., 2022) found that smoking-self administration was significantly lower in the active dTMS group (H4-coil) at the post-treatment session following HF stimulation of the bilateral insula ($p = 0.044$), but not in the sham group ($p = 0.30$). Moreover, one trial (Zangen et al., 2021) demonstrated that active dTMS using H4-coil was clinically superior to sham in terms of continuous quit rates and cigarette consumption. Interestingly, decreases in craving levels after dTMS treatment were predictive of smoking cessation only within the active group (OR: active = 1.57, $p = 0.004$; OR: sham = 0.85, $p = 0.46$). Furthermore, one trial (Ibrahim et al., 2023) reported that abstinence rates were significantly higher at week 12 in the active dTMS + varenicline group (82.4%) compared to the sham + varenicline group (30.7%; $p = 0.013$). However, group differences were no longer present week 26 ($\chi^2_{[1]} = 0.015$, $p = 0.90$). Authors noted a trend-level treatment effect on nicotine

dependence favouring the active arm to the sham arm (p =0.071, n^2 = 0.08; Ibrahim et al., 2023). In line with existing literature, the insula is thought to play a central role in nicotine cravings and the maintenance of smoking behaviors (Menossi et al., 2013). Hence, the insula has gained recognition as a viable neurostimulation target to induce smoking cessation (Regner et al., 2019). Based on the findings of this review, dTMS presents as an effective, non-invasive treatment option that can be used to stimulate the insula and assist patients struggling with nicotine/tobacco use disorder.

One aspect that requires further investigation is the implementation of smoking cues. Dinur-Klein et al. (2014) noted that the presence or absence of smoking cues had a significant effect on certain measures (i.e., The Fagerström Test for Nicotine Dependence [FTND]), whereas for other measures, there was no effect (i.e., number of cigarettes smoked per day and response rates). For example, there was cue x treatment effect on FTND scores in the HF group ($F_{(2,73)}$ = 3.77, p = 0.028), yet there was no significant effect of cue on response rates (i.e., a reduction in cigarette consumption by 50%; χ^2_1= 1.2, p = 0.26). Potential moderators of treatment success, such as the presence or absence of smoking cues, should be further systematically investigated.

Cocaine use disorder. In patients with CUD, two clinical trials (Bolloni et al., 2016; Martinez et al., 2018) found no effect of treatment condition (i.e., active vs sham dTMS) on cocaine cravings levels (Martinez et al., 2018) or cocaine intake (Bolloni et al., 2016), although significant reductions in cocaine use were observed in the active groups. Martinez et al. (2018) targeted the mPFC and dACC using the H7-coil, whereas Bolloni et al. (2016) targeted the bilateral PFC using the H1-coil. Cocaine administration in rat

models have shown reduced ACC activity (Vázquez et al., 2020). Human trials have also demonstrated diminished activity in the ACC and mPFC in cocaine dependent users (Canterberry et al., 2016). It is possible that the authors of the former study (Martinez et al., 2018) aimed to revert this hypoactivity by applying stimulation to the ACC and mPFC. Further research is needed to investigate the efficacy of dTMS for CUD using sham-controlled conditions, as it is a relatively new area of research with the addition of CUD to DSM-5 occurring within the past decade.

Comorbid conditions

Comorbid schizophrenia / schizoaffective disorder & tobacco dependence. A single trial by (Moeller et al., 2022) examined active versus sham dTMS in patients with (1) schizophrenia or schizoaffective disorder and (2) tobacco dependence. After 15 sessions of dTMS using the H4-coil to target the insula, smoking-self administration was notably reduced in the active dTMS group ($b = -0.30$, SE = 0.15, $p = 0.044$) but not in the sham group ($p = 0.30$). Although, no effect of treatment was observed for number of cigarettes smoked. Correspondingly, TMS of the insula has been researched in substance use disorders for its involvement in decision-making processes, pain, and reward associated with addictive behaviours (Droutman et al., 2015) and has shown promising results (Ibrahim et al., 2019).

Regarding schizophrenia or schizoaffective symptoms, a reduction in positive symptoms across four timepoints was found in active dTMS group ($b = -0.91$, SE = 0.36, $p = 0.011$) but not in the sham group ($p = 0.84$). Conversely, negative symptoms did not change in either group. Existing TMS research suggests negative symptoms of

schizophrenia may be effectively mitigated by targeting the left DLPFC (Cole et al., 2015; Lorentzen et al., 2022). Therefore, it is possible that individuals suffering from comorbid schizophrenia/schizoaffective disorder may benefit from dTMS to the DLPFC to treat and alleviate refractory negative symptoms.

Comorbid alcohol use disorder & dysthymic disorder. One clinical trial (Girardi et al., 2015) compared the effectiveness of active dTMS of the DLPFC using the H1-coil as an adjunct to standard pharmacotherapy – versus standard pharmacotherapy alone – in individuals with comorbid AUD and dysthymic disorder. Following treatment, craving scores and depressive symptoms were notably more reduced in the active dTMS group compared to the standard pharmacotherapy group ($p < 0.001$ and $p < 0.02$, respectively). There was an effect of treatment condition on HDRS scores from week 1 to post-treatment, with the active dTMS group showing greater reductions in HDRS scores compared to the control group. However, this significant group difference was lost at the sixth month follow-up. Nonetheless, this trial supports dTMS as a multimodal intervention which could be used to alleviate various symptoms associated with comorbid psychiatric conditions in a single course of treatment.

Table 5. Summary of Clinical Outcomes Across Studies

Study by Psychiatric/Cognitive Disorder	Clinical Outcomes
Alzheimer's disease	
(Leocani et al., 2021)	▪ Active dTMS group showed a trend-level mean decrease score of −1.01 per time point (95% CIs = −0.02 to −3.13, $p < 0.04$) relative to the sham group. However, this trend disappeared 2 months post-treatment. ▪ Changes in ADAS-cog scores greatly varied depending on the participant. ▪ Active dTMS in comparison to sham dTMS showed no effects on MMSE, CGI-I, and BDI changes over time.
Attention-deficit/hyperactivity disorder	

(Bleich-Cohen et al., 2021)	▪ CAARS observer total and self-report subscales demonstrated no effect of group on score changes from baseline to end of treatment ($F_{(2,56)} = 1.325$, $p = 0.27$ and $F_{(2,56)} = 1.495$, $p = 0.23$ respectively). ▪ A significant group effect was found for CAARS self-report Inattention/Memory Problems subscale ($F_{(2,56)} = 4.03$, $p = 0.023$) relative to baseline. This effect was observed between the rPFC and sham conditions ($p = 0.018$). ▪ rPFC and lPFC groups showed CAARS improvements in the self-report Inattention/Memory Problems subscale at the first FU visit (rPFC $p < 0.00005$; lPFC $p < 0.05$) which were maintained at later FU visits (rPFC $p < 0.00005$; lPFC $p < 0.05$), whereas no change was observed in the sham group. ▪ CGI scores improved in all 3 conditions (with greatest improvement in the rPFC arm) but were only trend-level.
(Alyagon et al., 2020)	▪ Mean CAARs improvements: H6-coil group= 8.27 ± 1.83, active control (F8-coil)= 2.84 ± 1.96, sham= 1.86 ± 1.90. Improvements were only significant in the H6-coil group. ($F_{(1,39)} = 20.45$, $p_c = 0.00085$; $\eta^2_p = 0.34$; Cohen's $d_{(against\ Sham)} = 0.96$; Cohen's $d_{(against\ AC)} = 0.68$). ▪ Response rates (≥25% reduction in total CAARS score) in the H6-coil and sham groups were 40.0% and 7.1% ($p = 0.08$), respectively. ▪ Response rates between the H6-coil and F8-coil group (40.0% and 21.4%, respectively) were nonsignificant ($p = 0.43$). ▪ There was a trend-level time x group effect favouring H6-coil group ($F_{(2,32)} = 1.14$, NS) at the 1-month FU. Mean improvements in CAARs were 9.55 ± 3.17, 3.09 ± 3.17, and 4.61 ± 2.92 for the H6-coil, F8-coil, and sham groups respectively at this timepoint. ▪ Responses rates were 36%, 25%, and 15% for the real, active control, and sham groups respectively at the 1-month FU. ▪ Distinct improvements in the CAARS' "hyperactivity/impulsivity" domain were observed in the H6-coil group compared to control groups. ▪ No significant changes in BDI scores were observed in any condition ($F_{(2,39)} = 1.17$). ▪ Stroop task performance significantly improved in the active group compared to sham ($F_{(1,26)} = 21.21$, $p_c = 0.00057$; $\eta_p^2 = 0.45$), but not when compared to the F8 group ($F_{(1,26)} = 0.19$, n.s). ▪ Stroop task performance and clinical improvement in ADHD symptoms were positively correlated in the H6-coil group ($r_{(13)} = 0.85$, $p_c = 0.001$. However, this correlation was not found in either the F8-coil ($r_{(11)} = -0.09$, n.s) or sham ($r_{(11)} = 0.26$, n.s) groups.
(Paz et al., 2018)	▪ There was no effect of treatment condition ($F_{(1,20)} = 0.148$, $p = 0.704$, $\eta^2_{partial} = 0.01$) or treatment condition x time ($F_{(1,20)} = 0.022$, $p = 0.833$, $\eta^2_{partial} = 0.001$) on CAARS scores. ▪ There was an effect of time on CAARs improvement in both conditions ($F_{(1,20)} = 8.688$, $p < 0.01$, $\eta^2_{partial} = 0.3$). Participants in the active condition had a baseline and endpoint mean of 79 ± 3.02 and 72.11 ± 4.34, respectively. Sham participants had scores of 77 ± 3.22 and 70.77 ± 3.05 for the same measures. ▪ TOVA scores did not improve over time and no group differences were observed. Effect of time ($F_{(3,60)} = 1.267$, $p = 0.29$, $\eta^2_{partial} = 0.06$), effect of treatment ($F_{(1,20)} = 3.36$, $p = 0.08$, $\eta^2_{partial} = 0.14$), and effect of treatment x time ($F_{(3,60)} = 0.16$, $p = 0.92$, $\eta^2_{partial} = 0.01$.) on TOVA were nonsignificant.

Autism spectrum disorder

(Enticott et al., 2014)	▪ Significant improvements in the RAADS social relatedness items were seen in the active but not sham group. RAADs symptoms were significantly reduced in the active group compared to sham at both post-treatment ($F_{(1,26)} = 9.86$, $p = 0.004$, d = 1.18) and the 1-month follow-up ($F_{(1,26)} = 14.05$, $p = 0.001$, d = 1.41). ▪ Treatment had no effect on the communication, language, or sensorimotor functioning. ▪ Active group participants had significantly lower self-oriented anxiety regarding emotional social situations, according to the IRI personal distress items, ($F_{(2,28)} = 4.16$, $p = 0.026$) at the 1-month follow-up. This effect was not observed in sham participants ($F_{(2,24)} = 0.92$, $p = 0.412$). However, no significant group differences were observed. ▪ Participants in the active condition showed a reduction on the IRI fantasy subscale from baseline to the 1-month FU ($p = 0.026$). This change was nonsignificant from baseline to posttreatment ($p = 0.580$) and from posttreatment to the 1-month FU ($p = 0.079$). ▪ Neither condition had an improvement in the IRI "perspective taking" or "empathic concern" subscales. ▪ There was no time x condition effect for the AQ social relating subscale.
Bipolar disorder	
(Tavares et al., 2017)	▪ Authors found an effect of time ($F_{(5,240)} = 25.38$, $p < 0.001$) and a significant time x group interaction ($F_{(5,240)} = 2.26$, $p = 0.046$) on treatment outcomes (ITT analysis). ▪ Active dTMS was superior to sham at weeks 4 (difference= 4.88 points, 95% CI = 0.43 to 9.32, $p = 0.03$) and 6 (difference= 5.2 points, 95% CI = 0.75 to 9.64, $p = 0.02$) but not at other time points (ITT analysis). ▪ At week 4, 48% of participants from the active condition and 24% of sham participants had a significant response (i.e., ≥ 50% improvement from baseline HDRS score). However, this group difference was not statistically significant (OR = 2.92, 95% CI 0.87–9.78, $p = 0.08$). ▪ Remission rates did not differ between active and sham conditions at any time point.
Bipolar disorder/ Major depressive disorder	
(Matsuda et al., 2020)	▪ From baseline to week 6, the active group had larger reductions in HDRS-21 scores relative to sham that were considered to be superior ($p = 0.045$). ▪ There were no significant group differences in response (active: 15%, sham: 15%, p = 1.0) and remission rates (active: 20%, sham: 15%, p = 0.677) at week 6. ▪ No significant differences were found between the sham and active groups for the Trail Making Test, Stroop test, or Young Mania Rating Scale at any timepoint.
Major depressive disorder	

(Gajšak et al., 2023)	▪ Reduction in BHS scores was greater in the dTMS group (10.8%; 95% CI: −17.8% to −3.9%) compared to the control group (0.7%; 95% CI: 7.5% −6.1%; $p = 0.037$; FDR < 5%). ▪ Efficacy of dTMS treatment did not differ between patients with mild (HDRS-17 score 7–16) vs. moderate-to-severe (HDRS-17 score ≥17) depression at baseline (dTMS vs. control and severity of depressive symptoms $F_{(1, 99)} = 0.47$, $p = 0.495$, $\eta^2 = 0.01$). ▪ After 4 weeks, there was a significant reduction in BHS scores of −1.1 (95% CI: −1.74 to −0.49) in the rTMS group ($F_{(1, 50)} = 12.99$; $p < 0.001$; $\eta^2 = 0.21$; FDR < 5%). At the same timepoint, reductions in BHS scores in the control group were nonsignificant ($F_{(1, 51)} = 0.46$; $\eta^2 = 0.01$; $p = 0.503$; FDR > 5%). ▪ No significant group difference was observed for the following BHS dimensions: feelings about the future ($F_{(1, 88)} = 0.00$; $\eta^2 = 0.00$; $p = 0.991$), loss of motivation ($F_{(1, 88)} = 3.36$; $\eta^2 = 0.04$; $p = 0.070$), and expectations ($F_{(1, 88)} = 1.95$; $\eta^2 = 0.01$; $p = 0.166$)
(Filipčić et al., 2019)	▪ The odds ratio for remission was 11.3 (CI 95% 4.00–32.10; $p < 0.001$) in the H1-coil group and OR = 7.20 (CI 95% = 2.30–22.54; $p = 0.001$) in the F8-coil group compared to the standard pharmacotherapy control group. ▪ Remission rates (HDRS-17 score ≤ 7) were better in both H1 and F8 coil groups relative to the control. Remission rates were 60% (CI 95% = 48–71%), 43% (CI 95% = 31–55%) and 11% (CI 95% = 5–20%) in the H1-coil, F8-coil, and control groups, respectively ▪ Remission rates did not significantly differ between the H1-coil and F8-coil groups. The odds ratio for remission was 1.74 (Cl 95% = 0.79- 3.83; $p = 0.17$) in the H1-coil group compared to the F8-coil group. ▪ Patients with more moderate-to-severe depression at baseline who treated with the H1-coil were more likely to remit compared to those who were treated with the F8-coil (OR = 4.59; CI 95% = 1.69–12.48; $p = 0.003$). This pattern was not observed in patients with more mild depression at baseline. ▪ The H1-coil was superior to the F8-coil regarding changes in HDRS-17 scores relative to baseline. ($F_{(1,132)} = 3.97$; $p = 0.05$; $\eta^2 = 0.03$). ▪ Response rates (HDRS-17 ≥ 50% decrease) were significantly higher in H1-coil group compared to the F8-coil group (OR= 2.33; CI 95% = 1.04–5.21; $p = 0.040$). ▪ HDRS-17 scores were reduced by 59% in the H1-coil group, 41% in the F8-coil group (H1 vs. F8: $p = 0.048$), and 17% in the control (H1-coil vs. control: $p < 0.001$; F8-coil vs. control: $p = 0.003$).

(Kaster et al., 2018)	▪ Significantly higher remission rates were shown in the ITT active group (10/25, 40.0%; Cl = 21.1-61.3%) compared to sham (4/27, 14.8%; CI = 4.2–33.7%; $\chi^2 = 4.2$, d.f. = 1, $p < 0.05$) The NNT to achieve remission was 4.0 (CI = 2.1–56.5). ▪ In the PP sample, remission rates were significantly greater in the active group (n = 10; 50.0%; CI = 28.1–71.9%) relative to sham (n = 4; 14.8%; CI = 1.4–28.2; $\chi 2 = 6.8$, d.f. = 1; $p < 0.05$). The NNT achieve remission was 2.8 (CI = 1.6–10.5). ▪ Response rates (>50% reduction in HDRS-24 scores relative to baseline) were 44% (11/25; CI = 24.5–63.5%) and 18.5% (5/27; CI = 3.9–33.2%; $\chi^2 = 4.0$, d.f. = 1, $p < 0.05$) in the ITT active vs sham groups, respectively. The NNT to achieve response was 3.9 (CI = 2.0–89.3). ▪ In the PP sample, response rates were significantly greater in the active group (n = 11; 55.0%; CI = 33.2–76.8%) compared to sham (n = 5; 18.5%; CI = 3.9–33.2%; $\chi 2 = 6.8$, d.f. = 1; p < 0.05). The NNT was 2.7 (CI = 1.6–9.8). ▪ No effect of treatment condition (F = 3.3, d.f. = 49.0; $p = 0.08$) nor time x treatment condition (F = 0.9, d.f. = 189.0; $p = 0.438$) on HDRS-24 scores were observed. ▪ No changes were observed in any measure of executive function.
(Levkovitz et al., 2015)	▪ In the ITT analysis, the difference between active dTMS vs. sham dTMS HDRS-21 score changes from baseline to week 5 fell short of reaching statistical significance (-2.23 point difference; 95% CI: -4.54, 0.07; $p = 0.0578$; effect size = 0.58). ▪ In the PP analysis, the active dTMS group had a 6.39-point improvement in HDRS-21 scores, while a 3.28-point improvement was shown in the sham condition (-3.11 point difference; 95% CI: -5.40, -0.83; $p = 0.008$; effect size 0.76). ▪ Response rates at week 5 (PP set) were higher in the active dTMS group than in the sham (38.4 vs. 21.4%, respectively, $p = 0.0138$) ▪ Remission rates at week 5 (PP set) were greater in the active dTMS group relative to sham (32.6 vs. 14.6%, respectively, $p = 0.0051$). ▪ There was significant difference in HDRS-21 score changes from baseline to week 16, favouring the active dTMS group (-2.47 point difference; $p = 0.0259$) ▪ At week 16, response rates were 44.3% and 25.6% in the active dTMS and sham groups ($p = 0.0086$), respectively. ▪ At week 16, there were no significant group differences in remission rates (31.8% and 22.2% for the active and sham groups, respectively; $p = 0.1492$). ▪ Remission rates in participants who previously failed 1-2 medications were 36.6% and 16.7% for the active vs. sham groups, respectively (p = 0.032). ▪ Remission rates in participants who previously failed 3 or more medications were 28.9% and 12.2% for the active vs. sham groups, respectively (p = 0.057).

Obsessive-compulsive disorder

(Carmi et al., 2019)	▪ At the posttreatment assessment (week 6), reductions in YBOCS scores were significantly greater in the active dTMS group (-6.0 points, 95% Cl = 4.0, 8.1) compared to sham (-3.3 points, 95% Cl = 1.2, 5.3; p = 0.01*;* effect size = 0.69). ▪ At the posttreatment assessment, CGI-S scores were improved significantly in the active dTMS group compared to the sham group (61% and 32.6%, respectively; p = 0.022). At the same timepoint, 49% (20/41) of active group and 21% (9/43) of sham group (p = 0.011) reported moderate to high CGI-I improvements. ▪ Significant group differences in rate of full response (i.e., reduction of ≥ 30% in YBOCS score) were found between active (38.1%) vs. sham (11.1%) conditions at the posttreatment assessment (p = 0.003) ▪ No group differences were found in SDS scores at the posttreatment assessment. ▪ At the 1-month FU, reductions in YBOCS scores remained greater in the active dTMS group (-6.5 points, 95% Cl = 4.3, 8.7) compared to sham (-4.1 points, 95% Cl = 1.9, 6.2; p = 0.03*;* effect size = 0.62). ▪ At the 1-month FU , the rate of full response (i.e., reduction of ≥ 30% in YBOCS score) was 45.2% (19/42) and 17.8% (8/45) in the PP active and sham groups (p = 0.006), respectively. Moreover, the rate of partial response (i.e., reduction of ≥ 20% in YBOCS score) was 59.5% (25/42) and 42.2% (19/45) in the PP active and sham groups (p = 0.106). ▪ CGI-S and CGI-I scores were not significantly different between groups at the 1-month FU.
(Carmi et al., 2018)	▪ A near significant group x time interaction was found for the HF group ($F_{1,20}$ = 5.38, p = 0.055), but not for the LF, ($F_{1,20}$ = 1.23, p = 0.28) compared to sham. ▪ Following 5 weeks of treatment, the HF group had a higher response rate (7; 43.75%) compared to the sham group (1; 7.14%; χ^2 = 5.11, p < 0.05). The response criteria were a 30% reduction in YBOCS relative to baseline. Using a more restrictive analysis, 29.41% (n = 5) and 7.14% (n = 1) were considered responders in the HF and sham groups, respectively (χ^2 = 2.71, p < 0.10). ▪ At the 1-week FU, 5 (45.45%) of the HF group and 1 sham participant (7.69%) were considered responders (χ^2 = 4.53, p < 0.05). This group difference was significant (t_{22} = 3.46, p_c < 0.05). ▪ At the 1-month FU, 4 (44.44%) of the HF group and 0 sham participant were defined as responders (χ^2 = 5.12, p < 0.05). This group difference was nonsignificant (t_{16} = 2.06, p_c < 0.6). ▪ For CGI-I scores, 64.7% of the participants from the HF group (n = 11) and 7.1% of the sham group (n = 1) reached the response criteria at week 5 (χ^2 = 11.80, p < 0.001). Significance was maintained at the 1-week FU with 5 (45.45%) of HF participants and 1 (7.69%) of sham participants achieving response (χ^2 = 8.39, p < 0.05). However, significance was lost at the 1-month FU (p = 0.23).

Posttraumatic stress disorder

(Isserles et al., 2021)	▪ Mean adjusted improvement in the CAPS-5 score was 15.48 (95% Cl = 11.88- 19.08) points in the dTMS group and 19.05 (95% Cl = 15.98-22.12) points in the sham condition at week 5 (p = 0.0593; ITT analysis). ▪ At week 9 (FU visit), improvement continued in CAPS-5 score in both groups but remained smaller in dTMS (17.03 points; 95% Cl = 12.97-21.10) versus sham (22.86 points; 95% Cl = 19.39-26.33; p = 0.011; ITT analysis) . ▪ Active group responses rates (i.e., ≥ 50% improvement in CAPS-5 scores relative to baseline) were 42.5% and 53.8% at 5 and 9 weeks, respectively. In the sham group, response rates were 54.9% and 68% at the same timepoints (p > 0.05). ▪ Improvements were greater in the sham group compared to the dTMS group for all CAPS-5 items at week 9. However, greater sham improvements at week 5 (compared to dTMS group) were nonsignificant for the "intrusion" and "avoidance" clusters. ▪ Remission rates were minimal. No group differences in remission rates were observed.
(Isserles et al., 2013)	▪ There was no significant time x condition effect on CAPS scores posttreatment (p = 0.12). ▪ Posttreatment Improvements in CAPS scores were only found to be significant in the EXP-STIM group (p values of 0.0003, 0.164 and 0.122 for the EXP-STIM, NOEX-STIM & EXP-SHAM groups, respectively). ▪ There was a significant time x condition interaction for the CAPS intrusion domain ($F_{(2,23)}$ = 3.75, p = 0.039). Significant improvements were found in the EXP-STIM group (p < 0.0001), but not in the NOEXP-STIM (p = 0.117) and EXP-SHAM (p = 0.265) groups. ▪ 4/9 patients (44%) from the EXP-STIM group and 1/8 patients (12.5%) from the NOEXP-STIM group met the response criteria (i.e., ≥ 50% improvement in CAPS-5 scores relative to baseline). No patient from the EXP-SHAM group achieved response. (p = 0.055, Fisher's exact test). ▪ At week 4, time x condition effects for PSS-SR, HDRS-24 and BDI measures were insignificant. However, improvements in PSS-SR, HDRS-24 and BDI scores were only significant in the found EXP-STIM group. ▪ ***Note**** *The cross-over phase of this study was not included in our analysis due to absence of a sham/control group.*
Schizophrenia / schizoaffective disorder	
(Rabany et al., 2014)	▪ SANS scores were significantly reduced in the dTMS group (-7.7) but not in the sham condition (-1.9). However, group differences were not statistically significant at any time point. ▪ Group differences in response rates (i.e., a change in SANS scores from baseline to end of treatment of at least 20%) were nonsignificant: 62.5% (10/16 patients) and 33.3% (3/9 patients) in the active and sham groups, respectively (p = 0.2262). ▪ Active vs. sham conditions did not differ in terms of affective flattening (p = 0.13), alogia (p = 0.49), avolition–apathy (p = 0.50), anhedonia (p = 0.79), and attention (p = 0.10) post-treatment. ▪ Subjects in the active condition showed trend-level improvements in CGI, PANSS total, and SOFAS, whereas such improvements were not found in the sham group. However, group differences were not statistically significant. ▪ No significant group differences were found in the PANSS negative subscale, CDSS, PANSS total score, SOFAS, CSA, WHOQOL-BREF and CGI-S scales at any timepoint.

Schizophrenia

(Rosenberg et al., 2012)

- Auditory hallucination scores of both groups slightly improved post-treatment: AHRS scores decreased from 25.6 ± 6.5 to 22.6 ± 6.2 in the active group and from 26.6 ± 6.5 to 23 ± 5.8 in the sham group.
- There was a main effect of time within groups ($F_{(1,8)} = 5.54$, $p = 0.046$). However, between-group differences were not significant ($p > 0.05$).
- SAPS, SANS, CGI, and Q-LES-Q scores did not change posttreatment in either condition.

Substance use disorders

Alcohol use disorder/Alcohol dependence

(Harel et al., 2022)

- pHDD scores were significantly reduced in the active dTMS group (2.9 ± 0.8%) compared to the sham group (10.6 ± 1.9%) during the FU phase ($F_{(1,208)} = 4.40$, $p = 0.037$, mean difference = 7.7%, Cohen's d = 0.50)
- Both conditions had reduced pHDD scores after the treatment phase, but this effect was only sustained in the active group during the FU phase.
- There was a significant group effect on alcohol consumption during the FU phase ($F_{(1,486)} = 5.21$, $p = 0.02$, mean difference = 121.78, Cohen's d = 0.47), with lower consumption in the active vs. sham group.
- PACS scores were significantly lower in the active vs. sham group at week 3 of treatment ($t_{129} = 2.48$, $p = 0.01$; mean difference = 3, Cohen's d = 0.48)
- During the FU phase, group differences in PACs scores were trend-level ($F_{(1,185)} = 3.36$, $p = 0.07$, mean difference = 3.7, Cohen's d = 0.52)

(Perini et al., 2020)

- Drinking decreased during treatment in both active and sham conditions according to PEth ($F_{(1.18, 48.6)} = 10.3$, $p < 0.001$, $\eta^2p = 0.2$) and TLFB physiological measures ($F_{(1, 42)} = 50.2$, $p < 0.001$, $\eta^2p = 0.54$).
- Self-reports of drinking were lower during the FU phase relative to baseline irrespective of treatment condition according to TLFB ($F_{(4.1, 150.2)} = 6.3$, $p < 0.001$, $\eta^2p = 0.15$)
- There was no effect of treatment condition on alcohol consumption (measured by PEth) or self-reports of alcohol use (measured by TLFB) during treatment or the FU phase ($p > 0.3$).
- No time x group interaction was found for alcohol consumption (as measured by PEth) during treatment ($p = 0.6$) or at the FU ($p = 0.8$).
- No time x group interaction was found for self-reports of alcohol use (as measured by TLFB) during treatment or at the FU ($p > 0.4$).
- Alcohol consumption (i.e., PEth and TLFB measures) in the active dTMS group was not affected by stimulation strength ($p > 0.7$) or insular depth ($p > 0.6$).
- An effect of time was observed for AUQ ($F_{(4.35, 174.1)} = 17.27$, $p < 0.001$, $\eta^2p = 0.3$) and PACS ($F_{(1.4, 59.2)} = 5.3$, $p = 0.01$, $\eta^2p = 0.12$) scores in both conditions. However, no time x group interactions were observed for AUQ during treatment ($p = 0.4$) and PACS during treatment and follow-up sessions ($p = 0.6$, $p = 0.4$).
- Self-reported measures of depression and anxiety decreased overtime in both conditions (Depression: $F_{(4.13, 127.9)} = 6.14$, $p < 0.001$, $\eta^2p = 0.2$. Anxiety: $F_{(3.47, 93.8)} = 10.16$, $p < 0.001$, $\eta^2p = 0.3$). However, no group effect was found ($p > 0.6$).

(Addolorato et al., 2017)

- Craving levels did not change significantly in either condition.
- Reductions in state anxiety levels were seen in the active ($p = 0.049$, paired t-test) but not the sham group ($p = 0.43$, paired t-test).
- Number of abstinence days significantly increased in the active ($p = 0.03$), but not sham group ($p = 0.22$, paired t-test).
- Number of drinking days significantly decreased in the active ($p = 0.025$) but not sham group ($p = 0.26$, paired t-test).
- Number of drinks per drinking days and total drinks were significantly reduced in the active group ($p = 0.009$ and $p = 0.008$, respectively). Such measures were nonsignificant in the sham group ($p = 0.44$ and $p = 0.38$, respectively).
- Trend-level decreases in number of heavy drinking days were seen in both conditions (real: $p = 0.06$; sham: $p = 0.26$).

(Ceccanti et al., 2015)

- Reductions in VAS for cravings were only significant in the active dTMS condition ($t = 2.84$; $p = 0.025$) and was sustained at the 1-month FU ($t = 2.65$; $p = 0.038$). However, no significant difference for VAS scores were achieved in the active dTMS or sham groups in later follow-up visits ($p > 0.05$).
- For the active group, the number of alcoholic drinks/day decreased significantly between pre- and post-stimulation ($t = 3.79$; $p = 0.009$), at 1 month ($t = 4.25$; $p = 0.008$) and 3 months ($t = 4.50$; $p = 0.046$). Significance was lost at later FU visits. For the sham group, trend-level decreases in the number of alcoholic drinks/day were found between pre- and post-stimulation ($t = 2.34$; $p = 0.058$), and at 1 month ($t = 2.73$; $p = 0.041$). Significance was lost at later FU visits ($p > 0.05$).
- For the active group, there was a significant reduction in drinks/DMAI between pre- and post- stimulation ($t = 3.29$; $p = 0.013$) and at the 1-month FU ($t = 3.22$; $p = 0.018$). However, this significance was lost after 2 months ($t = 2.17$; $p = 0.09$). For the sham group, though there was an initial decrease in drinks/DMAI post-stimulation, no significant reductions in drinks/DMAI were found at the post-stimulation FUs.

Cocaine use disorder

(Martinez et al., 2018)

- There was a treatment by occasion interaction on choice for cocaine (i.e., cocaine self-administration; $F_{(2, 15)} = 5.36$, $p = 0.02$). Changes in choice for cocaine were minimal in the LF and sham groups, whereas the HF group showed a drop in choice for cocaine at session 3.
- Significant differences in choices for cocaine (i.e., cocaine self-administration) between HF and LF groups were found at session 3. ($t = 2.31$, $p = 0.04$). However, differences between the HF and sham groups at session 3 were trend-level ($t = 1.84$, $p = 0.09$). The choice for cocaine was lower in the third session compared to the second session for the HF group ($t = 4.00$, $p = 0.001$).
- There was a significant decrease in break point (i.e., the maximum effort a subject will expend to receive a cocaine reward) from sessions 2 to 3 in the HF group ($t = 4.04$, $p = 0.001$). At session 3, significant differences in break point were observed between the HF and LF conditions. ($t = 2.37$, $p = 0.03$). However, no significant group differences were found between the HF and sham groups at the same timepoint. ($t = 1.94$, $p = 0.07$).
- No effect of treatment condition (HF, LF, vs. sham) on craving levels for cocaine was found ($F_{(2, 14)} = 0.77$, $p = 0.48$). Craving reductions from sessions 2 to 3 were seen in all conditions. ($F_{(1, 17)} = 12.08$, $p = 0.003$).
- *Note** Session 1 = baseline visit. Session 2= 4th day of dTMS treatment. Session 3= 13th day of dTMS treatment.

(Bolloni et al., 2016)

- No interaction between treatment condition x time on cocaine intake was found. ($F_{(4,32)} = 0.35$; $p = 0.84$).
- Cocaine intake was significantly reduced in the active group between baseline and 3-month post-treatment mark ($t = 3.30$; $p = 0.02$), and between baseline and 6-month post-treatment mark ($t = 3.72$; $p = 0.01$).
- Cocaine intake was significantly reduced in the active group ($F_{(3,23)} = 3.42$; $p = 0.04$) but not in the sham group ($F_{(3,15)} = 1.88$; $p = 0.20$).
- Cocaine intake had significantly diminished in the active group after comparing intake at baseline and 6-months post-treatment ($p < 0.05$).
- 2 (50%) sham participants relapsed three times post-treatment
- 2(33%) active group participants relapsed once after 6 months post-treatment.

Nicotine/ tobacco use disorder (dependence)

(Ibrahim et al., 2023)

- Abstinence rates were higher at week 12 in the active group (82.4%) relative to sham (30.7%) (Difference = 51.7%; 95% CI = 11.1–92.3%; $t_{(91)} = 2.53$; $p = 0.013$). This significant difference was not present at week 4 and week 26.
- Long-term abstinence at week 26 was nonsignificant with no reported group differences (χ^2 [1] = 0.015, $p = 0.90$).
- There was no time x condition effect on FTND (dependence) scores ($p = 0.98$, $\eta^2 = 0.01$), but there was a significant effect of time ($F(7131.56) = 37.95$; $p < 0.001$, $\eta^2 = 0.67$). Treatment effect on FTND scores favoured the active group vs. sham, but was trend-level ($p = 0.071$, $\eta^2 = 0.08$).
- No significant effect of time x condition ($p = 0.26$, $\eta^2 = 0.17$) or condition ($p = 0.141$, $\eta^2 = 0.05$) was found for craving scores. There was an effect of time on cravings ($F_{(7,45.74)} = 32.14$; $p < 0.001$, $\eta^2 = 0.83$).
- No significant effect of time x condition ($p = 0.24$, $\eta^2 = 0.07$) or condition ($p = 0.98$, $\eta^2 < 0.001$)) was found for withdrawal symptoms. There was an effect of time on withdrawal symptoms ($F_{(7127.85)} = 5.51$; $p < 0.001$, $\eta^2 = 0.23$).
- No significant effect of time x condition ($p = 0.98$, $\eta^2 = 0.02$) or condition ($p = 0.91$, $\eta^2 < 0.001$) was found for cigarette consumption. There was an effect of time on cigarette consumption ($F_{(12, 230.08)} = 37.43$; $p < 0.001$, $\eta^2 = 0.66$).

(Zangen et al., 2021)

- The continuous quit rate was higher in the active group (25.3%) compared to sham (6.4%) at Week 6 ($X_2 = 11.885$, $p = 0.0006$).
- Abstainers at week 6 were followed until week 18. During this period, 63% (active) and 50% (sham) participants abstained from smoking ($X_2 = 8.46$, $p = 0.003$)
- Up until week 18, the continuous quit rate was higher in the active (19.4%) vs. sham group (8.7%; $X_2 = 5.655$, $p = 0.017$). In the PP analysis, the rate was 28.0% and 11.7%, respectively ($X_2 = 7.219$, $p = 0.007$).
- A significant reduction in number of cigarettes consumed and craving levels were found in the active group relative to sham (PP analysis).
- From baseline to week 6, the average difference in number of cigarettes consumed between active vs. sham groups was –79.9 (95% CI: –136.69 to –23.05, $p = 0.0061$; ITT analysis). In the PP analysis, this difference was -95.5 (95% CI: –159.16 to –31.91, $p = 0.0035$).
- Active group showed greater mean weekly reductions in cigarette consumption relative to sham (group difference: 15.01, 95% CI: 2.17-27.85, $p = 0.022$).
- Total craving score was significantly lower in the active group vs. sham (mean weekly group difference: 5.71, 95% CI: 0.62-10.81, $p = 0.028$).
- Significant reductions in VAS cravings were only observed in the active group following treatment ($F_{1,253} = 4.85$, $p = 0.028$).
- Decreases in VAS cravings after dTMS were predictive of smoking cessation in the active (but not sham) group (OR: active = 1.57, $p = 0.004$; OR: sham = 0.85, $p = 0.46$).

(Dinur-Klein et al., 2014)

- There was a significant effect of treatment on the number of cigarettes smoked per day ($F_{(2,76)} = 14.56$, $p < 0.0001$). Reductions in the HF group were significantly greater than the LF (ES = 9.9 ± 3.2, $p = 0.0031$) and sham (ES = 13.2 ± 2.5, $p < 0.0001$) groups. No differences were observed between the LF and sham conditions.
- No significant effect of cue (ES= 0.07 ± 2.47, $p = 0.97$), or cue x treatment ($p = 0.42$), was found on number of cigarettes smoked per day
- The HF conditions had significantly reduced cigarette consumption (14.45 ± 1.33) compared to the LF (8.56 ± 1.99, ES = 5.89 ± 2.39, $p = 0.0153$) and sham conditions (7.01 ± 1.46; ES= 7.44 ± 1.98, $p = 0$ .0003). Group differences between the LF and sham conditions were nonsignificant ($p = 0.53$). No significant effect of cue ($p = 0.30$), or cue x treatment ($p = 0.13$), was found.
- Response rates (i.e., reduction in cigarette consumption by 50%) were significantly greater in the HF group compared to the sham ($\chi^2_1 = 21.4$, $p < 0.0001$) and LF groups ($\chi^2_1 = 10.2$, $p = 0.002$). No significant differences in response rates were found between the LF and sham conditions ($\chi^2_1 = 0.45$, $p = 0.49$). No significant effect of cue ($\chi^2_1 = 1.2$, $p = 0.26$) on response rates was found.
- Following treatment, abstinence rates were significantly greater in the HF (cue) and HF (no cue) conditions (43.75% and 25%, respectively) compared to the sham groups (13.3%, 0%; $\chi^2_1 = 6.1$, $p = 0.039$). Abstinence rates were trend level among the LF (cue) and LF (no cue) groups (0% and 14.3%, respectively; $\chi 2_1 = 3.66$, $p = 0.075$), and were not statistically different between LF and sham groups ($\chi^2_1 = 0.005$, $p = 0.94$).
- Reductions in FTND scores were greater in the HF groups compared to the LF groups ($p = 0.045$) or the sham groups ($p = 0.0144$). No significant effect of cue was found on FTND scores ($F(1,73) = 0.66$, $p = 0.41$). However, there was cue x treatment effect for the HF group ($F_{(2,73)} = 3.77$, $p = 0.028$).

- At the 6-month FU, cigarette consumption had significantly decreased in the HF groups (11.68 ± 2.25) compared to the sham groups (0.35 ± 2.49; ES = 11.33 ± 3.35, $p = 0.0026$). Differences between the HF and LF groups were nonsignificant (6.57 ± 3.53; ES= 5.11 ± 4.18, $p = 0.1533$). No group differences were found between the LF and sham groups. ($p = 0.159$). No significant effect of cue ($F = 0.04$, $p = 0.84$), or cue x treatment ($F = 1.19$, $p = 0.31$), was found.
- Abstinence rates at the 6-month FU were greater in HF conditions vs. sham conditions ($p = 0.06$). There was a trend towards higher abstinence rates in the HF (cue) than the HF (no cue) condition.

Comorbid conditions

Schizophrenia/ schizoaffective disorder & tobacco dependence

(Moeller et al., 2022)

- Smoking-self administration was lower in the active dTMS group at post-treatment session ($b = -0.30$, SE = 0.15, $p = 0.044$) but not in the sham group ($p = 0.30$)
- No treatment effect on number of cigarettes smoked.
- A reduction in PANSS positive scores across 4 timepoints was found in active dTMS group ($b = -0.91$, SE = 0.36, $p = 0.011$) but not in the sham group ($p = 0.84$). PANSS negative and general scales did not change in either group.

Alcohol use disorder & dysthymic disorder

(Girardi et al., 2015)

- At the end of 20-sessions of dTMS or an equivalent period in the SDT group, craving scores and depressive symptoms in the dTMS-AO dropped significantly more than in the SDT group ($p < 0.001$ and $p < 0.02$, respectively).
- There was an effect of treatment condition, with the dTMS-AO group showing a larger reduction in HDRS scores compared to the control group ($F_{(1,13)} = 11.74$; $p = 0.0045$) from week 1 to posttreatment. No group difference was found at the 6-month FU.
- There was an effect of time on HDRS improvement ($F_{(4,64)} = 19.20$, $p < 0.0001$) in both conditions, and a time x treatment interaction ($F_{(4,64)} = 6.41$, $p = 0.0086$).
- Trend-level response/remission rates were found favoring the dTMS-AO group to sham ($\chi^2 = 3.662$; $p = 0.056$)
- There was a significant treatment effect ($F_{(1,13)} = 85.21$, $p < 0.0001$) on OCDS scores and time x treatment interaction ($F_{(4,64)} = 13.39$, $p < 0.0001$), with the dTMS-AO group displaying greater improvement than the control group at all timepoints. Both conditions showed improvement in OCDS over time ($F_{(4,64)} = 56.46$, $p < 0.0001$).
- Both conditions had CGI improvements over time ($F_{(4,64)} = 39.86$, $p < 0.0001$).
- Authors found a time x treatment interaction for reductions in CGI scores ($F_{(4,64)} = 4.21$, $p = 0.0203$).
- There was a significant effect of treatment condition on CGI scores from week 1-3 ($F_{(1,13)} = 15.36$, $p = 0.0018$), with the dTMS-AO group showing larger reductions in CGI scores compared to the control group. Significant group differences were lost at posttreatment and at the 6-month FU.
- No group differences in response/remission rates were found according to CGI criteria ($\chi^2 = 0.117$; $p = 0.732$)
- A significant effect of treatment was found on GAF scores, with the dTMS-AO group showing greater improvements ($F_{(1,13)} = 29.64$, $p = 0.0001$).

Abbreviations: ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive subscale, ADS= Alcohol Dependence Scale, AHRS= Auditory hallucinations rating scale, AO= add-on, AUQ= Alcohol Urge Questionnaire, AQ= Autism Spectrum Quotient, BHS= Beck Hopelessness scale, BDI= Beck Depression Inventory, CAARS= Conner's Adult ADHD Rating Scales, CAPS= Clinician-Administered PTSD Scale, CAPS-5= Clinical-Administered PTSD Scale for DSM-5, CDSS= Calgary Depression Scale for Schizophrenia, CGI= Clinical Global Impression Scale, CGI-I= The Clinical Global Impression – Improvement scale, CGI-S= Clinical Global Impressions-Severity, CSA= Cognitive Self-Assessment, DMAI= drinks on days of maximum alcohol intake, dmPFC= dorsomedial prefrontal cortex, dTMS= deep transcranial magnetic stimulation, EXP-SHAM dTMS= exposure + sham dTMS, EXP-STIM dTMS= exposure + active stimulus (dTMS), FTND= The Fagerström Test for Nicotine Dependence, FU= follow-up, F8 = figure-8 coil, GAF= Global Assessment of Functioning, HDRS= Hamilton Depression Rating Scale, HF= high-frequency, IRI= Interpersonal Reactivity Index, LF= low-frequency, lPFC= left prefrontal cortex, MDD= major depressive disorder, MMSE= Mini-Mental State Examination, NNT= number needed to treat, NOEXP-STIM dTMS= no exposure + active stimulus (dTMS), NR= not reported, OCD= obsessive compulsive disorder, OCDS= Obsessive Compulsive Drinking Scale, OR = odds ratio, PACS= Penn Alcohol Craving Scale, PANSS= Positive and Negative Syndrome Scale, PEth= phosphatidyl ethanol, pHDD= percentage of heavy drinking days, PSS-SR= PTSD Symptom Scale-Self Report, PTSD= posttraumatic stress disorder, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, RAADS= The Ritvo Autism Asperger Diagnostic Scale, rPFC= right prefrontal cortex, SANS= Scale for the Assessment of Negative Symptoms, SAPS= Scale for the Assessment of Positive Symptoms, Schizophr= Schizophrenia, SDS= Sheehan Disability Scale, SDT= standard detoxification treatment, SOFAS= Social and Occupational Functioning Assessment Scale, STAI= State-Trait Anxiety Inventory, STCQ= short version of the Tobacco Craving Questionnaire, TD= tobacco dependence, TLFB = The Alcohol Timeline Followback Method, TOVA= Test of Variables of Attention, VAS= Visual Analogue Scale, WHOQOL-BREF= World Health Organization Quality of Life Questionnaire, YBOCS= Yale–Brown Obsessive Compulsive Scale.

Discussion

In recent years, the worldwide increase of dTMS research has been substantial, especially given that the H1-coil only gained FDA approval in 2013. This systematic review is the first to date to provide a detailed overview of the clinical efficacy of dTMS, as assessed by the presence of a sham/control condition, across psychiatric and cognitive disorders. Overall, there is moderate evidence supporting the use of dTMS as a non-invasive, clinically efficacious intervention for various psychiatric and cognitive disorders, including comorbid conditions.

dTMS as a Valuable Addition to Psychiatric Care

Following a comprehensive review of the literature, the most compelling evidence supports the use of dTMS as a valuable treatment option for (1) depressive episodes in

patients with bipolar disorder (BD) or major depressive disorder (MDD), (2) obsessive-compulsive disorder (OCD), and (3) substance use disorders (SUDs), particularly alcohol use disorder (AUD) and nicotine use disorder (NUD).

Six clinical trials (Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) utilizing the dTMS H1-coil for the treatment of depressive episodes in patients with BD or MDD noted significant improvements in depressive symptoms, outperforming sham dTMS (Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) and standard pharmacotherapy (Filipčić et al., 2019; Gajšak et al., 2023). The H1-coil by BrainsWay™ gained FDA approval in 2013 and demonstrated its clinical efficacy in a large multicenter study (Levkovitz et al., 2015). Treatment resistance in MDD is a common barrier to effective psychiatric care, with approximately 30% of individuals with MDD experiencing treatment resistance to first-line antidepressants (Rush et al., 2006; Zhdanava et al., 2021). While there has been a marked increase in research interest in treatment resistance (Howes et al., 2022; Voineskos et al., 2020), this challenge persists in psychiatric care. Most individuals who are prescribed first-line antidepressants encounter several side effects, including fatigue, weight gain, sleep disturbances, and sexual dysfunction (Ferguson, 2001; Ramic et al., 2020). Although dTMS is a novel form of treatment, previous research has established its adverse events and risks to be relatively low. In line with these findings, we found that the most frequent side effects were headaches and application site pain or discomfort, with rare reports of severe adverse events. Considering the challenges associated with treatment-resistance and negative side

effects in response to first-line antidepressants, dTMS could act as a safe, non-invasive replacement of traditional pharmacotherapy. Alternatively, it may be administered in conjunction with pharmacological treatment. Two clinical trials (Filipčić et al., 2019; Gajšak et al., 2023) reported that standard of care pharmacotherapy combined with dTMS was more efficacious compared to standard of care pharmacotherapy alone. Importantly, this valuable addition to psychiatric care may allow psychiatrists to offer a wider range of treatment options to their patients, thereby promoting patient autonomy and informed decision making.

We additionally uncovered compelling evidence supporting the use of dTMS to target the ACC and mPFC using the BrainsWay™ H7-coil in patients with OCD. Two clinical trials (Carmi et al., 2019, 2018) reported clinical superiority of active dTMS over sham treatment. The most recent trial (Carmi et al., 2019) was a large prospective multicenter trial that led to the FDA approval of the H7-coil in 2018. A post-hoc analysis (Harmelech et al., 2022) of this trial (Carmi et al., 2019) reported an average durability of dTMS of ≥ 1.98 years, suggesting its clinical effects may persist well beyond the stimulation period. Moreover, post-marketing data from 22 clinical sites further support the dTMS H7-coil as a beneficial treatment for OCD (Roth et al., 2021). Notably, another post-hoc analysis (Roth et al., 2020) of Carmi et al. (2019) demonstrated the efficacy of dTMS for OCD even in patients with prior treatment-resistance. First-line interventions for OCD include antidepressants, such as serotonin-reuptake inhibitors (SRIs), and cognitive behavioural therapy (CBT; Nezgovorova et al., 2022). However, treatment resistance in OCD persists as an ongoing barrier for clinicians and patients alike (Albert

et al., 2018). Treatment-resistance occurs in approximately 40 to 60% of patients with OCD in response to such interventions (Bloch et al., 2013; Pallanti and Quercioli, 2006). As such, dTMS of the ACC and mPFC using the H7-coil may offer a valuable non-invasive treatment option for patients with a history of treatment resistance, thus expanding available treatment options.

Furthermore, while the H7-coil was originally approved for the treatment of OCD in 2018, its treatment use has been expanded to MDD populations. In 2022, the H7-coil gained FDA clearance following a multicenter noninferiority trial (Zangen et al., 2023) comparing the H1-coil to the H7-coil. The data revealed comparable response rates between treatment groups. Interestingly, MDD patients who had higher C-DEPTH scores (i.e., an electrophysiological measure) at baseline were more likely to respond to the H1-coil. Conversely, patients with lower C-DEPTH scores at baseline were more likely to respond to the H7-coil. Thus, MDD patients with lower C-DEPTH scores may benefit more from medial stimulation of the PFC using the H7-coil, as opposed to lateral stimulation of the PFC provided by the H1-coil. Considering its adaptability, the H7-coil presents as a versatile treatment option that may be used to alleviate symptoms of both OCD and MDD.

We also found convincing evidence supporting the use of dTMS to target the insula in patients with NUD (i.e., nicotine dependence) and TUD (i.e., tobacco dependence). Four trials (Dinur-Klein et al., 2014; Ibrahim et al., 2023; Moeller et al., 2022; Zangen et al., 2021) noted significant reductions in smoking behaviours in the active dTMS treatment arm relative to the sham arm. One trial (Moeller et al., 2022)

involved patients with comorbid schizophrenia/schizoaffective disorder and tobacco dependence. The H4-coil by BrainsWay™ (used in Dinur-Klein et al., 2014; Moeller et al., 2022; and Zangen et al., 2021) gained FDA approval in 2020 as a short-term treatment for smoking cessation. This unique coil design stimulates the insula and PFC. Notably, one trial (Ibrahim et al., 2023) used the H11-coil to target the bilateral insula. The authors observed higher abstinence rates in the active dTMS group versus the sham group, even when both groups were administered 12 weeks of varenicline (Ibrahim et al., 2023). Varenicline is an effective pharmacotherapy for smoking cessation and has demonstrated superiority over the commonly prescribed nicotine patch and inhaler (Mills et al., 2012; Shang et al., 2023). The findings of Ibrahim et al. (2023) highlight the potential use of dTMS as an add-on treatment for smoking cessation, producing clinically superior results when used in conjunction with varenicline compared to varenicline alone. Furthermore, dTMS may also be effective in treating tobacco dependance in individuals with comorbid conditions. For example, tobacco use is highly prevalent among individuals with psychotic disorders (Ziedonis et al., 2008). The trial by Moeller et al. (2022) was shown to mitigate positive symptoms of schizophrenia and tobacco dependence. Further research is warranted to explore the efficacy of dTMS in alleviating differential symptoms in patients with comorbid conditions.

Lastly, we found moderate evidence supporting the use of dTMS for AUD (i.e., alcohol dependence). Four clinical trials (Addolorato et al., 2017; Ceccanti et al., 2015; Girardi et al., 2015; Harel et al., 2022) reported dTMS as superior to sham in patients with alcohol dependence (*Note.* One of these trials [Girardi et al., 2015] was in patients

with comorbid AUD and dysthymic disorder). By contrast, one trial (Perini et al., 2020) reported no effect of treatment condition on alcohol consumption or self-reported use. Pharmacotherapy remains significantly underused for the treatment of AUD. Fewer than 9% of individuals with AUD are prescribed the necessary medications needed to treat their condition (Kranzler and Soyka, 2018). Naltrexone, though a standard treatment for AUD, has been shown to only reduce the likelihood of binge drinking and alcohol consumption by 10% and 5%, respectively (Kranzler and Soyka, 2018). Evidence from the current review supports dTMS as a promising treatment for AUD. Further research should examine the importance of dTMS maintenance sessions, which may lead to longer lasting abstinence rates. Subsequent research should investigate the use of dTMS either in conjunction with or in comparison to standard pharmacotherapy for AUD (e.g., naltrexone) to determine the efficacy of dTMS.

Overall, the clinical efficacy of dTMS was heterogenous in psychiatric disorders characterized by hyperactivity or hyperarousal (i.e., ADHD, PTSD, and schizophrenia). Moreover, due to limited number of studies for particular psychiatric (e.g., ASD) and cognitive disorders (i.e., Alzheimer's disease), further sham-controlled trials are needed to appraise the efficacy of dTMS for such conditions.

Durability of dTMS: An Important Consideration

A fundamental aspect of dTMS treatment that requires further investigation is dTMS durability – that is, *how long can we expect these treatment effects to last?* This is an important question for both practitioners and patients considering dTMS treatment. A grey area of dTMS research lies in formulating the optimal treatment regimen (i.e.,

frequency and duration of sessions within a given treatment phase) and determining if repeated maintenance sessions are necessary to produce a sustained clinical effect. Several clinical trials noted significant improvements in the active arm versus the sham arm yet reported that this significance was lost at later timepoints. For instance, one trial (Ibrahim et al., 2023) delivered four weeks of dTMS treatment combined with 12 weeks of varenicline for smoking cessation. At week 4, no group differences in abstinence rates were found. Though at week 12, abstinence rates were significantly higher in the active dTMS + varenicline arm (82.4%) compared to the sham + varenicline arm (30.7%). However, significance was lost at week 26. Likewise, after a 4-week dTMS intervention for bipolar depression (Tavares et al., 2017), the authors noted active dTMS as clinically superior to sham at weeks 4 and 6, but not at week 8. Therefore, a systematic investigation of the optimal treatment periods to maximize and sustain clinically superior effects is highly warranted. Furthermore, future studies should appraise the long-term efficacy of dTMS on various psychiatric and cognitive disorders. A longitudinal post-hoc analysis (Harmelech et al., 2022) of the multi-center sham-controlled trial by Carmi et al. (2019) analyzed the durability of the cognitive effects of dTMS beyond the treatment period. The results suggest that the average durability of dTMS for OCD is ≥ 1.98 years. However, further investigation is necessary to determine the varying durability of dTMS among other psychiatric and cognitive disorders.

Moderators of dTMS efficacy

Moderators of dTMS efficacy could be of valuable interest to researchers and clinicians and should not be overlooked. For example, a recent post-hoc analysis (Guzick et al., 2022) of a multi-center trial (Carmi et al., 2019) found that participants' level of perceived distress following exposures played a key role in dTMS treatment efficacy. Specifically, higher distress during provocations was associated with an increased active versus sham response, while this difference was less pronounced among patients who reported lower levels of distress (Guzick et al., 2022). Another trial (Dinur-Klein et al., 2014) had heterogenous findings. The authors noted that the presence or absence of smoking cues had a significant effect on certain measures, whereas for other measures, there was no effect. Future research should build on these findings to highlight potential moderators of treatment success in neurostimulation as an interdisciplinary way to enhance treatment outcomes.

Age and illness severity are additional factors that should be considered. In a post-hoc analysis (Storch et al., 2021) of Carmi et al. (2019), older participants and those with lower OCD severity/disability exhibited quicker response rates to both active dTMS and sham treatments. In patients with higher OCD severity, greater clinical improvements were observed in the active dTMS group relative to sham, whereas differences between treatment groups were less pronounced in those with lower OCD severity. Thus, clinicians should take age and illness severity of patients into account when constructing a tailored treatment plan to improve the course of OCD.

Furthermore, electrophysiological markers should be integrated into dTMS research, with the long-term aim of customizing interventions for patients. In the recent

non-inferiority trial by Zangen et al. (2023), patients with MDD who had higher C-DEPTH scores (i.e., an electrophysiological measure) at baseline were more likely to respond to lateral stimulation of the PFC using the H1-coil. Conversely, patients with lower C-DEPTH scores at baseline were more likely to respond to medial stimulation of the PFC using the H7-coil. Further research is warranted to investigate electrophysical markers moderating treatment outcomes to produce individualized treatment options.

Strengths and Limitations

A strength of this review is that we limited the included studies to dTMS clinical trials with sham/controlled conditions to effectively measure clinical efficacy and rule out the placebo effect. We comprehensively searched multiple databases and conducted a risk of bias assessment (GRADE criteria) to ensure that only quality evidence was included. Most studies incorporated in the current review were double-blind, randomized-controlled trials to reduce risk of bias. However, limitations should be noted. First, we did not perform a meta-analysis as there were not enough sham/controlled trials for a given psychiatric/cognitive disorder to report sufficient quantitative data. There is considerable variability in patients with different psychiatric disorders in the literature. As such, very few studies have repeatedly employed dTMS in patients with the same diagnoses. Secondly, some clinical trials employed a standard of care pharmacotherapy control arm, which is unlikely to be as effective as a sham dTMS condition.

Conclusion

dTMS is a promising neurotechnology capable of non-invasively targeting disturbed networks in several psychiatric and cognitive disorders. Overall, we found moderate evidence supporting the clinical efficacy of dTMS for various psychiatric and cognitive disorders. The largest body of evidence supports the efficacy of dTMS for the treatment of (1) depressive episodes in patients with BD or MDD, (2) OCD, and (3) SUDs. The sustainability of these treatment effects requires further investigation beyond the treatment phase to determine if recurrent maintenance of dTMS is necessary for remission. Moderators associated with treatment success should also be identified. Of greater importance, few studies have implemented a sham-controlled design, hindering a proper assessment of the dTMS clinical efficacy. To corroborate our review's preliminary findings, a greater number of sham-controlled clinical trials is necessary to reach a definite conclusion about the efficacy of dTMS across psychiatric and cognitive disorders. Nevertheless, the results are encouraging. dTMS may offer a viable and alternative route for patients who have not responded to traditional medications, thereby expanding treatment options.

Declaration of competing interest

We would like to acknowledge that our co-author, Dr. James MacKillop, is a principal in BEAM Diagnostics, Inc and a Consultant to Clairvoyant Therapeutics, Inc. The other authors declare no potential competing interests.

Appendix A. Supplementary data.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.05.011.

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Chapter 3

Study 2: Recruitment for clinical research in older populations with depression: A retrospective longitudinal study

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Context and implications: This study has valuable implications for enhancing clinical research in underrepresented populations, particularly, older adults with depression. Conducting analyses on the effectiveness of various recruitment strategies, as well as identifying facilitators and barriers to recruitment, are necessary to promote dTMS research in older adults.

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Abstract

Background: Recruitment challenges are inherent in clinical research, particularly with special populations like older adults with depression, who may have a unique set of barriers such as medical comorbidities, mental health symptoms, and infrequent help-seeking behaviour. Neurostimulation techniques like deep transcranial magnetic stimulation (dTMS) are often unfamiliar and may sound intimidating. Existing literature lacks insight into the associated costs, as well as guidance, related to recruitment strategies used in dTMS trials for older adults.

Methods: This retrospective longitudinal study analyzed recruitment data from our pilot study exploring the effects of dTMS in older adults with depression. We assessed diverse recruitment methods by analyzing enrollment rates and conducting an enrollment-cost analysis. Furthermore, we examined potential facilitators and barriers to recruitment.

Results: Between April 1, 2023, and May 27, 2024, we received 185 referrals, yielding 22 enrollments. Healthcare provider outreach to affiliated inpatient and outpatient mental health clinics was the most effective recruitment method, with an enrollment-cost ratio (ECR) of 0.00189 ($537.63 CAD/person enrolled) and 12 enrollments (12/22; 54.55%). The second most effective recruitment method was Facebook, producing an ECR of 0.00099 ($925.93 CAD/person enrolled) and 10 enrollments (10/22; 45.45%). Social support from research personnel was a potential facilitator of recruitment, while time-intensiveness and accessibility challenges were noted as potential barriers.

Conclusion: Our findings highlight the effectiveness of healthcare provider outreach within inpatient and outpatient mental health clinics, and Facebook, as recruitment methods. Future research is warranted to evaluate other facilitators and barriers to recruitment in dTMS interventions for older adults with depression.

Keywords: Accrual rates, clinical trials, deep TMS, deep transcranial magnetic stimulation, dTMS, geriatrics, neurostimulation, older adults, psychiatry, recruitment, seniors.

Introduction

Recruitment is an ongoing challenge in clinical research. Low recruitment rates increase the likelihood of significant delays, prolonged expenses, insufficient sample sizes (Bower et al., 2009; Caldwell et al., 2010; Chaudhari et al., 2020; Gul & Ali, 2010) and early trial termination (Bernardez-Pereira et al., 2014; Williams et al., 2015). A cross-sectional analysis of over 600 terminated trials from ClinicalTrials.gov reported that 57% were ceased due to low recruitment rates (Williams et al., 2015). Moreover, in a review (McDonald et al., 2006) of 114 randomised controlled trials, only 31% of the trials met their recruitment goals, with 53% requiring an extension.

Special populations, such as older adults with depression, pose an added challenge for clinical trial recruitment. Older adults have higher rates of comorbidities (Divo et al., 2014; Ho et al., 2019; Salive, 2013) which may affect their eligibility to participate in clinical trials. Older adults are also more likely to have functional and mobility impairments (Gray-Miceli, 2017; Jia et al., 2019), potentially affecting their ability to travel to in-person sessions. Transportation challenges may also affect an older individual's willingness to participate in research (Rigatti et al., 2022). A survey (Bloch & Charasz, 2014) of 150 older adults revealed that only 44% were inclined to participate in a clinical trial, with the most common reasons for declining being (1) fear of harming their health and (2) believing they are too old. Older adults with psychiatric conditions are also less likely to seek professional help as compared to younger age groups (Elshaikh et al., 2023; Karlin et al., 2008; Lavingia et al., 2020), possibly due to negative perceptions towards mental health care, medical comorbidities, and limited access to geriatric

healthcare providers (Lavingia et al., 2020). In older adults with anxiety and depression, these concerns may come hand in hand with additional worries, including apprehension about social stigma and skepticism toward mental health treatments and related costs, thus deterring them from seeking professional help (Elshaikh et al., 2023).

The current literature lacks in-depth information on recruitment strategies for clinical trials research in older adults with psychiatric conditions, such as major depressive disorder (MDD). Of the limited articles examining recruitment in older adults with depression, the respective studies investigated psychotherapy (Tegeler et al., 2022) and preventative wellness interventions (Albert et al., 2016). However, the effectiveness of recruitment methods used in neurostimulation interventions for older adults with MDD remain unexamined. Such research would provide critical insights into the effectiveness of recruitment methods employed in clinical trials utilizing novel, and unfamiliar, neurostimulation interventions. It is possible that unknown and intimidating-sounding neurostimulation interventions could pose a barrier to recruitment.

Therefore, this retrospective longitudinal study aims to analyze the effectiveness of the diverse recruitment methods used in our pilot trial (ClinicalTrials.gov: NCT05855850). This trial aimed to examine the feasibility, tolerability, and clinical effects of a non-invasive neurostimulation technique, known as deep transcranial magnetic stimulation (dTMS), in older adults with treatment-resistant MDD. Insights into the effectiveness of various recruitment techniques in older adults are pivotal advance recruitment processes in clinical research examining this population.

Methods

2.1 Study Overview

This retrospective longitudinal study analyzed data from our open-label clinical trial (Clinicaltrials.gov ID: NCT05855850) located at St. Joseph's Healthcare Hamilton, Ontario, Canada. We recruited older adults aged 60 to 85 with moderate-to-severe MDD according to *the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). The main inclusion criteria were a score of 20 or greater on the Hamilton Depression Rating Scale 24-Item (HDRS-24) and treatment resistance to antidepressant pharmacotherapy, identified as either one failed trial or two inadequate trials (i.e., intolerance) during the current episode. The study received ethics approval from the Hamilton Integrated Research Ethics Board (HiREB) on January 29, 2023 and began recruitment in April 2023.

Prospective participants were assessed for eligibility either through an online or telephone screening assessment. If eligible, participants were invited to attend an in-person eligibility assessment performed by the principal investigator (PI) to review prior medical history and identify contraindications to dTMS (i.e., history of seizures, pacemaker, alcohol dependence, etc.). After researchers obtained informed consent, participants received a brief adaptation demonstration of the dTMS BrainsWay™ device. This demonstration aimed to (1) ensure the comfortability of participants while receiving stimulation and (2) provide participants with insight into whether 20 sessions of dTMS would be tolerable and suited to their needs.

All participants provided written informed consent prior to enrollment. Enrolled participants received one dTMS session per day, for five days a week over four weeks, excluding weekends and holidays (i.e., 20 sessions total). Each session lasted approximately 30 minutes. Depressive symptoms and electroencephalography (EEG) were recorded at baseline and at every fifth visit. Side effects were routinely evaluated at each dTMS session (Figure 1).

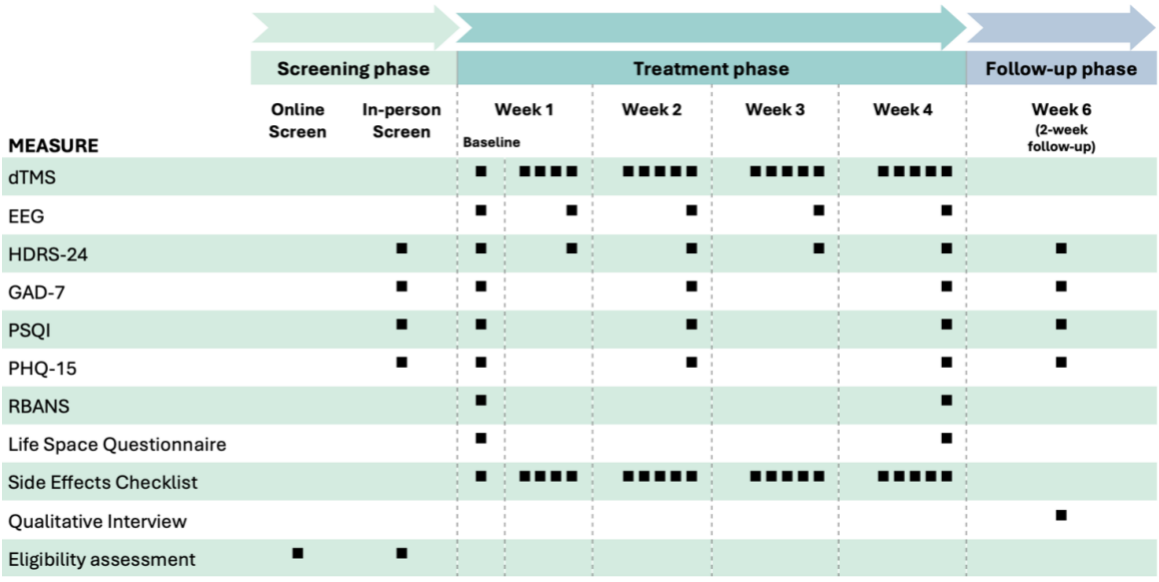

Figure 1. Study timeline and outcome measures.

Abbreviations: BL = baseline; dTMS = deep transcranial magnetic stimulation; EEG = electroencephalogram; GAD-7 = Generalized Anxiety Disorder 7; GDS-30 = Geriatric Depression 30-item Scale; HDRS-24 = Hamilton Depression Rating Scale 24-item; PHQ-15 = Patient Health Questionnaire; PSQI = Pittsburgh Sleeping Quality Index; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

2.2 Recruitment strategies

To enhance recruitment rates, we employed various recruitment strategies. Prospective participants were asked to provide information about how they had learned of the study.

For detailed information on recruitment strategies and implementation dates, refer to the Supplementary Table S1.

2.2.1. Community engagement. We emailed various organizations with a request to help spread awareness of our study within the Greater Hamilton community, including university-affiliated groups and retirement homes.

2.2.2. Family medical clinic outreach. We contacted local family medical clinics and provided healthcare staff with recruitment flyers, patient info-sheets, and physician info-sheets to family medical clinics. Flyers and information sheets were posted in patient waiting areas after receiving consent from medical staff.

2.2.3. Healthcare provider outreach within affiliated inpatient and outpatient mental health clinics. We invited case managers, nurses, psychiatrists, geriatricians, psychologists, and research coordinators within St. Joseph's Healthcare Hamilton inpatient and outpatient mental health clinics to refer eligible candidates to our study.

2.2.4. Newspaper advertising. We advertised in the local newspaper, Coffee News®, targeting residents of Hamilton, Ontario, Canada. Coffee News® reaches approximately ten million readers per week, identifying the newspaper as a potential recruitment platform to broadly target Hamilton residents.

2.2.5. Online advertising. We created online advertisements using several platforms: Craigslist, Facebook, Google, and Kijiji. Individuals were able to self-refer by completing an online, linked screening questionnaire assessing their eligibility.

2.3 Measures of recruitment method effectiveness

2.3.1. Enrollment rates. We calculated the number of referrals received, number of participants, and the enrollment rate (Equation 2.3.1) per recruitment source. Enrollment rates were calculated to provide insight into the effectiveness of each recruitment method. For online advertising methods, enrollment rates were calculated separately for each platform (i.e., Craigslist, Facebook, Google, and Kijiji). Enrollment rates were calculated according to the following formula:

$$\text{Enrollment rate} = \frac{N_E}{N_R}$$

N_E = number of participants enrolled
N_R = number of referrals received

2.3.2. Enrollment-cost analysis. We conducted an enrollment-cost analysis as an additional measure of recruitment method effectiveness. First, research personnel were asked to provide an estimate of time spent (in hours) for each recruitment method. The specific recruitment activities involved in this calculation are detailed in Section 2.2. Second, the cost ($ CAD dollars) incurred for each recruitment method, where applicable, was tracked by research staff. Using these variables, we calculated an *enrollment-cost ratio (*ECR), which was used to evaluate recruitment effectiveness by comparing the number of enrolled participants to the time spent/cost incurred per recruitment method. For online advertising methods, time-cost referral and time-cost enrollment ratios were calculated separately for each platform (i.e., Craigslist, Facebook, Google, and Kijiji).

Greater values for the time-cost referral and time-cost enrollment ratios were indicative of higher recruitment method effectiveness.

$$\text{Enrollment-cost ratio (ECR)} = \frac{N_E}{w\,t + c}$$

w = Median hourly wage of research personnel ($CAD)
t = Time spent (in hours)
c = Cost of recruitment method ($CAD)
N_E = Number of participants enrolled

This ECR analysis aimed to account for the labour costs incurred by each recruitment method. In this study, postsecondary research assistants were primarily responsible for recruitment. Accordingly, we determined the median hourly salary of postsecondary research assistants located in Ontario, Canada— the location of the study site. According to the Canadian Labour Force Survey of 2024 (Government of Canada, 2024), the median hourly salary for post-secondary research assistants in Ontario was $CAD 29/hour from 2021 to 2022**.** Therefore, this hourly wage was used as an estimate for the variable w in ECR calculations.

2.4 Facilitators and Barriers to Recruitment

We examined qualitative interview data to identify facilitators and barriers affecting recruitment. A qualitative interview was performed at the 2-week follow-up to assess participants' perceptions and overall attitudes towards the study. The interview contained

open-ended questions (e.g., "What are some things you may have liked or disliked?" and "How was your experience during the study?", etc.) and participants were invited to provide feedback. We conducted a verbal thematic analysis of the qualitative interview data, whereby common themes were identified and manually coded to identify facilitators and barriers to recruitment. The frequency of each theme was recorded.

Results

3.1 Sample characteristics

This longitudinal retrospective study analyzed data collected over 14 months from our pilot study (Clinicaltrials.gov ID: NCT05855850). From April 1 2023 to May 27 2024 (i.e., the enrollment date of the final participant), a total of 22 participants with MDD were enrolled and 19 completed the study.

The ITT sample (n = 22) consisted of 13 females (59.09%) and 9 males (40.91%) with a mean age (SD) of 69.41 (6.0). All were of White/European ancestry. Regarding education level, 10 participants (45.45%) had a Bachelor's degree or higher (i.e., a Master's degree or a professional degree). Five participants (22.73%) reported having undergone some college or university and two (9.09%) had an associate's degree. Four participants (18.18%) had completed high school and one participant (4.55%) had less than a high school education. Nearly all participants were retired (19; 86.36%). Two participants (9.09%) were working full-time and part-time hours, respectively. One participant (4.55%) was on disability. The mean HDRS score (SD) at baseline was 30.18 (4.94), with all participants having moderate-to-severe major depressive disorder.

3.2 Recruitment, referrals, and enrollment

From April 1 2023 to May 27 2024, we received 185 referrals (Figure 2). Of the 185 referrals, 138 (74.59%) were self-referrals from Facebook; 38 (20.54%) were referrals from inpatient and outpatient mental health clinics within the St. Joseph's Healthcare Hamilton hospital network; 5 (2.70%) were self-referrals from individuals who viewed our local newspaper advertisement; 2 (1.08%) derived from community engagement methods, specifically, the *McMaster* Institute for Research on Aging (n = 1) and the Centre for Medicinal Cannabis Research (n = 1); 1 (0.54%) was a self-referral from Craigslist; and 1 (0.54%) was a self-referral from Kijiji. No referrals were received via Google or family medical clinics.

After receiving 185 referrals, 45 participants did not show interest in enrolling and 92 participants were ineligible (Figure 2). Twenty-six referrals were excluded due to miscellaneous reasons, such as duplicate referrals (i.e., potential participants who mistakenly filled out a form twice). Please refer to Supplementary Material for more detailed information on reasons for ineligibility across recruitment methods.

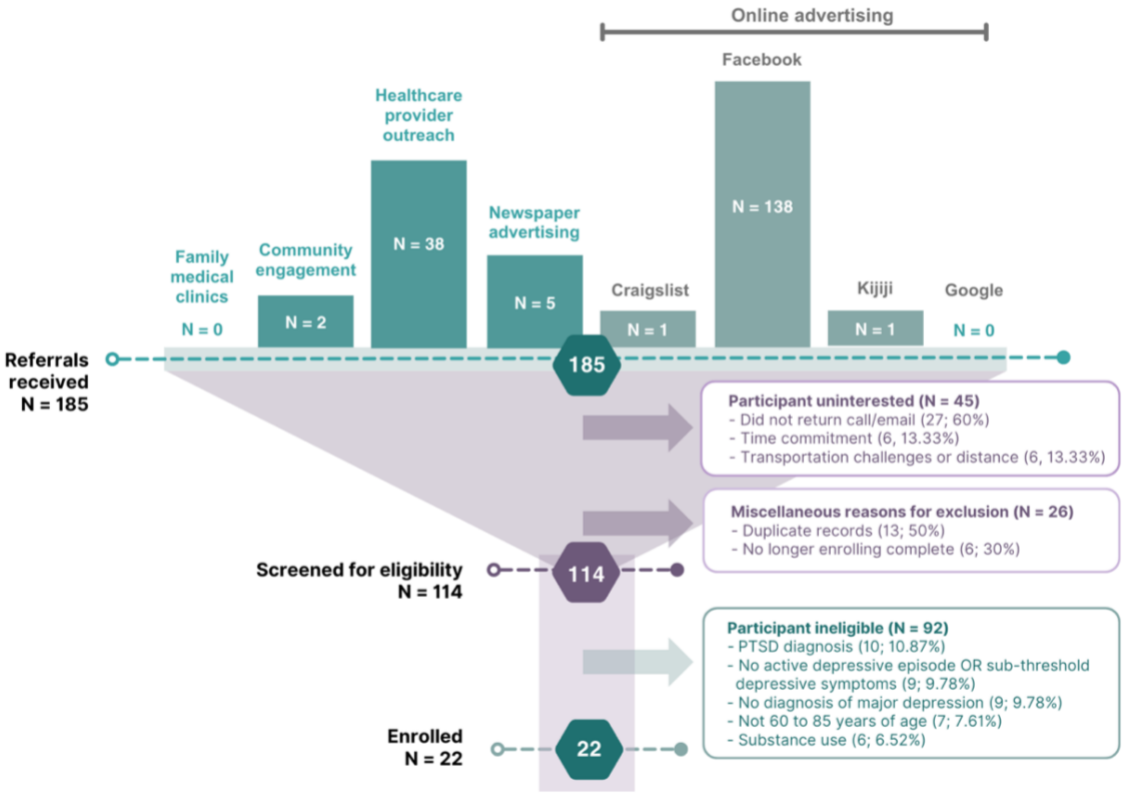

Figure 2. Recruitment flowchart. *Note*. Please note that some prospective participants had overlapping or multiple exclusion criteria, hence percents are not cumulative.

3.3 Recruitment method effectiveness

3.3.1 Enrollment rates

The most effective recruitment method regarding enrollment rates was healthcare provider outreach within inpatient and outpatient mental health clinics (i.e., within the affiliated St. Joseph's Healthcare network). This recruitment method produced the highest enrollment rate of 0.316 enrolled participants per referral received (95% CI: 0.190 –

0.475). Facebook was the second most effective recruitment method, with an enrollment rate of 0.072 enrolled participants per referral received (95% CI: 0.038 – 0.130). Following a two-tailed Fisher's exact test, we found a significant difference in enrollment rates between recruitment methods ($p = 0.028$). Following a post-hoc test for multiple comparisons, we noted a trend-level difference in enrollment rates between (1) healthcare provider outreach within inpatient and outpatient clinics and (2) Facebook recruitment methods ($p_{adj} = 0.079$). Other comparisons were nonsignificant. All other methods had enrollment rates of zero.

Table 1. Enrollment rates across recruitment methods.

Recruitment method	N_R	N_E	Enrollment rate	95% CI[b]
Community engagement	2	0	0	n/a
Family medical clinics	0	0	0	n/a
Inpatient and outpatient mental health clinics[a]	38	12	0.316	0.190 – 0.475
Newspaper advertising	5	0	0	n/a
Online advertising				
Craigslist	1	0	0	n/a
Facebook	138	10	0.072	0.038 – 0.130
Google	0	0	0	n/a
Kijiji	1	0	0	n/a

[a] Located within the St. Joseph's Healthcare Hamilton Network. [b]Agresti-Coull Method. Abbreviations: CI = Confidence interval. N_E = number of participants enrolled. N_R = number of referrals received. n/a = not applicable.

3.3.2 Enrollment-cost analysis

Following a comprehensive analysis of the estimated time spent (in hours), advertising costs, and labour costs, we calculated enrollment-cost ratio (ECR) for each recruitment method. Healthcare provider outreach within inpatient and outpatient mental health

clinics was the most effective recruitment method, with an ECR of 0.00186 persons enrolled per $CAD, or an estimated $537.63/enrolled participant. This recruitment method produced 12 enrollments (12/22; 54.55%) and incurred an estimated cost of $6452.50. The second most effective recruitment method was Facebook with an enrollment cost ratio of 0.00108 persons enrolled per $CAD, or approximately $925.93/enrolled participant. Facebook yielded 10 enrollments (10/22; 45.45%) and emerged as the most expensive recruitment method, incurring an estimated cost of $9235.35. The remaining recruitment methods generated an ECR of zero, as they produced no enrollments. Newspaper advertising, Google, Kijiji, and Craigslist recruitment methods were terminated due to producing no significant referrals.

Table 2. Enrollment-cost ratios.

Recruitment method	N_R	N_E	Estimated time spent (hours)	Advertising cost ($CAD)	Final estimated cost ($CAD)	ECR	Estimated cost per enrollment ($CAD)
Community engagement	1	0	17.5	0	507.50	0	n/a
Family medical clinics	0	0	12	0	348	0	n/a
Inpatient and outpatient mental health clinics[a]	38	12	222.5	0	6452.50	0.00186	537.63
Newspaper advertising	5	0	2	366.40	424.40	0	n/a
Online advertising							
Craigslist	1	0	1	0	29	0	n/a
Facebook	138	10	235	2,420.35	9235.35	0.00108	925.93
Google	0	0	6	30	204	0	n/a
Kijiji	1	0	2	0	58	0	n/a

[a] Located within the St. Joseph's Healthcare Network. Abbreviations: ECR = enrollment cost ratio. N_E = number of participants enrolled. N_R = number of referrals received. n/a = not applicable

3.4 Facilitators of and Barriers to Recruitment

Of the 19 participants who completed the trial, 17 (89.47%) were interviewed at the 2-week follow-up to allow for an open discussion of their experience participating in the clinical trial. One participant was lost to follow-up as they could not complete the questionnaire due to strong emotional reactions during the interview. The other participant had not yet approached the two-week follow-up and therefore was excluded from this analysis. Following a manual thematic analysis of qualitative interview data across n = 17 participants, we identified 10 facilitators and six barriers to recruitment

(Table 3). The most common facilitators of recruitment were perceived social support from research staff (n = 15; 88.24%), reports of a positive and/or worthwhile experience (n = 13; 76.47%), and flexible scheduling and/or offering schedule accommodations (n = 8; 47.06%). The most common barriers to recruitment were a high level of time commitment (n = 6; 35.29%), and accessibility challenges entering and exiting the research facility (n = 3; 17.65%). The remaining facilitators and barriers to recruitment are listed in Table 3.

Table 3. Potential facilitators and barriers to recruitment

Theme identified across N = 17 participants	Frequency of theme	% of participants reporting theme
Facilitators		
Perceived social support from research staff	15	88.24
Positive and/or worthwhile experience	13	76.47
Flexible scheduling / accommodation	8	47.06
Promoting autonomy/self-reflection/ self-esteem	3	17.65
Transportation coverage and/or parking vouchers	3	17.65
Incorporating a daily routine	2	11.76
Making positive impact participating in research	2	11.76
Monetary incentives (i.e., gift cards)	2	11.76
Receiving support from loved ones	2	11.76
Abstaining from maladaptive habits during treatment	1	5.88
Barriers		
High level of time commitment	6	35.29
Accessibility challenges (e.g., entering and exiting the research facility)	3	17.65
Far distance/long commute to research center	2	11.76
Hesitant to enroll in study and/or negative expectations	2	11.76
Daily sessions felt overly routine/monotonous	1	5.88
Not a replacement of medical care	1	5.88

Discussion

We conducted a retrospective longitudinal study analyzing recruitment data, strategies, and costs from our dTMS clinical trial in older adults with depression (ClinicalTrials.gov: NCT05855850). The results of this study demonstrated (1) healthcare provider outreach within inpatient and outpatient mental health clinics at the associated hospital (i.e., St. Joseph's Healthcare) and (2) Facebook advertising as the greatest source of referrals, producing 20.54% and 74.59% of the total 185 referrals, respectively. Furthermore, we found evidence supporting the effectiveness of (1) healthcare provider outreach within inpatient and outpatient mental health clinics and (2) Facebook advertising as recruitment methods for older adults with MDD, with enrollment ratios of 0.316 and 0.072 persons enrolled per referral received, respectively. Other recruitment methods yielded no enrollments, such as recruitment to providers outside of the mental health system (e.g., family physicians).

Several important aspects of recruitment must be considered when understanding accrual challenges: first, the ability of researchers to effectively target the desired demographic through traditional or digital recruitment methods. Traditional methods primarily include patient referrals, flyers, or public advertisements (Adams et al., 1997; Feman et al., 2008). In the post-COVID era, clinical research has adapted to digital research designs (Mahoney & Sridhar, 2023; McGregor et al., 2024; Steinhilber et al., 2023). In line with this shift, online recruitment modalities should be considered. Recent data suggest online recruitment methods may lead to faster, more effective recruitment compared to traditional methods (Moseson et al., 2020; Reuter et al., 2021). In

accordance with these data, we found Facebook advertising generated nearly 75% of all referrals over the course of 14 months. However, in comparison to recruitment via inpatient and outpatient mental health clinics, the enrollment rate (i.e., persons enrolled per referral received) for Facebook was lower. This may be explained by a greater ability for healthcare providers — with often years of experience in clinical assessments — to correctly identify eligible individuals. Thus, additional education related to identifying eligible clinical research participants may have further improved recruitment. Successfully recruiting individuals who meet a study's eligibility criteria poses a significant barrier to recruitment (Institute of Medicine (US) Forum on Drug Discovery, 2010). As such, incorporating recruitment methods aimed at healthcare networks is essential. Conversely, although Facebook yielded the highest number of referrals, such referrals were self-referrals, and less likely to translate into active participant status. That is, they were often excluded for not meeting our study's inclusion criteria. These individuals voluntarily participated in the screening survey and may not have been suitable candidates. In addition, this strategy was the most expensive per ECR. Nonetheless, this online recruitment method yielded 10 (45.45%) of the total enrollments and was a worthwhile recruitment strategy. Future researchers should aim to diversify recruitment methods to maximize enrollment. This includes considering recruitment methods such as Facebook, despite its lower referral-to-enrollment rate, as it can increase the likelihood of study enrollment.

Regarding the ECR analysis, we found Facebook produced an ECR of 0.00108 persons enrolled per $CAD, or approximately $925.93/enrolled participant. Recruitment

from providers within the affiliated inpatient and outpatient mental health clinics yielded an ECR of 0.00186 persons enrolled per $CAD, or, an estimated $537.63/enrolled participant. To compare these costs with published data, a systematic review by Speich et al. (2018) found that the median cost per recruited participant across 56 trials was $409 USD (converted: ~$530 CAD), with a range of $43 USD (~$56 CAD) to $103,254 USD (~$133,869 CAD). The large body of referrals from Facebook required additional time and costs related to screening referrals, calling potential participants, and booking in-person screening visits. Considering the fewer number of referrals from inpatient and outpatient mental health sources, less time was spent screening, calling participants, and booking visits for prospective participants. However, research personnel spent a comparable amount of time meeting with healthcare professionals to encourage recruitment from clinics and to discuss referral strategies. The data from our study suggest the more time and/or money spent on a recruitment strategy, the more referrals it is likely to produce, and in turn, enrollments.

It is also important to consider the relatively high cost of Facebook advertising in addition to labour costs. The ECR for inpatient and outpatient mental health clinic recruitment only encapsulated labour costs, as additional advertising costs were not required. In contrast, Facebook can be a high-cost advertising method, with additional time spent screening a large number of referrals. Thus, both recruitment strategies demonstrated value and suggest that multiple strategies may be necessary to diversify recruitment strategies and expedite enrollment. A recent analysis (Murphy et al., 2022) from a clinical trial found that Facebook was the most efficacious recruitment method (in

terms of enrollments per cost) for older adults with sedative use, outcompeting TV advertisements, newspaper advertisements, Google, and healthcare provider referrals, among other methods. Moreover, research indicates that older adults exhibit higher click-through rates on Facebook for clinical trial recruitment advertisements compared to younger age groups (Cowie & Gurney, 2018). In line with these findings, we were able to recruit and enroll a significant number of older adults from Facebook. Thus, Facebook may be a valuable recruitment method which can be used to target older adult populations.

In addition to the recruitment cost analysis, we conducted a verbal thematic analysis of potential facilitators and barriers to recruitment. We identified several common facilitators experienced by participants, including (1) perceived social support from research personnel, (2) having a positive and/or worthwhile experience, and (3) flexible scheduling and accommodation. A recent cardiovascular clinical trial (Addison et al., 2022) found that social support from peers and health coaches significantly increased participation. Importantly, older adults with low social support have increased risk of depression (Ng et al., 2014). While social support is a known determinant of physical health and well-being (Chollou et al., 2022; Reblin & Uchino, 2008), research studies demonstrating the importance of social support in clinical trial participation are lacking. Considering the association between low social support and depression in older populations, we encourage future researchers to examine the impact of social support on clinical trial recruitment for older adults with depression, as this may help reduce costs by enhancing recruitment.

Conversely, the most common recruitment barriers included (1) a high level of time commitment, (2) accessibly challenges when entering and exiting the research facility (3) a considerable commute to the research center, and (4) negative expectations or hesitancy towards enrolling in the dTMS study. Given that neuromodulation is an emerging area of research, there is a paucity of research exploring recruitment barriers in clinical trials with brain stimulation interventions, such as dTMS. Examining these factors may help with strategic recruitment. In accordance with our clinical trial, dTMS interventions for depression typically occur over a time-intensive acute period spanning 20 sessions, in which participants visit the research facility five days a week for four weeks (Di Passa et al., 2024). This high level of time commitment should be further investigated as a potential barrier to recruitment for dTMS interventions. In a recent nationwide survey from the United States (Cortright et al., 2024), individuals with depression, their caregivers, and other community members identified "a lack of understanding of intervention" as a significant barrier to accessing TMS treatment. It is possible that this lack of understanding may contribute to negative expectations or hesitancy towards dTMS treatment, thus acting as a potential barrier to recruitment for dTMS trials in older adults. Researchers should consider this potential knowledge barrier when designing effective recruitment methods and aiming to improve accrual rates. Thus, researchers should aim to bridge the knowledge gap between the public and neuromodulation interventions to increase the likelihood of participant recruitment and enrollment.

Another important consideration concerns transportation coverage and accessibility. During the recruitment phase of our trial, several prospective participants were discouraged from participating due to transportation challenges. Two participants who completed the trial voiced this challenge at the follow-up session. Older adults often present with mobility impairments (Gray-Miceli, 2017; Jia et al., 2019), affecting their ability to travel to in-person sessions. Transportation challenges may also affect an older individual's willingness to participate in research (Rigatti et al., 2022). Notably, some participants who completed the trial expressed their appreciation for the transportation coverage provided by our research team. Participants were routinely provided with free parking vouchers or bus passes at each visit. To assist with potential mobility and accessibility challenges within this special population, regular transportation compensation should be provided to older adult participants in clinical research as a means to (1) enhance recruitment and (2) offer accommodation.

Limitations

This retrospective longitudinal study has limitations. First, we were not able to provide a comprehensive evaluation of effectiveness for recruitment methods that were terminated early due to funding limits and/or a low number of referrals. Therefore, an adequate trial analyzing their effectiveness was not feasible. Second, the ECR calculation was based on two estimations: (1) an estimation of the time spent performing recruitment activities, and (2) an estimation of the research staff's hourly wage. Though we aimed to measure the median hourly wage of research assistants in Ontario, Canada, the research personnel

differed in their hourly wage. Thus, this estimation may not precisely reflect the actual labour costs incurred. Lastly, due to the retrospective nature of this study, the methodological design implemented in our original clinical trial was not constructed to assess the recruitment aspects of our study. Therefore, data was retrospectively collected to evaluate recruitment outcomes most accurately.

Conclusion

We found evidence supporting the use of (1) healthcare provider outreach within the affiliated inpatient and outpatient mental health clinics and (2) Facebook as effective recruitment methods to target older adults with depression for a dTMS clinical trial. The impact of social support provided by research personnel and the time-intensive aspect of dTMS interventions should be further investigated as potential facilitators of and barriers to recruitment among older adults with depression.

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Conflicts of Interest Statement

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Chapter 4. Discussion

4.1. Summary

This dissertation aimed to provide insights into the applications of dTMS in older adults with depression. In study 1, we found predominant evidence supporting the clinical efficacy of dTMS for the treatment of depressive episodes among patients with bipolar disorder (BD) and major depressive disorder (MDD). Though studies in older adults were limited, one randomized controlled trial in older adults with treatment-resistant depression (TRD) showed positive findings, with reports of greater remission rates in the active dTMS condition compared to the sham condition. In study 2, we explored the effectiveness of diverse recruitment methods in an ongoing dTMS trial for older adults with TRD. Following an enrollment-cost analysis, we determined (1) health provider outreach within the affiliated inpatient and outpatient mental health clinics and (2) Facebook, to be the most effective recruitment strategies. Finally, social support from research staff and the time-intensiveness aspect of dTMS treatments were identified as potential facilitators and barriers to recruitment, respectively.

4.2. Clinical Efficacy of Deep Transcranial Magnetic Stimulation in Older Adults with Depression

Following a systematic review of current evidence regarding the clinical efficacy of dTMS across psychiatric and cognitive disorders (study 1), we found that the majority of evidence supports the use of dTMS for the treatment of depressive episodes in patients with BD or MDD. Specifically, evidence of its clinical efficacy was found across six

studies investigating the H1-coil (Filipčić et al., 2019; Gajšak et al., 2023; Kaster et al., 2018; Levkovitz et al., 2015; Matsuda et al., 2020; Tavares et al., 2017) adding further support for the H1-coil's clinical applications in depression. While the growing number of trials support dTMS as a viable treatment option for individuals with depression, we encourage researchers to conduct dTMS interventions specially targeting older populations with depression. Research exploring such interventions in older adults is limited. Following a review of dTMS literature, a single study (Kaster et al., 2018) demonstrated the clinical efficacy of the dTMS H1-coil, relative to sham, in older adults with TRD. Specifically, remission and response rates were significantly higher in the H1-coil group compared to the sham group. The findings from this sham-controlled study (Kaster et al., 2018) hold clinical value for older adult populations with depression, as controlled dTMS studies in older adults are highly warranted to inform clinicians of clinical efficacy. In fact, very few studies to date (with or without controlled conditions) have examined the applications of dTMS in older adults. A real-world post-marketing study (Roth et al., 2024) collected data from 247 patients, aged 60 to 91, with treatment-resistant MDD. Following a minimum of 20 dTMS sessions with H1-coil, there we notable improvements in the Hamilton Depression Rating Scale (HDRS) scores, with response and remission rates of 73% and 73%. Moreover, treatment was well-tolerated, with no reports of serious adverse events. From this study's findings (Roth et al., 2024), it is apparent that the H1-coil is a tolerable treatment modality providing significant clinical benefit which can be extended to older populations. Furthermore, a conference abstract (Stultz et al., 2023) showcased findings from a study in which older adults (over the age

of 70) with TRD underwent a mean of 33.22 dTMS sessions. Following treatment, the authors observed significant improvements in Beck Depression Inventory (BDI) scores ($t = 6.19$, $p < 0.001$), with only mild side effects, such as headaches, vertigo, and muscle twitching, being reported (Stultz et al., 2023).

The findings of these studies (Roth et al., 2024; Stultz et al., 2023) offer great prospects for the treatment of geriatric depression, with dTMS treatment appearing to be a clinically beneficial and tolerable intervention in older adults with TRD. However, while the findings of these studies are encouraging, a thorough assessment of the clinical efficacy of dTMS in older adults is restricted by the lack of a sham/control condition. The paucity of sham-controlled studies is alarming. To date, only one study (Kaster et al., 2018) has examined the H1-coil relative to a controlled condition. A comprehensive evaluation of dTMS clinical efficacy in older adults with depression is vital to inform clinicians, assist with healthcare decision-making processes, and to provide patients with evidence-based solutions. The research developments on the forefront of geriatric depression remain low. According to the ClinicalTrials.gov database, only four clinical trials (ClinicalTrials.gov ID: NCT03978182, NCT01521052, NCT03665831, NCT05855850) are currently conducting dTMS research in older adults with depression. Of note, one of these trials (NCT05855850) is the pilot study discussed in Chapter 1, from which the data for study 2 was gathered. When comparing these four trials to the number of ongoing dTMS trials for depression in non-geriatric populations, this number becomes trivial. The lack of dTMS research among older adults remains a principal

barrier to a global assessment of dTMS clinical efficacy (including efficacy by H-coil type), hindering the development of evidence-based and generalizable clinical practices.

4.3. Underrepresentation of Older Adults in Clinical Research on Deep Transcranial Magnetic Stimulation

The systemic underrepresentation of older adults in clinical trials has been long reported. Importantly, the paucity of dTMS research in older populations is a significant barrier to enhancing evidence-based practice for geriatric depression. With most dTMS trials being conducted in younger or middle-aged adults, evidence of clinical efficacy from these trials may not be generalizable to older populations, thus preventing a thorough assessment of dTMS's applicability in geriatric psychiatry. Older adults are often excluded from clinical trial research for a variety of reasons, such as researchers implementing arbitrary upper age limits and implementing exclusion criteria for certain medical conditions which are more common among older age groups (Herrera et al., 2010; van Marum, 2020). Other cited reasons for the possible underrepresentation of older adults in clinical research include, but are not limited to, ageism (Briggs et al., 2012; Cherubini et al., 2010; Schroyen et al., 2014), health bias towards older patients (Caskie et al., 2022), and transportation challenges (Rigatti et al., 2022). In line with these findings, we identified transportation challenges as a potential barrier to recruitment in study 2, which could potentially affect an older individual's willingness to participate. Moreover, researchers may be less inclined to recruit and enroll participants who are more likely to encounter transportation challenges.

Considering the vast underrepresentation of older adults in clinical research, recruitment studies are highly valuable, offering a blueprint for future clinical trials in older adults. Study 2 aimed to address this underrepresentation in the literature by providing researchers with a detailed "blueprint" on how to effectively recruit older adults with depression for dTMS research. With study 2 acting as a preliminary step to advance dTMS research in older adults, future sham-controlled trials are necessary to examine the moderators of dTMS treatment efficacy and tolerability in older populations. For instance, it is possible that concomitant medication use in the elderly may impact dTMS treatment outcomes. In a former real-world study, the authors (Deppe et al., 2021) examined differences in response rates within a cohort of middle-aged adults with depression who were using lorazepam (i.e., a benzodiazepine) compared to those who were not. Though both groups showed improvements in depressive symptoms following a course of rTMS, such improvements were less noticeable in individuals taking lorazepam. Notably, global reports of benzodiazepine use point towards older adults as the highest users, particularly those 85 years and older (Brett et al., 2018; Smith & Tett, 2009). Therefore, concomitant medication use in older adults, such as the use of benzodiazepines, should be investigated as potential moderators of treatment efficacy. However, the identification of valuable moderators of dTMS treatment response, tolerability, and efficacy, can only be achieved with substantial research developments in older adults and by overcoming the prevalent issue of their underrepresentation in clinical research.

4.4. Social Support: An Important Consideration for Clinical Research in Older Adults with Depression

In study 2, we identified potential facilitators and barriers to recruitment following a verbal thematic analysis of qualitative interview data. The most frequently reported facilitator of recruitment was perceived social support from research staff (n = 15, 88%). This facilitator was the most commonly identified compared to all other facilitators and barriers, such as having a positive experience and the time-intensive aspect of dTMS interventions, respectively.

Lack of social support and loneliness are key risk factors for depression in older adults (Czaja et al., 2021; Donovan & Blazer, 2020; Son et al., 2022; Tengku Mohd et al., 2019; Turner et al., 2022). Older adults with limited social resources or low social support tend to have poorer prognoses, including higher rates of disability (Dehghankar et al., 2024) and reduced well-being (Czaja et al., 2021; Lu et al., 2023). Notably, higher perceived social support and fewer interpersonal conflicts have been found to be predictive of treatment response in older adults with depression (Woods et al., 2021). Considering the protective nature of perceived social support, it warrants attention for clinical researchers in the field of geriatric depression. Indeed, research has highlighted the importance of social support and socialization for older adults participating in clinical research (Schlenk et al., 2009). However, studies analyzing the impact of recruitment facilitators, such as social support, in older adults with depression are scarce. An existing study (Polacsek et al., 2019) emphasized the importance of mental health nurses providing support to older adults with depression as a means to promote health-seeking

behaviours. Though this study did not involve clinical research, it nonetheless demonstrates the instrumental value of social support as a method to recruit and provide supportive care to older adults with depression.

4.5. Future Directions

The current literature lacks insights into the clinical efficacy of dTMS for older adults with depression. Though several clinical trials highlight the clinical efficacy of dTMS interventions for depression, much of this research has been conducted in younger-to-middle age groups. Importantly, the lack of dTMS research in older populations is a principal barrier to evidence-based care, as the findings from younger-to-middle aged adults may not be generalizable to older age groups. Therefore, future researchers should aim to conduct sham-controlled dTMS studies in older adults with depression to determine if current evidence surrounding clinical efficacy of dTMS for depression is also applicable to older populations. As a preliminary step, researchers should investigate other important facilitators and barriers of recruitment in older adults with depression as a means to expedite clinical research in this underrepresented age group.

4.6. Conclusion

As determined by study 1, the current literature supports the use of dTMS as a clinical efficacious treatment for depression. However, the extendibility of this clinical efficacy remains ambiguous in older populations, with a single trial (Kaster et al., 2018) showing evidence of efficacy in older adults. More research in older adults is needed to address the

unique needs of this special population, including moderators of dTMS outcomes. The underrepresentation of older adults in clinical research remains a prevalent barrier to evidence-based care among older age groups. Clinical research should focus on determining different facilitators and barriers of dTMS research in older adults, especially the role of social support, in facilitating recruitment.

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