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Improving Transcranial Magnetic Stimulation (TMS) Treatment for Depression

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique with proven efficacy for treating depression. However, its effects are limited by individual and condition-related heterogeneity, leading to unsatisfactory outcomes in many cases. As most patients only begin TMS after unsuccessful pharmacological and/ or psychotherapeutic treatments, there is an urgent need to improve TMS outcomes. To address this issue, this thesis investigates ways to improve TMS treatment and consists of the following two parts. (1) A scoping review of augmentation strategies for TMS in depression. We conducted a comprehensive literature search for tested additional interventions alongside a TMS course. Following data extraction and quality assessment, two broad categories were identified including additional non-invasive neuromodulation techniques (including additional TMS) and additional non-neuromodulation approaches. Despite high heterogeneity of study design and treatment parameters, some strategies stood out with early-evidence efficacy. Suggestions were made as to clinical implications and future research directions. (2) A feasibility pilot study testing a dual neuromodulation approach synchronising TMS pulses to peak waves of transcranial alternating current stimulation (tACS). We specifically tested a newer form of repetitive TMS called intermittent theta burst stimulation (iTBS) and thus termed the dual technique “tsiTBS”. This pilot study expanded on a prior study in healthy participants and confirmed the feasibility of multi-session tsiTBS in a patient group of mild-to-moderate depression. Consistent with previous findings, participants showed a more positive shift in emotional bias following the tsiTBS compared to iTBS alone, indicating possible enhanced antidepressant efficacy. In addition, the tsiTBS had generally good acceptability as revealed by interview data and self-reported side-effect measures.

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Abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDI	Beck Depression Inventory
BLT	Bright light therapy
CBT	Cognitive-behavioural therapy
CGI	Clinical Global Impressions Scale
CRT	Choice reaction task
cTBS	Continuous theta burst stimulation
dIPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
dmPFC	Dorsomedial prefrontal cortex
dTMS	Deep transcranial magnetic stimulation
EBT	Emotional bias task
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
FPN	Frontoparietal network
GAD-7	General Anxiety Disorder-7
HDRS	Hamilton Rating Scale for Depression
HF	High-frequency stimulation
ICA	Independent component analysis
iTBS	Intermittent theta burst stimulation
LF	Low-frequency stimulation
LTD	Long-term depression
LTP	Long-term potentiation
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MRI	Magnetic resonance imaging

NMDA	N-methyl-D-aspartate
OCD	Obsessive compulsive disorder
PET	Positron emission tomography
PHQ-9	Patient Health Questionnaire-9
rACC	Rostral anterior cingulate cortex
RCT	Randomised controlled trial
rlOFC	Right lateral orbitofrontal cortex
rMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious adverse event
SBL	Sequential bilateral
sgACC	Subgenual anterior cingulate cortex
SN	Salience network
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TPS	Transcranial pulse stimulation
TRD	Treatment-resistant depression
WSAS	Work and social adjustment scale

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General introduction

Distinguished from transient mood state experienced in everyday life, major depressive disorder (MDD) is clinically characterised by persistent low mood and anhedonia, neurovegetative symptoms (e.g., disrupted sleep and appetite), cognitive difficulties (e.g., reduced concentration and inappropriate guilt), psychomotor retardation or agitation, and/ or suicidal thoughts (Marx et al., 2023; Otte et al., 2016). It is identified as a primary cause of disability worldwide and a leading contributor of global health-related burden (WHO, 2017). First-line therapeutic modalities include antidepressant medications and psychotherapy, but the treatment effect can be limited (Voineskos et al., 2020). At least 30% of patients with MDD have treatment-resistant depression (TRD) who fail to show clinically meaningful improvement after a minimum of 2 antidepressants (McIntyre et al., 2023). More than half of the patients have less than 50% reductions in symptoms despite at least 3 months of usual treatments (El-Hage & Fakra, 2016). In this aspect, neuromodulation has been developed as a complementary or alternative approach to traditional pharmacotherapy and psychotherapy and hold promise for the treatment of TRD (Conroy & Holtzheimer, 2021; H. Li et al., 2021; Piccoli et al., 2022). By modulating the electrical activity of the central nervous system, such techniques regulate the neural activity of specific brain regions, address the dysfunctional communication between neuronal networks, and target the depressive brain at a circuit level for behavioural changes (Conroy & Holtzheimer, 2021; Guo et al., 2023).

TMS: basic mechanisms and application in depression

Transcranial magnetic stimulation (TMS) is a non-invasive form of neuromodulation intervention for depression. Its high cost-effectiveness and clinical efficacy have been confirmed by an extensive series of clinical trials supported by multiple meta-analyses, network meta-analysis and umbrella reviews progressively collated since its clearance by the US Food and Drug Administration (FDA) in 2008 and by the UK National Institute for Health and Care Excellence (NICE) in 2015 (Fitzgerald et al., 2022; Miron et al., 2021; Vida et al., 2023). On the principle of electromagnetic induction, a TMS device delivers rapidly changing electrical current through a magnetic coil placed on the scalp and thereby generates a changing magnetic field penetrating the skull without impedance. This in turn induces electrical currents at the cortical surface leading to action potentials in the brain (Bhattacharya et al., 2022). Repeated stimulation, or repetitive TMS (rTMS), is used to induce changes in neuronal excitability lasting beyond the stimulation period as a therapeutic method for

neurological and psychiatric conditions (Klomjai et al., 2015). In general, lower frequencies ($< 1\text{Hz}$) have inhibitory while higher frequencies ($> 5\text{Hz}$) have excitatory effects. Such rTMS aftereffects are believed to depend on mechanisms similar to long-term potentiation (LTP) and long-term depression (LTD), which involve N-methyl-D-aspartate (NMDA)-dependent postsynaptic calcium influx supporting long-lasting changes in synaptic strength (Bliss & Cooke, 2011). Preclinical evidence further identified plasticity-related changes at a range of neurobiochemical systems including neurotransmitters, genetic expressions, neuroprotection, and neurotropic factors (Chervyakov et al., 2015).

The most used stimulation target is the dorsolateral prefrontal cortex (dlPFC), a brain region critically involved in cognitive control and emotion regulation processes (Helion et al., 2019). This is based on the hypothesis of prefrontal imbalance that postulates the relative hypometabolism of the left dlPFC and the relative hypermetabolism of the right dlPFC in MDD (Grimm et al., 2008; M. Zhang et al., 2021). High-frequency and low-frequency rTMS are therefore typically applied over the left and the right dlPFC to increase or decrease brain activity respectively. Although the exact therapeutic mechanism of rTMS remains unknown, the current emphasis is on its global impact on the brain activity by engaging multiple sites of neural networks beyond the stimulation site (Borrione et al., 2020; Philip et al., 2018; Taib et al., 2018). Under the network model of depression, there shows a general tendency of increased emotional processing and decreased cognitive regulation, involving altered functional connectivity within and between key intrinsic networks (B. J. Li et al., 2018; Pizzagalli & Roberts, 2022). This mainly involves the default mode network (DMN), which is predominantly engaged in resting states and self-referential processes, the frontoparietal network (FPN), which is critical for goal-directed behaviours and decision-making processes, the salience network (SN), which is responsible for directing attention to external stimuli, and parts of the limbic system (Dichter et al., 2015). MDD is consistently characterised by the hyperconnectivity within the DMN, which is often linked to the hypoconnectivity within the FPN and the SN as well as the hyperconnectivity between the DMN and the FPN (To et al., 2018). This is associated with cyclic negative thought pattern, worsened cognitive control, and excessive rumination as parts of depressive symptoms (Hamilton et al., 2015). The connectivity between the dlPFC and the anterior cingulate cortex (ACC), both taking a hub position in these key intrinsic networks, plays a prominent role in the successful application of rTMS over the dlPFC (Salehinejad et al., 2021). Treatment effects have been associated with the attenuation of the DMN hyperactivity through remote suppression of the subgenual ACC (sgACC) by the dlPFC as well as a selective reversal of grey matter deficits in ACC

(Fox et al., 2012; Lan et al., 2016; Liston et al., 2014). More on the possible ACC modulation mechanism as a basis of rTMS therapy will be discussed in Chapter 2 [2.1.1].

The current gold-standard protocol for depression is high-frequency rTMS at 10Hz to the left dlPFC totalling 3000 pulses over 37.5 minutes per treatment session (Lefaucheur et al., 2020). A typical treatment course involves 20 to 30 daily sessions over 4 to 6 weeks. Novel forms are being investigated, for example, using new coil types such as H-coil to target deeper brain regions, using new stimulation targets such as the dorsomedial prefrontal cortex and the lateral orbitofrontal cortex, and using accelerated schedules with multiple treatment sessions delivered daily (Chen et al., 2023; Feffer et al., 2018; Miron et al., 2021). As one of the most established new protocols, theta burst stimulation (TBS) involves triplet bursts of 50Hz pulses repeated at 5Hz, mimicking the natural firing pattern within the hippocampus that underlies the induction of synaptic plasticity (Chung et al., 2017; Li et al., 2019). The intermittent form of TBS (iTBS), patterned as 2s-on and 8s-off, produces long-lasting excitatory effects by means of LTP-like mechanisms (Suppa et al., 2016; Lee et al., 2021). Its non-inferiority to standard 10Hz rTMS was proven by the THREE-D trial, the largest randomised multicentre trial to date in this area of research, where a head-to-head comparison between the two protocols was performed in patients with TRD (Blumberger et al., 2018). This result was later replicated in a real-world clinical sample (Spitz et al., 2022) and in patients with higher degrees of treatment resistance with a long follow-up period of 6 months (Bulteau et al., 2022). With significantly shorter treatment time involved (3 to 10 minutes), iTBS allows better clinical capacity and reduced hospital exposure compared to conventional protocols without compromising treatment effectiveness (Mendlowitz et al., 2019).

Thesis aims and structure

Although TMS is a promising treatment for depression, its response and remission rates remain modest and evidence to support its long-term benefits is limited (Downar et al., 2016; Somani & Kar, 2019). Clinical responsiveness highly varies among individual patients with a general tendency showing poorer treatment outcomes associated with severer medication resistance (Gonterman, 2023; Voigt et al., 2019). Considering the amount of time and resources committed to a course of treatment, better treatment strategies are urgently needed to optimise the clinical utility of rTMS in depression. To address this, this thesis consists of the following two projects with the overarching goal to improve TMS treatment in depression.

Scoping review

We conducted a scoping review to explore the augmentation strategies for rTMS to treat unipolar depression as described in Chapter 1. It aimed for a comprehensive and up-to-date review of approaches that clinicians can take when a standard course of rTMS treatment only yields limited antidepressant response in patients. The method of scoping review was chosen based on the initial literature search showing a wide range of potential augmentation interventions but a limited number of studies per se.

Feasibility pilot study

A randomised, sham-controlled pilot study was conducted to test the feasibility and tolerability of synchronising iTBS pulses with peak waves of transcranial alternating current stimulation (tACS) in a patient group with mild-to-moderate depression. This approach capitalised on the state-dependency of rTMS, meaning that its therapeutic effect is a combined result of the stimulation and the neural context at the time of stimulation, and tACS was hypothesised to create a favourable oscillatory environment for its performance. The background, method, results and discussion of the study were written into Chapter 2.

Chapter 1. Scoping review: Augmentation Strategies for TMS in Depression

1.1 Introduction

rTMS is a safe and well-tolerated neuromodulation technique to treat depression with well-established clinical efficacy (Miron et al., 2021). Standard rTMS protocols involve applying high-frequency ($> 5\text{Hz}$) and low-frequency ($< 1\text{Hz}$) electromagnetic pulses to the left and right dlPFC respectively, commonly used as an adjunct to pharmacotherapy or psychotherapy for the management of refractory depression (Idlett-Ali et al., 2023). However, the treatment effect of rTMS can be limited in some patient groups, which may be explained by patient and disease heterogeneity (Brini et al., 2023; Kar, 2019; Wen & Zheng, 2023). Depression is a highly complex condition characterised by a wide range of aetiologies and clinical presentations and multidimensional changes across cognitive, emotional, sensorimotor and homeostatic functions (De la Torre-Luque & Bornas, 2017; Y.-C. Tsai et al., 2023). Treatment effect can vary as a function of clinical factors including demographic features (e.g., age and gender), brain states (or brain activity at a given moment in time), and distinct disorder profiles (e.g., dominant symptoms and episode severity) (Dalhuisen et al., 2022; Kar, 2019). This is further complicated by the uncertainty regarding optimal rTMS stimulation parameters for depression including stimulus intensity, frequency, coil placement, and number of doses. Given that most patients resort to rTMS only after inadequate response to available medication or psychotherapeutic treatment regimes, there is an urgent need to optimise rTMS for enhanced and prolonged clinical performance. Current efforts in this aspect mainly focus on the following areas: (1) adjustments to stimulation parameters and targeting techniques, (2) manipulations of the brain state, (3) interactions with antidepressant medications, and (4) development of better maintenance protocols (Giandomenico Schiena et al., 2020; Trapp et al., 2024). Nonetheless there is still a lack of consensus as to what to do when there is inadequate response to a standard course of rTMS.

To address this issue, this scoping review focuses on “augmentation” which refers to the addition of a second agent to an existing treatment in order to increase the response and remission rates of patients (Moret, 2005; Schweitzer et al., 1997). This is a well-established strategy when patients do not achieve sufficient response to an antidepressant medication. A similar approach is likely applicable to rTMS. Synergistic effects may be obtained by a combined approach working across

different levels such as pharmacological, psychological, cognitive, and neuromodulatory (Baeken et al., 2019). An initial literature search identified reviews on specific combination or augmentation approaches. For example, treatment effects can be optimised by personalising stimulation parameters with neuroimaging techniques, priming one rTMS protocol with another, or adopting a bilateral approach (Wen & Zheng, 2023). In addition, rTMS has been combined with ketamine (Arubuolawe et al., 2024), types of antidepressants (Kochanowski et al., 2024; Sohn et al., 2024), psychotherapy (Bajbouj & Padberg, 2014; He et al., 2022; Sathappan et al., 2019), modalities of deep brain stimulation (D'Onofrio et al., 2023), or acupuncture (Xiao et al., 2024) as attempts for better results. A comprehensive review is still needed to synthesize the available evidence.

In this review, we aimed to (1) comprehensively search the peer-reviewed literature for studies that combined an rTMS protocol with an additional intervention (including additional rTMS) to treat unipolar depression and (2) synthesise available evidence on the efficacy, safety and acceptability of each intervention type to guide future research. A preliminary search on Google Scholar revealed a published abstract of a systematic scoping review on the topic (Giron et al., 2023). However, it was limited to non-pharmacological adjunctive methods and only searched the PubMed database. In addition, it included broadly “neuropsychiatric patients” without focusing on depression alone. We identified at least one pharmacological intervention as an augmentative strategy for rTMS (J. Cole et al., 2022) and anticipated that many studies that meet our criteria should fall outside the scope of the above-mentioned review. No other review on this topic was identified. Based on the initial search, we expected a small number of studies per intervention and a wide variety of augmentation options. The main goal of this study is to identify and map types of available evidence. Therefore, a scoping review was proposed as the most appropriate approach to provide a comprehensive overview in comparison to systematic review or meta-analysis.

1.2 Methods

This scoping review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist (Figure 1.1) (Peters et al., 2022; Tricco et al., 2018). A protocol was prospectively registered with the Open Science Framework on the 8th of December 2024 and updated on 25th of January 2025 (<https://osf.io/hv29p/>).

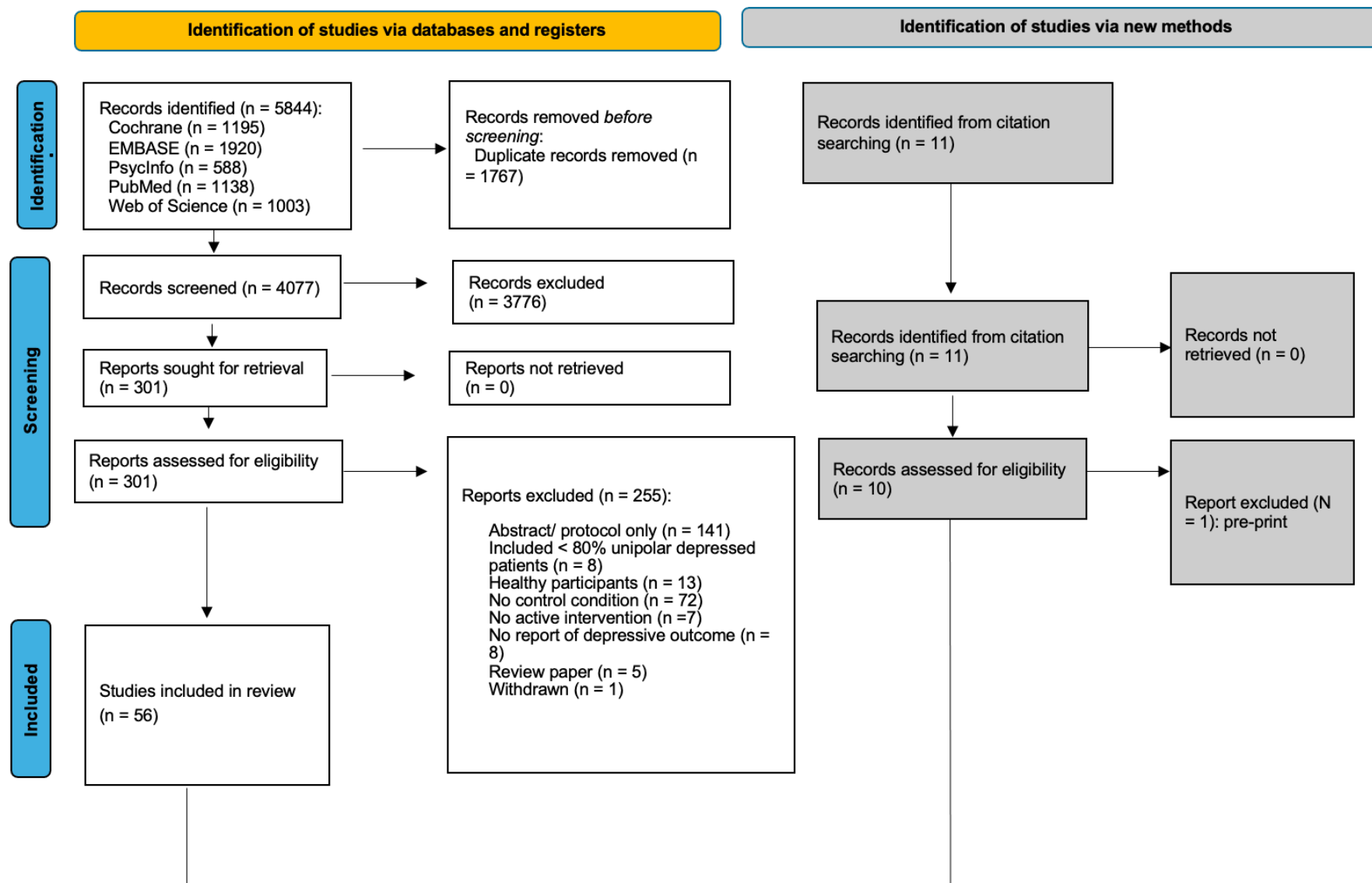


Figure 1.1 PRISMA flow diagram of the systematic review search, screening, and selection process (Haddaway et al., 2021).

1.2.1 Search strategy and eligibility criteria

Eligibility criteria

To be included in the review, studies needed to include (1) an rTMS-only group or, for studies with an uncontrolled design, patients who have already received rTMS monotherapy before with inadequate response, and (2) an augmentation group combining rTMS with an additional intervention at the same time or shortly before or after an rTMS treatment course. This additional intervention could include additional rTMS (e.g., with a different target or pulse sequence, or personalisation of rTMS parameters). Medication could be present if it was present in both groups. To be included, 80% or more of the participants needed to have a diagnosis of a current unipolar depressive episode based on any standard diagnostic instrument or by clinical interview, or a separate analysis should have been reported for patients in line with the diagnosis specified above. Outcome measures needed to include quantified changes in a measure of depressive symptoms before, versus after, treatment. To be included, studies needed to have accessible full report. In the cases of protocols and abstracts, we sought later published full-text articles wherever possible.

Information sources

We considered experimental studies and case reports that intended to enhance rTMS efficacy by combination with additional intervention. The following databases were searched systematically from inception up to August 2024: PubMed, EMBASE, PsychInfo, Web of Science and Cochrane Central Register of Controlled Trials (see Appendix A.1 for full strategies). The search terms were defined as “transcranial magnetic stimulation” and its variants, “depression” and its variants, and “augmentation” and related expressions:

(“transcranial magnetic stimulation” OR “TMS” OR “theta burst stimulation”) AND (“depression” OR “major depression”) AND (“augmentation” OR “priming” OR “combination” OR “optimis” OR “individuali*” OR “personali*” OR “adjunct*”)*

There was no restriction to language. Reference lists from relevant studies and reviews were investigated to further identify studies that meet our eligibility criteria.

1.2.2 Selection of sources of evidence

The search yielded 5844 articles of which 1767 duplicates were removed. One author (Y.P) screened all titles and abstracts for assessment against the inclusion criteria and all citations were then

independently assessed by one of the following authors for agreement (P.B and L.W), with initial agreement between reviewers at 92%. In cases of uncertainty or disagreement, articles at this stage were included for full text review. 301 out of 4077 articles were included for full-text screening where two independent reviewers assessed eligibility for inclusion. Disagreements on study selection were addressed by discussion among the three reviewers. 255 articles were excluded at the stage of full-text screening. Exclusion reasons were not included here due to word limit (55% were excluded due to no available full report, 28% no control condition, 5% testing in healthy participants, 3% including less than 80% unipolar depressed patients, 3% no report of depressive outcome, 2% no active intervention, 2% published as review paper and 1 study was withdrawn). A total of 56 articles, including 10 articles newly identified from references, were eligible for review. All three reviewers participated in the process of data extraction and quality assessment. At least 20% of studies were extracted independently by two reviewers to assess for agreement. A form was developed to record the characteristics of each study including general information, sample characteristics, experimental design, reported depression outcomes and reported side effects or acceptability (see Appendix A.2 for details).

1.2.3 Quality assessment

Appraisal of study quality was based on the quality assessment tools developed by the National Heart, Lung, and Blood Institute (NHLBI; <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>): (1) randomised controlled studies: the Quality Assessment of Controlled Intervention Studies (for studies that randomised patients into groups receiving TMS with and without augmentation intervention); (2) non-randomised controlled studies: the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (for studies that compared TMS with and without an augmentation intervention, without having randomised patients to these groups); (3) non-controlled experimental studies: the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (for studies without a control group that used TMS alone, but including non-responders or non-remitters to a previous course of non-augmented TMS who subsequently received augmented TMS); (4) case studies: the Quality Assessment Tool for Case Series Studies (for studies following a single case study design). Please see Appendix A.3 for all criteria items included under the quality assessment by type.

Quality was assessed by the reviewer conducting data extraction of individual studies. In response to each item in the tool, reviewers selected “yes”, “no”, “cannot determine (CD)”, or “not applicable

(N/A)". Studies were deemed "good" quality if $\geq 80\%$ of criteria were met (percentage expressed as the number of items selected as "yes" divided by the total number of items minus the number of items selected as "not applicable"), "fair" quality if $\geq 50\%$ of criteria were met, and "poor" quality if $< 50\%$ of criteria were met. These thresholds matched those used in a previous report (Briley, Webster, Boutry, et al., 2024). Due to overlapping with the overall risk-of-bias assessment tool (see below), one item was deleted under "case studies" – "Was the length of follow-up adequate?" – and several items were deleted under "randomised controlled studies":

- *Were the exposure(s) of interest measured prior to the outcome(s) being measured?*
- *Was there sufficient timeframe to see an effect?*
- *Was the exposure(s) assessed more than once over time?*

Considering that we only assessed single-case case studies with the case study tool, several items were deleted for simplification:

- *Were the cases consecutive?*
- *Were the subjects comparable?*
- *Were the statistical methods well-described?*

In addition, A 5-item tool was developed to assess the overall risk-of-bias (Table 1.1): (1) Study design adequacy. Case studies and non-controlled experimental studies (i.e., with a crossover design) were considered as "high risk", non-randomised controlled studies as "some concerns" and randomised controlled trials (RCTs) as "low risk". (2) TMS course adequacy. Regarding the length of TMS treatment course in the control condition, studies were high risk if containing fewer than 20 sessions, with some concerns if containing 20-29 sessions and low risk if containing at least 30 sessions or if delivering treatment till remission was achieved. (3) Sham adequacy. Study quality was "high risk" if no sham of the augmentation intervention was used, "some concerns" if insufficient sham was used and "low risk" if sufficient and realistic sham was used. (4) Follow-up adequacy. Studies were high risk if follow-up measures were conducted less than 1 week following the acute course, with some concerns if 1-4 weeks and low risk if more than 4 weeks. (5) Confounding control. Studies without requirement for washout or stable medications prior to commencement were of high risk. Studies including adequate washout or requiring stable medications for at least 2 weeks prior to commencement without tracking changes during the treatment were of "some concerns". Studies including adequate washout or requiring stable

medications for at least 2 weeks prior to commencement and tracking changes during the treatment were low in risk.

	High risk	Some concerns	Low risk
Study design adequacy	Case studies or non-controlled experimental	Non-randomised controlled	RCT
TMS course adequacy	< 20 sessions	20-29 sessions	30+ or till remission
Sham adequacy	No sham	Insufficient sham	Sufficient sham
Follow-up adequacy	< 1 week	1-4 weeks	> 4 weeks
Confounding control	No control strategies	Washout or stable meds prior to start without tracking during	Washout or stable meds prior to start with tracking during

Table 1.1 summary of overall risk-of-bias assessment.

1.2.4 Data summary and synthesis

Following data extraction, all three reviewers went through the extracted data to identify types (themes) of augmentation interventions. Through discussion, a three-level representation was created (Figure 1.2). It was presented to the Neuromodulation Experts-by-Experience Team (NEAT) PPI group at Institute of Mental Health, University of Nottingham. The six group members discussed intervention similarities and differences, and prospective acceptability and feasibility from a patient point of view. The representation was then further refined in discussion with the fourth author (R.M.) and an experienced TMS clinician and researcher who was not part of the research team, followed by a further presentation to the NEAT PPI group. A narrative summary of the literature was performed, focusing on the types of interventions performed, types of evaluation of these interventions, and evidence for acceptability and tolerability.

1.3. Results

1.3.1 Overview of included studies

In total, 56 articles met inclusion criteria (Figure 1.1). The countries of origin included US (10), China (10), Canada (8), Australia (8), India (4), Germany (4), France (2), Italy (2), Austria (2), Russia

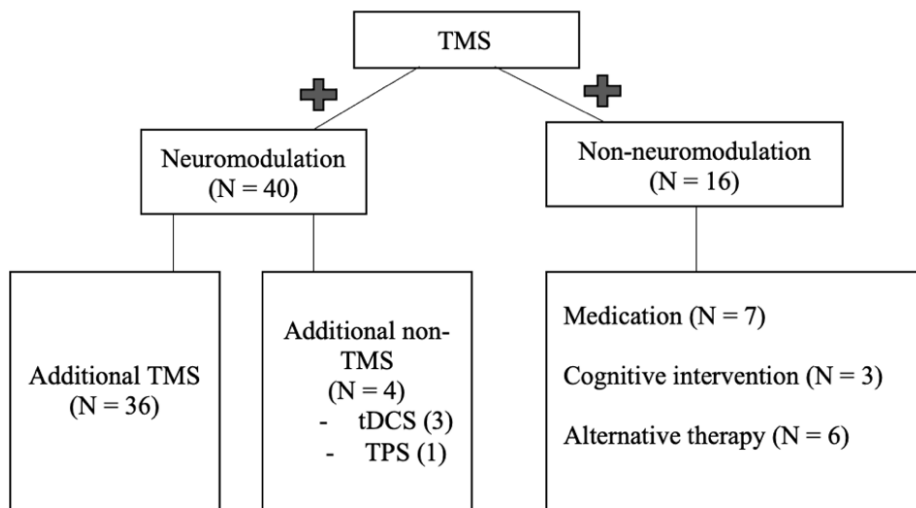
(1), Switzerland (1), Taiwan (1), as well as 2 collaborated by US and Israel, and 1 by US and Netherlands.

For studies using controlled experimental designs, 4572 participants (including 17 bipolar patients) were included in the control group and 1749 (including 36 bipolar patients) in the intervention group. For studies without a separate control group, 533 participants (including 56 bipolar patients) were included. 23 studies included patients with resistance to at least 2 antidepressants after adequate trials and 6 included patients with resistance to at least 1 family of antidepressants after adequate trials. Commonly used outcome measures included Hamilton Rating Scale for Depression (HDRS; N = 34), Beck Depression Inventory (BDI; N = 16), Montgomery-Åsberg Depression Rating Scale (MADRS; N = 16), Clinical Global Impressions Scale (CGI; N = 8), and Patient Health Questionnaire-9 (PHQ-9; N = 6). Multiple rating scales were used in some studies. In terms of the control condition, most studies applied high-frequency stimulation (HF) to the left dlPFC including 44 used 10Hz, 8 used 20Hz, 4 used iTBS protocol, 2 used 5Hz, and 1 used individual alpha frequency. 2 targeted dorsomedial prefrontal cortex (dmPFC) with 20Hz HF. 1 targeted visual cortex with 10Hz HF. 8 studies applied 1Hz low-frequency stimulation (LF) to the right dlPFC, while 1 applied it to the electroencephalogram (EEG) parietal P8 site. 4 studies used deep TMS (dTMS) including 1 used 20Hz dTMS with H1 coil (mainly targeting the left prefrontal), 1 used 18Hz dTMS with both H1 and H7 (mainly targeting the medial prefrontal) coil, 1 used 18Hz dTMS with H1 coil, and 1 used 18Hz dTMS without specifying the use of coil. Some studies included more than one conditions as control.

At the first level, augmentation interventions were categorised into neuromodulation (including additional TMS and non-TMS subgroups) and non-neuromodulation methods (Figure 1.2). Among studies using additional TMS, 19 used a bilateral protocol (Table 1.2.1), 8 personalised TMS parameters (Table 1.2.2), 6 switched treatment target (Table 1.2.3), 4 applied priming (Table 1.2.4), and 4 included additional TMS sessions using the same parameters (Table 1.2.5). These included 1 study categorised under both “Bilateral vs. Unilateral” and “Switch target” (Prentice et al., 2023), 1 under both “Bilateral vs. Unilateral” and “Priming” (Lee et al., 2020), 1 under both “Additional sessions” and “Switch target” (McDonald et al., 2011), 1 under both “Additional sessions” and “Switch target” (Mielacher et al., 2020), and 1 under “Bilateral vs. Unilateral”, “Switch target” and “Additional sessions” (Fitzgerald et al., 2018). In terms of non-TMS neuromodulation interventions (Table 1.3), 3 used transcranial direct current stimulation (tDCS) and 1 used transcranial pulse stimulation (TPS). In terms of non-neuromodulation interventions (Table 1.4), 7 used medications,

3 used cognitive interventions, and 6 used alternative therapies. Note that standard practices included in the control group in some studies were used as interventions in other studies such as optional additional sessions and MRI-neuronavigated targeting method. A summary table of study information is presented under each category. Full study characteristics are not included here due to word limit but will be available upon request for further review.

A.



B.

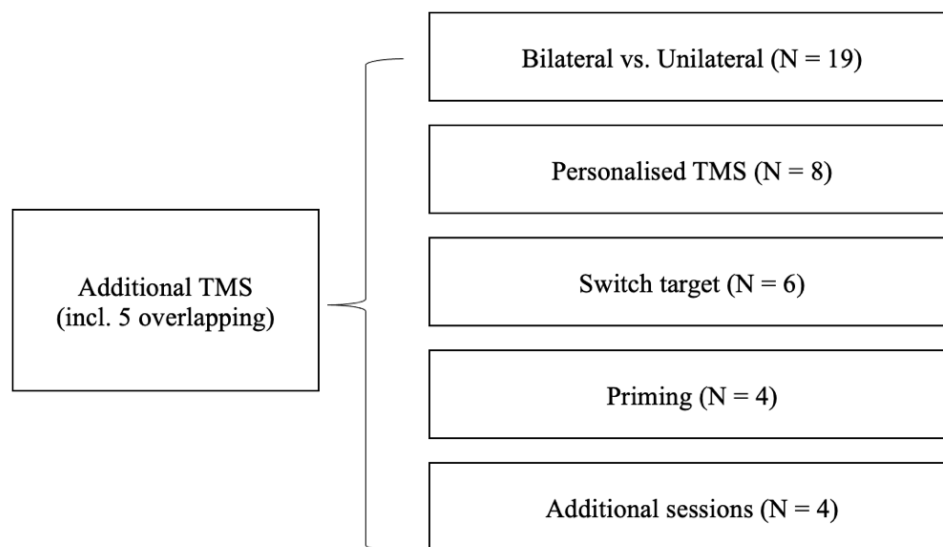


Figure 1.2. A: Overview of intervention categorisation; B: subgroups within additional TMS. tDCS = transcranial direct current stimulation, TPS = transcranial pulse stimulation.

1.3.2 Quality of included studies

We adapted the NHLBI tool to assess study quality by type. Among the 38 RCTs, 9 (23.7%) were rated as “good”, 24 (63.2%) as “fair” and 5 (13.2%) as “poor”. Only 3 studies met the “high adherence” criterion due to lack of information regarding changes in stimulation intensity and numbers of sessions completed. All 3 single-case case studies were rated as “good”. Among the 5 non-randomised controlled studies, 2 (40%) were rated as “good” and 3 (60%) as “fair”. None provided justification for sample size or blinded outcome assessors. Among the 12 non-controlled experimental studies, only 1 (8.3%) was deemed as “good” and the rest (91.7%) as “fair”. Similar to non-randomised controlled category, most studies neither provided justification for the sample size or blinded outcome assessors. Only 3 studies took outcome measures at multiple timepoints before and after the intervention. We used the “robvis” (Risk-of-bias VISualization) R package to generate risk-of-bias assessment figures based on the 5-item overall risk-of-bias assessment tool. Please see Figure 1.3 for an overview of neuromodulation and non-neuromodulation groups (see Appendix A.4 for all-group traffic light figures). A similar trend was seen among all groups showing insufficient use of sham augmentation intervention (most using none) and short outcome follow-up periods (most tracking less than a week following the end of treatment course).

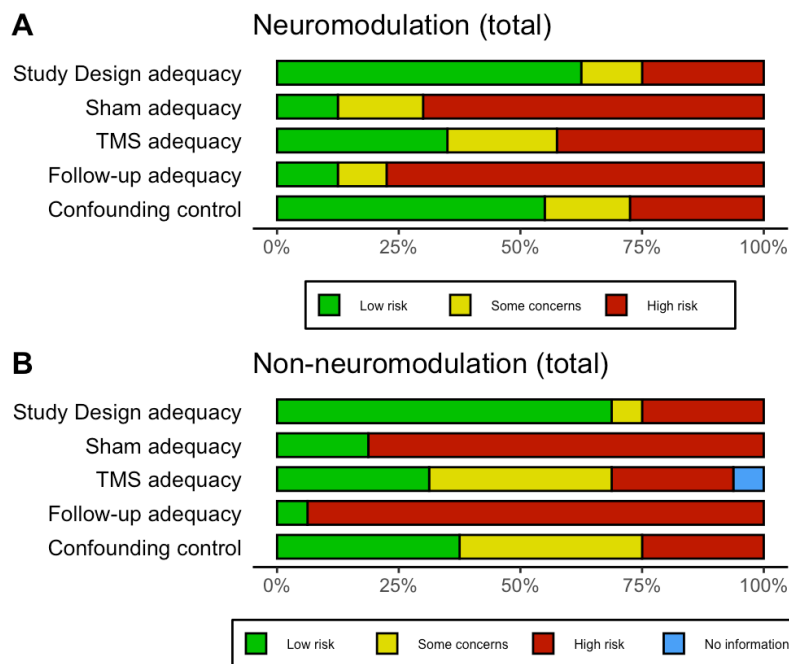


Figure 1.3. Summary risk-of-bias figures for neuromodulation (including both additional TMS and additional non-TMS) (A) and non-neuromodulation (B) group.

1.3.3 Neuromodulation: additional TMS

Bilateral vs. Unilateral

19 studies compared the effects of unilateral and bilateral TMS protocols with great variations between studies regarding sample sizes, study duration, stimulation parameters, target method, choice of outcome measures and control for medications (Table 1.2.1 for summarised study information). In terms of unilateral control conditions, most studies (N = 15) used HF to the left dlPFC, 1 used the right dlPFC, 2 included both as control groups and 1 did not specify the dlPFC protocol used as control. All studies apart from 1 (T. Zhang, Y. Huang, et al., 2021) examined sequential bilateral (SBL) approaches which sequentially applied stimulation to left or right hemisphere in either order. T. Zhang, Y. Huang, et al. (2021) used a round coil which was placed at the centre along the mid-prefrontal cortex covering both left and right dlPFC concurrently. 2 studies applied correction to stimulation intensity as a function of age (Blumberger et al., 2012) or the coil-to-cortex distance (Blumberger et al., 2016). 2 studies (Blumberger et al., 2016; Rybak et al., 2005) controlled the total stimuli in each condition to be the same, while the majority applied more stimuli in the bilateral group and 2 applied more in the unilateral group.

With only 2 exceptions (Blumberger et al., 2012; Mi et al., 2022), most controlled studies (N = 13) suggested non-superiority of bilateral protocols. 4 studies reported numerically better clinical outcomes in the unilateral group, using the following stimulation protocols: 10Hz HF to the left dlPFC alone or followed by 1Hz LF to the right dlPFC (Aaronson et al., 2022), iTBS alone or the combination of iTBS and continuous TBS (cTBS) in either order (Cheng et al., 2016; Li et al., 2014), and sham or active 1Hz LF to the right dlPFC followed by 10Hz HF to the left dlPFC (Fitzgerald et al., 2011). In contrast, 3 studies reported a trend favouring the bilateral protocol. Rybak et al. (2005) tested an “aggressive” form of HF to the left dlPFC at 20Hz unilaterally or bilaterally by combining with 1Hz LF to the right dlPFC. Despite no significant difference in endpoint results, a midpoint numerical trend was reported favouring the bilateral approach. The other 2 studies examined strategies for early non-responders to 10Hz HF to the left dlPFC. Compared to continuation with the same HF protocol, both reported a numerical advantage of switching to SBL using 1Hz LF to the right dlPFC followed by 10Hz HFL to the left dlPFC (Fitzgerald et al., 2018) or the two protocols in either order (Lee et al., 2020).

Interestingly, the bilateral protocol using 1Hz LF to the right dlPFC followed by 10Hz HF to the left dlPFC might have age-specific advantage for older patients. In Blumberger et al. (2012), higher

stimulation intensity was used for patients aged over 60 years old based on previous findings of age-associated prefrontal atrophy. Compared to 10Hz HF to the left dlPFC, the bilateral condition showed significantly better results in remission rates, response rates, and mean decreases in HDRS scores. Even though the finding was not replicated in Blumberger et al. (2016) where no significant difference was found between these two approaches, a sub-analysis of these 2 RCTs (Trevizol et al., 2019) reported dramatic advantages of bilateral treatment in patients over 60 years, with remission rates being 40% and 0% in bilateral and unilateral conditions respectively and response rates being 45% and 0%.

In Aaronson et al. (2022), even though no significant advantage was found comparing SBL protocols to 10Hz HF to the left dlPFC, the sequential order seemed to make a difference. It was observed that HL to the left followed by LF to the right was superior to the other way round, supported by significantly greater improvement in CGI scores. This was further evidenced by the 3 crossover studies where clinical improvement was observed when non-responders to 10Hz HF to the left dlPFC subsequently received the same HF protocol followed by 1Hz LF to either right dlPFC (Cristancho et al., 2019) or right lateral orbitofrontal cortex (rIOFC) (Prentice et al., 2023; Tadayonnejad et al., 2023). Moreover, in Mi et al. (2022), the bilateral group (iTBS followed by 1Hz LF to the right dlPFC) led to significantly higher response rates and HDRS decreases.

In terms of tolerability and safety, most studies did not directly compare side effects or withdrawal rates between groups. 10 studies reported general good tolerability without serious adverse events (SAEs). 2 trials reported development of manic symptoms in 1 patient who received 20Hz HF to the left dlPFC followed by 1Hz LF to the right dlPFC (Hausmann, Kemmler, et al., 2004; Hausmann, Pascual-Leone, et al., 2004) and in 3 bipolar patients from the bilateral group (1Hz LF to the right dlPFC followed by 10Hz (N = 2) or 1Hz (N = 1) HF to the left dlPFC) (Fitzgerald et al., 2011). 1 trial reported 3 SAEs which nonetheless were judged unrelated to rTMS, including 1 case of “myocardial infarction” and 2 cases of suicidality requiring hospitalisation (Blumberger et al., 2012). 1 trial highlighted more cases of dizziness in the bilateral condition (iTBS and cTBS in either order) (Cheng et al., 2016; Li et al., 2014).

	Study type	Sample size	Control for medications	Interventions	Depressive Outcomes	Efficacy	Adverse effects
[1] * Hausmann, Kemmler, 2004	RCT	Unilateral = 12 (including 2 bipolar), Bilateral = 13 (including 3 bipolar)	Washout of five half lives from antidepressants. Lorazepam dose 1-5 mg accepted.	20Hz to the left dlPFC + sham/ active 1Hz to the right dlPFC	HDRS and BDI measured at baseline and on days 1, 3, 5, 7, 10, 14, and 28.	No significant difference in change in either measure up to day 14	1 dropped out from unilateral as could not tolerate sensation; 1 bilateral developed manic symptom.
[2] * Hausmann, Pascual-Leone, 2004						No significant different in change in either measure up to day 28	
[3] Rybak, 2005	RCT	Unilateral = 9 (including 2 bipolar), Bilateral = 9 (including 1 bipolar)	No medication changes for 3 weeks before entry into study.	20Hz to the left dlPFC + sham/ active 1Hz to the right dlPFC	HDRS measured at baseline, and after 5, and 10 treatments. Response: 50% reduction in the HDRS score. Remission: HDRS (17- item) score ≤ 8	Trend favouring the bilateral group at midpoint (session 5), otherwise no significant difference at the endpoint	Not reported
[4] Mi, 2022	Non- randomised controlled	Unilateral = 24, Bilateral = 30	Maintained medication with no new medication during the TMS course.	10Hz HF to the left dlPFC vs. iTBS + 1Hz LF to the right dlPFC	HDRS measured at baseline and after the final session. Response: 50% reduction in the HDRS score.	Significantly better results (greater change in HDRS and higher response rate) in the bilateral group	Not reported
[5] Cristancho, 2019	Crossover	N=17	No control specified over medication	Non-responders to 10Hz HF to the left dlPFC crossed over to bilateral treatment using 10Hz HF to the left dlPFC followed by 1Hz LF to the right dlPFC	HDRS, CGI, and QIDS measured at the start and end of crossover. Remission: HDRS (17- item) score ≤ 7	Improvement in all outcome scores and remission rates after crossover	Adverse effects were described as mild

[6] Prentice, 2023	Crossover	N = 41, including 25 in the rOFC-alone group and 16 in the rOFC-dlPFC bilateral group	No control specified over medication	Non-responders to dlPFC rTMS (unspecified protocol) switched to 1Hz LF to the rOFC monotherapy or bilateral augmentation to the HF to the left dlPFC	BDI measured at the start and end of crossover. Response: 50% reduction in the BDI score. Remission: a final treatment score of BDI ≤ 12	Improvement after crossover; better performance of bilateral protocol; higher trend towards remission in higher anhedonia	Not reported
[7] Tadayonnejad, 2023	Crossover	N = 33	No control specified over medication	Non-responders to 10 sessions of 10Hz HF to the left dlPFC and 10 sessions of iTBS-priming 10Hz HF to the left dlPFC switched to 1Hz LF to the rOFC as the bilateral augmentation to the HF protocol	IDS-SR and PHQ-9 measured at baseline, after every 5 sessions, and at the end of treatment. Response: 50% reduction in the PHQ-9 score.	Improvement in IDS-SR scores and response rates after crossover	No SAE and no subject discontinued treatment before completing the full course of treatment
[8] Blumberger, 2012	RCT	Unilateral = 22, Bilateral = 26	Stable medications 4 weeks prior to and during the trial	10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC (intensity adjusted for age)	HDRS measured at baseline, after every 5 sessions up to 30 sessions Response: 50% reduction in the HDRS score. Remission: a final HDRS (17-item) score ≤ 10 at either 3- or 6-week follow-up	Significantly better results (greater change in HDRS, higher response and remission rates) in the bilateral group	3 SAEs but judged as unrelated to rTMS treatment (1 myocardial infarction in bilateral, 2 suicidality requiring hospitalisation 1 in each of unilateral and sham). More withdrawal in unilateral (n = 10)

							than bilateral (n = 4). Both in unilateral, 1 reported persistent scalp discomfort and 1 recurrent headache.
[9] Blumberger, 2016	RCT	Unilateral = 40, Bilateral = 40	Stable medications 4 weeks prior to and during the trial	10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC (intensity adjusted for cortex-to-coil distance)	HDRS and BDI measured at baseline, 3 weeks and 6 weeks. Response (primary): 50% reduction in the HDRS score. Remission (primary): a final HDRS (17-item) score ≤ 7 at either 3- or 6-week Response and remission (secondary) criteria based on BDI not specified	No significant difference in response or remission rates, change in HDRS, or remission/ response rates based on BDI-II.	No SAE
[10] ** Trevizol, 2019	Sub-analysis of RCTs	Unilateral = 11, Bilateral = 20	Stable medications 4 weeks prior to and during the trial	In patients over 60 years, 10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC	See [8] and [9]	Significantly better outcomes (higher remission rates and greater change in HDRS) in bilateral.	1 reported insomnia and 1 headache in unilateral
[11] Fitzgerald, 2012	RCT	Unilateral = 24, Bilateral = 22	Stable medications 4 weeks prior to and during the trial	Sham/ active 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC	HDRS, MADRS, and BDI measured at baseline and end of treatment. Response (primary): 50% reduction in the HDRS score.	Numerically, but not significantly, greater changes in all three measures, and higher responder rates in unilateral.	No SAE. One patient with a history of needle phobic reactions had a mild vasovagal reaction during measurement of the rMT without loss of consciousness.

[12] Allen, 2024	Non-randomised controlled	Unilateral= 157, Bilateral = 59, Mixed = 59	No control specified over medication	10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC vs. A mixed group that switched between unilateral and bilateral protocols mid-course	PHQ-9 measured at baseline, after every 5 sessions up to 30 sessions.	No significant difference in change of PHQ-9 after controlling for baseline GAD-7. Greater decrease in PHQ-9 in unilateral than mixed.	Not reported.
[13] Fitzgerald, 2011	RCT	Unilateral = 71, Bilateral 1Hz/10Hz = 61, Bilateral 1Hz/1Hz = 76	Stable medications 4 weeks prior to and during the trial	1Hz LF to the right dlPFC + sham 10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC vs. 1Hz LF to the right dlPFC + 1Hz LF to the left dlPFC	HDRS and BDI measured at baseline and end of study. Response: 50% reduction in the HDRS or BDI score. Remission: HDRS (17-item) score ≤ 7 or BDI ≤ 9	No significant difference in HDRS improvement, response or remission rates; greater decrease in BDI in unilateral and 1Hz/1Hz than 1Hz/10Hz	No difference in withdrawal rates between groups. 3 participants developed hypomanic episodes towards the end or at conclusion of treatment (n=2 bilateral 1hz/10hz, n=1 bilateral 1hz/1hz)- all had diagnosis of bipolar. Four withdrew due to side effects, headaches n=1 unilateral, discomfort n = 1 bilateral 1hz/10hz, agitation n=1 unilateral, worsening of preexisting migraines n = 1 bilateral 1hz/1hz.

[14] Fitzgerald, 2018	RCT	Continued HF = 21, switched to right unilateral = 18, switched to SBL = 20	Stable medications 4 weeks prior to and during the trial	Non-responders to 10Hz HF to the left dlPFC continued the same HF protocol, or switched to 1Hz LF to the right dlPFC or switched to SBL using 1Hz LF to the right dlPFC followed by 10Hz HF to the left dlPFC	MADRS, HDRS, and BDI measured at the start and end of switching.	No difference in reductions in MADRS, HDRS or BDI among groups. Numerically greater changes in MADRS in the bilateral group, and numerically greater changes in HDRS in the two unilateral groups.	No SAE
[15]*** Li, 2014	RCT	iTBS = 15, cTBS = 15, bilateral = 15	Original medication regime maintained with no change allowed during the trial	iTBS to the left dlPFC vs. cTBS to the right dlPFC vs. iTBS + cTBS in either order	HDRS measured at baseline, 1-week and 2-week of, and 12 weeks after treatment. Response: 50% reduction in the HDRS at week 2.	iTBS and bilateral better than cTBS (greater changes in HDRS and higher response rates). with no different in between.	More patients in the combination group complained of dizziness, most of whom received a sequence from cTBS to iTBS (4/7). no association was reported between side effects and treatment response.
[16] *** Cheng, 2016						Cognitive improvement in iTBS group	
[17] Aaronson, 2022	Non-randomised controlled	Unilateral = 3327 (2618 completers), Bilateral = 544 (431 completers)	No control specified for medications	10Hz HF to the left dlPFC vs. 10Hz HF to the left dlPFC + 1Hz LF to the right dlPFC in either order	PHQ-9 and CGI measured at baseline and end of treatment.	No superiority of bilateral than unilateral with the indication that unilateral may be more effective. Left-to-right sequence order seemed to be more effective than right-to-left shown by better improvements in CGI scores.	Not reported

[18] Lee, 2020	Non-randomised controlled	Continued HF = 17, Switched to SBL = 69, Switched to iTBS priming = 17	No control specified for medications	Non-responders to 10Hz HF to the left dlPFC continued with the same HF unilateral protocol, or switched to SBL (1Hz LF to the right dlPFC + 10Hz HF to the left dlPFC in either order) or iTBS priming 10Hz HF to the left dlPFC	IDS-SR and PHQ-9 measured at baseline and end of treatment. Response: 50% reduction in the IDS-SR score. Remission: a final IDS-SR score ≤ 13	Numerically not non-significantly higher response rate in SBL than control. Significantly better results (higher response and remission rates) in iTBS priming than control.	Good tolerability
[19] T. Zhang, 2021	RCT	10Hz left = 55 (38 completed 6 weeks, 17 completed 12 weeks), 5Hz left = 53 (42 completed 6 weeks and 20 completed 12), 10Hz bilateral = 57 (40 completed 6 weeks and 19 completed 12), 5Hz bilateral = 56 (44 completed 6 weeks and 16 completed 12)	Antidepressant- and benzodiazepine-free or a minimum 2-week washout prior to the study	5Hz or 10Hz HF to the left dlPFC vs. 5Hz or 10Hz bilateral stimulation to the left dlPFC and right dlPFC concurrently using a round coil	HDRS and CGI measured at baseline, week 6 and week 12. Response: 50% reduction in the HDRS.	No significant difference in change in HDRS, or CGI, or response rate.	No SAE

Table 1.2.1 Study information “Bilateral vs. Unilateral”. *[1] and [2] analysed data from the same trial, while [2] included a longer follow-up period. **[10] is a sub-analysis of patients over 60 years in [8] and [9]. ***[15] and [16] analysed data from the same trial. [16] is an ancillary study of [15] and primarily analysed cognitive outcomes. In addition, [6] is included under both “Bilateral vs. Unilateral” and “Switch Target”.

[18] is included under both “Bilateral vs. Unilateral” and “Priming”. HDRS = Hamilton Rating Scale for Depression. BDI = Beck Depression Inventory. CGI = Clinical Global Impression. MADRS = Montgomery-Åsberg Depression Rating Scale. PHQ-9 = Patient Health Questionnaire-9. IDS-SR = Inventory of Depressive Symptomatology Self-Report. QIDS = Quick Inventory of Depressive Symptomatology.

Personalised TMS

8 studies personalised rTMS as an augmentation method, of which 6 located stimulation targets by neuroimaging techniques and 3 varied stimulus timing based on individual EEG activity (Table 1.2.2 for summarised study information). All studies used HF to the left-sided target as the control group where 4 used 10Hz, 2 used 20Hz, and 1 used iTBS in the cases of fixed frequency (no adjustment of frequency according to concurrent individual EEG during stimulation). All studies applied rTMS over the prefrontal cortex apart from 1 (Z. Zhang et al., 2021) over the visual cortex (VC).

Personalised target

Compared to the 5cm rule (the dlPFC localised as 5cm anterior to the motor cortex), 2 studies reported additional benefits using personalised targets, including 10Hz HF to the left dlPFC targeted by individual structural MRI (sMRI) neuronavigation (Fitzgerald et al., 2009), and 20Hz HF to an area of hypofusion detected by single-photon emission computed tomography (Jha et al., 2016). However, contrary findings were reported in the remaining 4 studies. When the left dlPFC was targeted for stimulation, no advantage was found in using sMRI-based neuronavigation compared to F3 method (targeting the F3 position of the standard 10-20 EEG system) (Hebel et al., 2021), PET-guided area of prefrontal hypometabolism compared to the 5cm rule (Paillère Martinot et al., 2010), or resting-state fMRI-based area of maximal negative functional connectivity with the sgACC compared to the 5cm rule (Poydasheva et al., 2019). In addition, no significant difference was detected comparing 10Hz HF to the left VC targeted by sMRI or task-related fMRI (Z. Zhang et al., 2021).

3 studies reported no difference in frequencies of adverse events or side effects between groups. 5 studies reported general good tolerability with no SAEs. In Hebel et al. (2021), 1 SAE of suicidality requiring detention occurred in the standard group (iTBS to the left dlPFC targeted as F3) but was judged not clearly associated with TMS. 1 dropout in the PET-guided group and 2 dropouts in the standard group were considered clearly associated with TMS-related side effects.

Personalised stimulus timing

2 double-blind RCTs explored the effects of synchronising rTMS stimulus timing to individual EEG activities. Both used EEG electrode placement system to target stimulation site at F3. Both studies showed comparable treatment effects between the personalised group and the standard group.

In Price et al. (2010), for the EEG-personalised group, a pattern recognition procedure was applied to signals from the Pz site of a continuously recorded EEG. The stimulation was initiated whenever

a pre-selected pattern was detected (or triggered by default if no matching pattern was recognised after 2.5s). The interactive group showed numeric but non-significant advantages over the standard group measured by changes in HDRS, response and remission rates. There was no significant difference in side effects as reported between groups.

George et al. (2023) developed a combined fMRI/ EEG/ TMS (fET) system to identify, on an individual basis, the optimal phase of stimulation that corresponds to the phase of prefrontal EEG alpha activity with maximal increase in TMS-evoked BOLD activity in the dorsal ACC. Both groups received HF to the left dlPFC at individual alpha frequency which was re-determined before each treatment session to account for its daily variation. The initial pulse in each stimulation train was phase-locked to the individual's optimal phase in the experimental ("SYNC") group, while it was applied randomly in the control ("UNSYNC") group. No significant difference was observed between groups regarding HDRS measures (continuous and remission). Although there showed significant improvement in HDRS scores over time for both groups, the UNSYNC group showed consistency in the trajectory while the SYNC group was inconsistent over time and showed fluctuations with some patients worsening. No treatment-related side effect was reported but 2 withdrew during baseline MRI due to claustrophobia.

	Study type	Sample size	Control for medications	Interventions	Depressive outcomes	Efficacy	Side effects
[1] Fitzgerald, 2009	RCT	Personalised group = 24; control group = 27	Stable medications 4 weeks prior to and during the trial	10Hz HF to the left dlPFC targeted by 5cm rule or sMRI-based neuronavigation	MADRS and BDI measured at baseline, week 3 and week 4. Response: 50% reduction in the MADRS score. Remission: not specified	MADRS significantly lower in the personalised condition at week 4 although not at week 3; numerically more responders and remitters in personalised group; significant group effect for BDI for personalised.	There was no difference in the rate of side effects reported by the two groups. No SAE.
[2] Hebel, 2021	RCT	Personalised = 16 (including 1 bipolar), control = 15 (including 2 bipolar)	Patients continued to receive standard-of-care treatment by their ward physicians for the duration of the trial.	iTBS to the left dlPFC targeted by F3 or sMRI-based neuronavigation	HDRS, PHQ-9, and CGI measured at baseline, after 5 sessions and 12-week follow-up. Response: 50% reduction in the HDRS score. Remission: HDRS (21-item) ≤ 10	No significant difference in all measures and a numeric trend favouring F3 in terms of HDRS change and response rate.	No difference between groups in dropout rates or side effects. 1 SAE in unilateral judged not necessarily related to rTMS treatment - suicidality and involuntary detention; 1 dropout in personalised group and 2 in control clearly associated with side effects
[3] Paillère, 2010	RCT	Personalised = 16, control = 18	Stable medications for at least 2 weeks	10Hz to either left dlPFC targeted by the 5cm rule or PET based on prefrontal hypometabolism	HDRS, MADRS and CGI measured at baseline and end of treatment.	No significant difference in changes in all measures but left-guided was superior to right-guided in change in MADRS.	No SAE.
[4] Jha, 2016	Non-randomised controlled	Personalised = 13, control = 7	Excluded patients with change in medication 6	20Hz to the left dlPFC or area of hypofusion identified by SPECT.	MADRS, BDI, and CGI measured at baseline, session 5 and 20.	SPECT group significantly better (greater changes in all measures)	No SAE

			weeks or less prior to the study				
[5] Poydasheva, 2019	RCT	Personalised = 17, control = 13	No control specified for medications	20Hz to the left dlPFC targeted by 5cm rule or an area within the left dlPFC based on rsfMRI with maximal negative functional connectivity with the sgACC	BDI measured at baseline, session 10 and 20.	No significant difference in the reduction of BDI scores.	No difference in frequency of adverse events between conditions
[6] Z.Zhang, 2021	RCT	Personalised = 24, control = 27	Drug-naïve or free of antidepressant more than 2 weeks prior to first rTMS session	10Hz to the left VC targeted by either sMRI neuronavigation or task-related fMRI	HDRS measured at baseline, day 1, 3, and 5. Response: 50% reduction in the HDRS score.	Numeric but not significant higher response rate in personalised than control.	Good tolerability - no dropout due to side effects
[7] Price, 2010	RCT	Personalised = 21, control = 23	Stable medications 2 weeks prior to and during the trial	10Hz HF to the left dlPFC or HF to the left dlPFC synchronised to concurrent personal EEG activity based on a pre-selected pattern	HDRS and BDI measured at baseline and end of treatment. Response: 50% reduction in the HDRS score. Remission: a final HDRS (24-item) ≤ 8	No significant difference in change in HDRS or BDI, response or remission rate.	No difference between groups in side effects
[8] George, 2023	RCT	Personalised = 15, control = 13	Stable medications 3 weeks prior to and during the trial	HF to the left dlPFC at individual alpha frequency synchronised or unsynchronised to individual optimal phase	HDRS measured at baseline and end of treatment. Response: 50% reduction in the HDRS score. Remission: a final HDRS (28-item) < 10	No significant difference in change in score or response or remission rate.	2 participants withdrew during baseline MRI (claustrophobia)

Table 1.2.2 Study information (“Personalised TMS”). sMRI = structural MRI. SPECT = single-photon emission computed tomography.
sgACC = subgenual anterior cingulate cortex.

Switch target

With one exception (Mielacher et al., 2020), most studies (N = 6) used a non-controlled study design that switched treatment target for non-responders or non-remitters to a previous course of rTMS, showing subsequent clinical improvement (Table 1.2.3 for summarised study information).

For non-responders to treatment targeting the prefrontal cortex, 3 studies adopted the same inhibitory rIOFC protocol where 1Hz LF was delivered to Fp2 (Fettes et al., 2017; Prentice et al., 2023) or AF8 (Feffer et al., 2018) EEG site. In one case study, effects were tracked 3 months following the end of rIOFC course, upon which time full remission was achieved (Fettes et al., 2017). In Prentice et al. (2023), switching to rIOFC unilateral treatment produced smaller effects than switching to rIOFC-and-left-dlPFC bilateral protocol (see also “Bilateral vs. Unilateral”).

3 studies switched treatment target to the contralateral dlPFC site (Fitzgerald et al., 2018; Fitzgerald et al., 2006; McDonald et al., 2011). In Fitzgerald et al. (2006), non-responders to 1Hz or 2Hz stimulation to the right dlPFC subsequently received 5Hz or 10Hz HF to the left dlPFC, leading to response and/ or remission in some with no difference between HF frequency conditions. Similarly, clinical improvement was reported when non-responders to 10Hz HF to the left dlPFC switched to 1Hz LF to the right dlPFC (Fitzgerald et al., 2018; McDonald et al., 2011). However, Fitzgerald et al. (2018) observed that this was not superior to simply continuing with more sessions of HF treatment or switching to SBL (see also “Additional sessions” and “Bilateral vs. Unilateral”).

Overall, among non-controlled studies, 5 reported good tolerability of treatment protocols with no SAE. In McDonald et al. (2011), 3 experienced significant worsening of depression after switching to the LF protocol.

In contrast, no additional benefit was reported in Mielacher et al. (2020) who investigated the effect of twice daily TMS sessions compared to once daily (also see “Additional sessions”). For each treatment day, all participants received a morning session (S1) of iTBS to the left dlPFC and were randomised to one of the following conditions for the afternoon session: identical to S1 (dlPFC-dlPFC group), iTBS to individualised bilateral parietal targets (dlPFC-iLPC group), and sham iTBS. The dlPFC-dlPFC showed the best improvement in HDRS, while no significant difference between groups was found regarding endpoint BDI. No difference in the frequency of rTMS-related side effects was observed between groups.

	Study type	Sample size	Control for medications	Interventions	Depressive outcomes	Efficacy	Side effects
[1] Mielacher, 2020	RCT	dIPFC-sham = 18, dIPFC-dIPFC = 17; dIPFC-iLPFC = 18	No control specified for medication	All conditions included a morning session using iTBS to the left dIPFC targeted by structural MRI-based neuronavigation. For the afternoon session, some received sham stimulation (dIPFC-sham), some received the same as morning (dIPFC-dIPFC), some received iTBS to individualised targets in left and right lateral prefrontal cortex that were positively connected to ipsilateral hippocampus (dIPFC-iLPFC).	HDRS measured prior to the first stimulation session of each week, and 3 days after the end of treatment. BDI measured before the first and after the final session and 4, 8 and 12 weeks after the treatment course.	Better results of post-treatment HDRS scores in dIPFC-dIPFC than the other 2 conditions. No significant difference in BDI at any timepoint.	There were no group differences in the occurrence of stimulation-related side effects.
[2] Fettes, 2017	Case study	N = 1	No control specified for medication	Previous rTMS: 30 sessions of 10Hz HF to the left dIPFC + 20 sessions of 20Hz HF to bilateral dmPFC; augmentation: 30 sessions of 1Hz LF to the rIOFC	HDRS measured before and end of treatment, and 3 months following the end of treatment.	Improvement in mood and anxiety symptoms; full remission (HDRS-17 = 6) achieved at 3 months follow-up.	Well-tolerated
[3] Prentice, 2023	See Table 1.2.1 [6]						

[4] Feffer, 2018	Crossover study	N = 30	Stable medication from 4 weeks a priori until the follow-up meeting	Non-responders to a previous course of dmPFC rTMS (not specified) switched to 1Hz LF to the right rOFC	HDRS measured at baseline, after every 5 sessions and 1-3 weeks after the end of treatment. Daily BDI. Response: 50% reduction in the BDI score. Remission: a final BDI ≤ 12	Some achieved response and/ or remission after crossover. Depressive symptoms improved as measured by change in HDRS in some.	No SAE and no dropout due to TMS side effects
[5] Fitzgerald, 2006	Crossover study	N = 30	Stable medications 4 weeks prior to and during the trial	Non-responders to 1Hz/ 2Hz stimulation to the right dlPFC switched to 5Hz/ 10Hz HF to the left dlPFC	HDRS and BDI measured before and after crossover. Response: 50% reduction in the HDRS score. Remission: HDRS (17-item) ≤ 7	Some achieved response and/ or remission after crossover. No difference between groups in change in scores, or response or remission rates.	No SAE.
[6] McDonald, 2011	Crossover study	N = 61	2-weeks of washout period before trial	Non-responders to a course of 10Hz HF to the left dlPFC continued 3-6 weeks of the same HF treatment, if still not responded, then switched to 1Hz LF to the right dlPFC	HDRS measured at baseline and weekly during treatment. Response: 30% reduction in the HDRS score. Remission: HDRS (24-item) ≤ 2 or 2 consecutive weekly HDRS scores ≤ 9	Some achieved response and/ or remission after continuation or crossover.	Continuation with HF: 1 increased suicidal ideation and 1 significant worsening of depression; switch to LF: 3 significant worsening of depression
[7] Fitzgerald 2018	See Table 1.2.1 [14]						

Table 1.2.3 Study information ("Switch target"). dmPFC = dorsomedial prefrontal cortex. rOFC = right lateral orbitofrontal cortex.

Priming

4 studies tested priming as an augmentation strategy, all showing enhanced rTMS effects (Table 1.2.4 for summarised study information). Fitzgerald et al. (2008) and Vidya et al. (2024) adopted the same priming method: applying 600 pulses of 6Hz rTMS to the right dlPFC to augment 1Hz LF to the same brain target. The priming group gained significantly greater improvement across depressive scores even after accounting for age and current use of antidepressant as potential covariates (Fitzgerald et al., 2008) or showed specific benefits for older patients (50-79 years) (Vidya et al., 2024). In a retrospective study, Lee et al. (2020) tested different augmentation strategies for non-responders to 10Hz HF to the left dlPFC: continuing HF, switching to SBL and switching to 600 pulses of iTBS priming HF (also see “Bilateral vs. Unilateral”). The priming group produced the greatest clinical benefits. The same group of researchers later explored the optimal parameters for this iTBS-priming approach, indicating that subthreshold iTBS at 80%-90% resting motor threshold (rMT) was superior to suprathreshold iTBS at 110%-120% rMT, while the number of pulses did not lead to significant effects (Lee et al., 2021). Overall, all 4 studies showed good tolerability and safety profile with no SAE reported.

	Study type	Sample size	Control medications for	Interventions	Depressive outcomes	Efficacy	Side effects
[1] Fitzgerald, 2008	RCT	Priming = 33 (including 5 bipolar); control = 28 (including 5 bipolar);	Stable medications 4 weeks prior to and during the trial	Sham/ active 6Hz to the right dlPFC priming 1Hz LF to the right dlPFC	MADRS and BDI measured at baseline and end of treatment. Response: 50% reduction in the MADRS score.	Significantly better results (greater reduction in MADRS and BDI) in the priming group. Numerically more responders in the priming group.	No SAE
[2] Vidya, 2024	RCT	Priming = 16; control = 15	Stable medications 6 weeks prior to and during the trial	Sham/ active 6Hz to the right dlPFC priming 1Hz LF to the right dlPFC	HDRS and GDS measured at baseline, week 1, 2, and 4. Response: 50% reduction in the HDRS score. Remission: HDRS (17-item) ≤ 10	Significantly better results (greater changes in HDRS and GDS, and higher response and remission rates) in the priming group.	No SAE
[3] Lee, 2020	See Table 1.2.1 [18]						
[4] Lee, 2021	Non-controlled experimental	N = 71	Stable medications during the trial	Non-responders to 10Hz HF to the left dlPFC subsequently received iTBS priming of the 10Hz HF to the left dlPFC using either 600 pulses at 80-90% rMT or 1200-1800 pulses at 110%-120% rMT.	IDS-SR measured at baseline and weekly during treatment	Those who received sub-threshold iTBS priming (<100 % rMT) showed greater symptom reduction (measured as change in IDR-SR) than suprathreshold. Pulse number similar outcomes.	No dropout or SAE

Table 1.2.4 Study information (“Priming”). rMT = resting motor threshold. GDS = Geriatric Depression Scale.

Additional sessions

4 studies, where additional sessions using the same rTMS parameters were included, all showed evidence of enhanced efficacy (Table 1,2.5 for summarised study information). Among these, 3 studies tested the effect of additional sessions for non-responders to the original protocol. In Yip et al. (2017), non-responders to daily 18Hz dTMS continued to receive twice weekly treatment for up to 12 weeks following the acute phase, showing dramatic clinical improvements following the continuation phase: 72.7% achieved responder status, and 63.6% achieved remission status on at least one of the weekly assessments. Similarly, when non-responders to a course of 10Hz HF to the left dlPFC continued on the same treatment, additional response and remission rates were achieved (Fitzgerald et al., 2018; McDonald et al., 2011). However, McDonald et al. (2011) reported 1 case of increased suicidal ideation and 1 significant worsening of depression during the continuation phase. Different in experimental design, Mielacher et al. (2020) reported enhanced treatment effect when the same treatment (iTBS to the left dlPFC) was delivered twice daily compared to once, without increasing the risk of side effects.

	Study type	Sample size	Control for medications	Interventions	Depressive outcomes	Efficacy	Side effects
[1] Yip, 2017	Non-controlled experimental	N = 33	1–2week meds washout prior to trial	Non-responders to 20 sessions of 18Hz dTMS switched to twice weekly dTMS using the same protocol	HDRS measured before and after the treatment. Response: 50% reduction in the HDRS score. Remission: HDRS (21-item) ≤ 9	Some achieved response/remission during the continuation	Not reported.
[2] McDonald, 2011	See Table 1.2.3 [5]						
[3] Fitzgerald, 2018	See Table 1.2.1 [14]						
[4] Mielacher, 2020	See Table 1.2.2 [6]						

Table 1.2.5 Study information (“Additional sessions”)

1.3.4 Neuromodulation: additional non-TMS

All 4 studies indicated additional treatment efficacy following augmentative intervention using other neuromodulation techniques than rTMS (Table 3 for summarised study information).

A double-blind RCT with a large sample size (total N = 240) explored whether the sequential combination of tDCS and rTMS can provide better treatment effectiveness than rTMS alone (Li et al., 2024; Zhou et al., 2024). Participants were randomised to receiving either sham or active tDCS followed by 10Hz HF to the left dlPFC within 30-60 minutes. The combination group showed significantly higher reductions in mean HDRS at both week 2 and follow-up week 4. In addition, remission rates were numerically higher in the combination group at week 2 and significantly higher at week 4. There was no significant difference in adverse incidents between groups, and the treatment was overall well-tolerated. Similarly, Jaiswal et al. (2024) tested high definition tDCS as a priming technique for iTBS, with significantly greater improvement in the priming group without increasing the risk of adverse events.

Seemann et al. (2023) reported a case study of combining rTMS and TPS for post-covid depression with comorbid anxiety symptoms. The anxiety symptoms were effectively alleviated towards the end of 30 sessions of rTMS (1Hz LF over P8 using a round coil) but not depressive symptoms. Following 6 sessions of subsequent TPS over the left dlPFC, depression remitted, which remained effective 6 weeks afterwards.

	Study type	Sample size	Control for medications	Interventions	Depressive outcomes	Efficacy	Side effects
[1]* Li, 2024	RCT	Combination = 60 (48 completers). rTMS-alone = 60 (52 completers)	Stable medications during the trial	Sham/ active tDCS (anode over the left dlPFC and cathodal over the right dlPFC, 2mA) 30-60min followed by 10Hz HF to the left dlPFC	HDRS measured at baseline and end of treatment. Response: a final 50% reduction in the HDRS score.	Significantly better results (greater change in HDRS and higher response rate) in the combination group at week 2	No significant difference in the incidence of AEs between groups. Good tolerability without SAEs.
[2]* Zhou, 2024						Still significantly better results (greater change in HDRS and higher response rate) in the combination group at week 4	
[3] Jaiswal, 2024	RCT	Combination = 18, rTMS-alone = 18	No control specified over medications	Sham/ active high-definition tDCS (cathode at F3, Anode at FC1, FC5, AF3, F7 EEG sites 2mA) followed by iTBS to the left dlPFC within 5 min	HDRS and CGI measured at baseline, week 1 and 2.	Significantly greater improvement in HDRS and CGI in the active combination group	Good tolerability
[4] Seemann, 2023	Case study	N = 1	No control specified over medications	30 sessions of 1Hz LF to P8 EEG sites by a round coil, followed by 6 sessions of TPS over the left dlPFC	BDI measured.	Depression (which remained, measured as BDI = 24, after the rTMS course) remitted (BDI = 2) after TPS and maintained 6 weeks after.	Not reported

Table 1.3 Study information (“Non-TMS neuromodulation”). *[1] and [2] reported on the same trial. [1] reported cognitive measures as the primary outcome, while [2] primarily reported depressive outcomes with an extended follow-up till 2 weeks after the end of treatment.

1.3.5 Non-neuromodulation treatments

Medication

4 studies showed that subsequent pharmacotherapy can potentially improve depressive outcomes in non/ partial responders to rTMS monotherapy safely and well-tolerably, nonetheless studies differed in terms of control method for concurrent other medications. Tendler et al. (2018) offered the combination treatment of 10Hz dTMS and SSRI (at tolerable but previously ineffective doses) to dTMS non-responders. No other medication was allowed apart from up to 3mg lorazepam or equivalent for insomnia. Post-treatment depressive scores showed significant improvement from baseline at week 2 and week 4, with 33.3% responding and 27.8% remitting. Similarly, with stable medications maintained as before trial, some non-responders to a previous course of HF to the left dlPFC responded and/ or remitted after 4 weeks of mirtazapine (with an optional augmentation treatment by lithium or carbamazepine) (Schüle et al., 2003), or 6 sessions of intravenous racemic ketamine (Payette et al., 2023). In addition, d'Andrea et al. (2023) reported a case of partial responder to 10Hz HF to the left dlPFC (with remaining symptoms of anhedonia and lack of motivation), who subsequently received pramipexole, achieved complete remission 2 weeks afterwards.

On the other hand, 3 RCTs adopted an adjunctive regime randomising participants to receiving rTMS with or without concurrent medication, leading to inconsistent results in efficacy and tolerability/ acceptability. In Brunelin et al. (2014), following a washout phase off medications, participants received 1Hz LF to the right dlPFC with concurrent venlafaxine or placebo. No significant difference was observed in changes of depressive scores, response or remission rates. Of note, 12 SAEs (7 in the venlafaxine-only group, 3 in combination, and 2 in rTMS-only) were reported with no difference in incident frequency between groups, with the most common one (N = 5) being exacerbation of depression requiring hospitalisation. In J. Cole et al. (2022), participants were treated with iTBS with D-cycloserine or placebo taken 60min before each stimulation session, with significantly greater improvement across depressive scores as well as higher response rates in the active group. Stable medications were maintained throughout the trial. The treatment was overall well-tolerated with no SAE. In Shanok et al. (2024), treatment effects were compared between a dual protocol of dTMS with and without ketamine (simultaneous IV and subcutaneous infusion). No significant difference was found in depressive outcomes. No SAE was reported, yet some patients expressed concern over using psychedelic anaesthetic drugs.

Cognitive interventions

3 studies reported the use of cognitive interventions as an additional intervention to rTMS. In Isserles et al. (2011), participants were randomised to either 20Hz dTMS monotherapy or additionally receiving cognitive-emotional reactivation (further divided into positive and negative groups). In the combination condition, participants were given a short paragraph to read before and during each stimulation session, with the aim to trigger positive or negative “cognitive-emotional themes”. The negative group showed significantly less improvement in HDRS than the control group, and in BDI than the positive group. No other significant effect was reported. One SAE was reported of seizure during treatment and the patient was on high doses of antidepressants. Similarly, no additional benefit was reported when participants additionally received internet-delivered cognitive behavioural therapy, compared to those receiving rTMS alone (Adu et al., 2023). In contrast, in Li et al. (2016), participants were treated with a pre-stimulation rACC-engaging cognitive task (“RECT”, a computerised task where participants were required to select the right side of target on the screen with concurrent competing stimuli) or a sham task using slideshows. The active combination group showed significantly better improvement in depressive scores.

Alternative therapies

4 RCTs combined rTMS and acupuncture with the overall result favouring the combination group. No SAE was reported. Acupuncture treatment was delivered during the same treatment course as rTMS but in separate sessions, with treatment frequency ranging from 3-5 times per week. 1 study tested on depression comorbid with anxiety (He et al., 2011), 1 on depression comorbid with insomnia (Yan et al., 2023), and 2 on post-stroke depression (Hu & Li, 2024; Yin et al., 2022). 3 studies reported significantly better outcomes in the combination group compared to rTMS alone (He et al., 2011; Hu & Li, 2024; Yan et al., 2023), while 1 group did not report any significant difference between groups (Yin et al., 2022).

Barbini et al. (2021) tested the effects of combining bright light therapy and rTMS, both completed daily at different timepoints of the day. Both groups improved significantly on HDRS over time while the combination group showed significantly better performance at all measured timepoints. In addition, the combination group also showed numerical but non-significant higher levels of response and remission rates across all time points. However, such effects were abolished when bipolar patients were excluded from analysis.

Ross et al. (2023) combined rTMS and aerobic training, showing overall good tolerability. Participants were randomised to receiving either rTMS monotherapy or with an additional treadmill training program completed on the same day as rTMS. 4 from the rTMS-only group and 2 from the combination group responded, within which 3 from rTMS-only and 2 from combination achieved remission. There was no statistical comparison conducted for group differences

	Study type	Sample size	Control for medication	Interventions	Depressive outcomes	Efficacy	Side effects
[1] Payette, 2023	Non-controlled experimental	N = 21 (including 14.3% bipolar)	No control specified over medications	Non-responders to a course of HF to the left side (using either 20Hz to the left dlPFC or 18Hz dTMS using H1 coil mainly targeting the left prefrontal cortex) then received intravenous ketamine	MADRS measured before and after treatment. Response: 50% reduction in the MADRS score. Remission: MADRS $\leq$ 9	Some reached response/ remission.	No SAE. More than half experienced mild to moderate dissociation.
[2] Shanock, 2024	Non-randomised controlled	Ketamine = 66; control = 129	Stable medications during the trial	Dual dTMS (18Hz HF using H1 coil mainly targeting the left prefrontal cortex and H7 mainly targeting the medial prefrontal cortex) with or without dual infusions of ketamine (intravenous + subcutaneous) in separate sessions of the same course	PHQ-9 measured before and after treatment. Response: 50% reduction in the PHQ-9 score. Remission: PHQ-9 $\leq$ 4	No significant difference in change in PHQ-9, or response or remission rates.	Well-tolerated
[3] Tendler, 2018	Crossover study	N = 34	No control specified over medications	Non-responders to a course of 10Hz dTMS using H1 coil subsequently received SSRI + dTMS 3 times/ week	HDRS, CGI, and QIDS measured at baseline, week 2 and 4. Response: final 50% reduction in the HDRS score. Remission: a final HDRS (21-item) $\leq$ 9	Some reached response/ remission.	No withdrawal

[4] d'Andrea, 2023	Case study	N = 1	No control specified over medications	Partial responder to a course of 10Hz HF to the left dlPFC subsequently received pramipexole	MADRS measured.	Complete remission (MADRS = 7) 2 weeks after pramipexole	Well tolerated
[5] Brunelin, 2014	RCT	Combination = 50; control = 54	Included a withdrawal and washout lead-in phase	1Hz LF to the right dlPFC concurrently with venlafaxine or placebo	HDRS, BDI, and MADRS measured at baseline and weekly during the treatment. Response: 50% reduction in the HDRS score. Remission: a final HDRS (17-item) ≤ 7	No significant difference in change in all measures, or response or remission rates.	12 SAEs: 7 in venlafaxine-only, 3 in combination, 2 in rTMS-only; The most common adverse event was an exacerbation of depressive symptoms requiring the hospitalization of 5 participants; no difference in the discontinuation rate
[6] Cole, 2022	RCT	Combination = 25, control = 25	Stable medications 4 weeks prior to and during the trial	iTBS to the left dlPFC preceded 1-2hrs by D-cycloserine or placebo	MADRS and CGI measured at baseline, week 2 and 4. Weekly QIDS Response: 50% reduction in the MADRS score. Remission: MADRS ≤ 10	Significantly better results (greater change in MADRS, higher response and remission rates, and greater improvement in CGI) in combination.	No SAEs
[7] Schüle, 2003	non-controlled experimental	N = 16	Psychotropic-free for at least a week days before the trial (promethazine allowed for sleep)	Non-responders to 10Hz to the left dlPFC subsequently received 4 weeks of mirtazapine	HDRS measured at the start of and weekly during the treatment. Response: 50% reduction in the HDRS score.	69% responded after 4 weeks mirtazapine	2 patients with psychotic depression displayed a pronounced and remarkable clinical deterioration during

							2-week rTMS treatment
[8] Li, 2016	RCT	Combination = 24, control = 24	No control specified over medications	Active/ sham RECT + 10Hz HF to the left dlPFC	HDRS measured at baseline, week 1 and 2. Response: 50% reduction in the HDRS score. Remission: a final HDRS (17-item) ≤ 7	Significantly better results (greater decrease in HDRS and higher response and remission rates) in the active group.	Not reported.
[9] Isserles, 2011	RCT	Control = 20; positive = 14; negative = 11	Stable medications 4 weeks prior to and during the trial	20Hz dTMS to the left dlPFC alone vs. With positive/ negative cognitive-emotional reactivation before and during the session	HDRS and BD measured at baseline and weekly during the treatment. Response: 50% reduction in the HDRS score. Remission: a final HDRS (24-item) ≤ 10	No significant difference in response and remission rates between control and positive conditions. Significantly smaller effect on HDRS and BDI scores in the negative condition.	One SAE: short tonic-clonic seizure during second session, did not require treatment. Participant on high doses of venlafaxine, mirtazapine and mianserine.
[10] Adu, 2023	RCT	Control = 39, experimental = 39	No control specified over medications	Unilateral rTMS (1Hz LF to the right dlPFC or 10Hz HF to the left dlPFC) with and without concurrent internet-delivered cognitive behavioural therapy	HDRS and QIDS measured at baseline and end of treatment.	No significant difference in change in either score.	Well-tolerated without SAE.
[11] He, 2011	RCT	Control = 45, experimental = 40	No control specified over medications	Unilateral rTMS (5 sessions of 1Hz LF to the right dlPFC followed by 5 sessions of 10Hz HF to the	HDRS measured at baseline and end of treatment.	Significantly lower endpoint HDRS in the experimental group.	Not reported

				left dlPFC) with and without electroacupuncture			
[12] Yan, 2023	RCT	Control = 30, experimental = 30	No control specified over medications	1Hz LF to the right dlPFC + sham/ active acupuncture	HDRS measured at baseline and end of treatment.	Significantly lower endpoint HDRS in the experimental group.	3 participants withdrew (n=2 for control. n=1 for experimental group). No SAE.
[13] Yin, 2022	RCT	Control = 29, experimental = 30	Maintained regular physical medications and rehabilitation activities	Both groups also received concomitant escitalopram. 20Hz HF to the left dlPFC with and without acupuncture.	HDRS measured at baseline and end of treatment.	Significantly lower endpoint HDRS in the combined group. Higher serum BDNF and 5-HT levels in the experimental group.	No SAE; Ecchymosis (N = 3 in experimental), improved without treatment; mild headache (N = 5)
[14] Hu, 2024	RCT	Control = 25, experimental = 26	Maintained regular physical medications and rehabilitation activities	5Hz HF to the left dlPFC with and without acupuncture	HDRS measured at baseline and end of treatment.	Significantly lower endpoint HDRS in the experimental group	No SAE; mild bleeding during acupuncture in a few cases
[15] Barbini, 2021	RCT	Control = 40, experimental = 40	Stable medications 4 weeks prior to and during the trial	10Hz HF to the left dlPFC with and without bright light therapy	HDRS measured at baseline and weekly during the treatment. Response: 50% reduction in the HDRS score. Remission: a final HDRS (17-item) ≤ 7	Significantly greater improvement of HDRS in the experimental group but no significant difference excluding bipolar patients	Not reported.
[16] Ross, 2023	RCT	Control = 6, experimental = 6	Stable medications 4 weeks prior to and during the trial	10Hz to the left dlPFC with and without treadmill training programme	Response: 50% reduction in the PHQ-9 score. Remission: PHQ-9 ≤ 4	No statistical comparison. 4 responded in control and 3 responded in experimental. 3	No SAE

						remitted in control and 2 remitted in experimental.	
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Table 1.4 Study information (“Non-neuromodulation”). SSRI = selective serotonin reuptake inhibitors. RECT = rACC engaging cognitive task.

1.4 Discussion

This review developed from the pharmacological concept of “augmentation” referring to the addition of a second antidepressant agent to an existing, suboptimal medication regime, and investigated its potential applications in TMS for better treatment results (Schweitzer et al., 1997). Additional effects may be induced through shared neuroplasticity mechanisms when therapeutic modalities are combined (Donse et al., 2018). In total, 56 studies were reviewed under the 3 main categories of additional TMS, additional non-TMS neuromodulation techniques, and additional non-neuromodulation techniques, wherein additional TMS was further subdivided into “bilateral”, “personalised TMS”, “priming”, “switch target”, and “additional sessions”. In general, included studies are characterised by high levels of heterogeneity regarding study designs and treatment parameters. Most studies did not include a long-term follow-up period or a sham form of augmentation intervention. However, some clinical implications can be drawn based on a synthesis of evidence, suggesting some directions for future research.

1.4.1 Bilateral protocols: implications for geriatric depression

Nearly half of the studies (N = 19) testing additional TMS compared the treatment effects of bilateral and unilateral stimulation. Based on the hypothesis of prefrontal imbalance (hypoactive left dlPFC and hyperactive right dlPFC in depression), bilateral stimulation was developed as an attempt to combine the excitatory effect of high-frequency and inhibitory effect of low-frequency protocols, likely leading to added efficacy by considering lateralised abnormality in cortical areas (Aaronson et al., 2022; Allen et al., 2024). However, most RCTs (N = 12) reported a lack of superiority of bilateral stimulation, with the exception in older patients over 60s, indicating a possible age-specific benefit. With fewer side effects than antidepressants and electroconvulsive therapy (ECT), rTMS is increasingly used in elderly patients with depression (Cappon et al., 2022). The current focus in this area is on optimising the stimulation protocol by accounting for age-related factors including altered neuroplastic functions and prefrontal atrophy (Cappon et al., 2022). In a sub-analysis of 2 RCTs, Trevizol et al. (2019) demonstrated that SBL stimulation (1Hz LF to the right dlPFC immediately followed by 10Hz HF to the left dlPFC) may be superior to using the HF protocol alone in treating patients 60 years or older. In line with the finding that, for geriatric depression, 2 most important efficacy factors are stimulation intensity and treatment duration (Cappon et al., 2022;

Iriarte & George, 2018; Sabesan et al., 2015; Valiengo et al., 2022), the 2 trials accounted for increased scalp-to-cortex distance in atrophic brains while also delivering a long treatment course of up to 6 weeks. Under this protocol, SBL showed dramatic advantages regarding both response (45% vs. 0%) and remission (40% vs. 0%) rates. The same group of researchers later showed the comparable efficacy of bilateral TBS which entailed much shorter session length (Blumberger et al., 2022). One explanation is that bilateral protocols likely target a broader range of neural substrates by stimulating both hemispheres, an approach particularly useful for geriatric depression characterised by a broader spectrum of pathology (Trevizol et al., 2019). However, it remains unclear whether such enhancement stems from the bilateral approach itself, or increased stimulation doses, or a combined result before more evidence can be provided by future research.

1.4.2 Priming as a promising augmentative technique

TMS effects depend on the interaction between external stimuli and the underlying neuronal state of targeted areas at the time of stimulation (Sack et al., 2024; G. Schiena et al., 2020; Silvanto & Pascual-Leone, 2008). It is possible to leverage such state-dependency by “priming” techniques that manipulate the pre-stimulation brain activities in a way that subsequent stimulation effects are boosted. In the current review, 3 types of priming interventions were evidenced to have enhanced efficacy by targeting different aspects of pre-TMS neuronal activity, including priming by stimulation, by D-cycloserine, and by cognitive-psychological tasks.

Priming by stimulation

Meta-plasticity, meaning “plasticity of synaptic plasticity”, is a regulatory mechanism that modulates the chances of inducing LTD/ LTP(-like) changes based on the previous activity at the same synapse (Abraham, 2008; Karabanov et al., 2015). Specifically, the Bienenstock-Cooper-Munro (BCM) theory proposes the “bi-directionality” of synaptic plasticity, that is, the history of postsynaptic activity adjusts the threshold for the subsequent induction of LTD/ LTP in the way that previously low postsynaptic activity favours the subsequent induction of LTP, while previously high postsynaptic activity favours that of LTD (Cooper & Bear, 2012; Karabanov et al., 2015). Based on such mechanisms, priming stimulation refers to the application of pre-treatment stimulation to enhance the inhibitory/ excitatory TMS effect that follows (G. Schiena et al., 2020). In general, two types of TMS priming protocol have been developed in line with the BCM principle and extensively tested in the M1 of healthy subjects,

inhibitory priming preceding excitatory stimulation and excitatory priming preceding inhibitory stimulation (Hassanzahraee et al., 2018; Zhang et al., 2024). For treating depression, the most studied of these involves low-intensity (80%-90% of rMT) stimulation at theta frequency (5-6 Hz) preceding LF to the right dlPFC with enhanced antidepressant responses as shown in the two RCTs included here (Fitzgerald et al., 2008; Vidya et al., 2024). Its superiority over other rTMS protocols (including HF to the left dlPFC, LF to the right dlPFC, and SBL) was evidenced by two recent network meta-analyses where theta priming of LF to the right dlPFC demonstrated better response, remission and acceptability rates, with summary odds ratio second only to ECT protocols (Brunoni et al., 2017; Mutz et al., 2019). As shown here, novel methods were also developed with preliminary efficacy to boost high-frequency protocols including subthreshold iTBS priming HF and high-definition cathodal tDCS priming iTBS (Jaiswal et al., 2024; Lee et al., 2021; Lee et al., 2020).

Priming by D-cycloserine

MDD is characterised by abnormalities in the NMDA receptor (NMDA-R), a glutamate receptor critical for inducing LTP (Jewett & Thapa, 2022; Serafini et al., 2013). Such impairment in synaptic plasticity may restrain the therapeutic effects of TMS. It is consistently evidenced that TMS effects are NMDA-R dependent as NMDA-R antagonists such as memantine and dextromethorphan could obliterate the plastic effects of TBS protocols (Kochanowski et al., 2024; Sohn et al., 2024). In recent years, D-cycloserine, a partial agonist of NMDA-R acting on the glycine-binding site of NMDA-R, has been increasingly studied for neurological and psychiatric conditions, with 100mg oral dose of D-cycloserine reliably enhancing LTP-like effects (Forsyth et al., 2015; Schade & Paulus, 2016). Cole et al. (2021) first investigated the relevance of D-cycloserine-induced NMDA-R agonism in the LTP-like processes induced by iTBS in patients with MDD. In this study, 100mg D-cycloserine or placebo was taken orally 1-2 hours before the onset of iTBS and corticospinal excitability was measured in multiple timepoints up to 90 min post-stimulation as well as in the following day. Patients pre-treated with placebo showed increased excitability in contrast to decreased excitability in healthy subjects, while patients pre-treated with D-cycloserine showed decreased excitability comparable to healthy subjects. Such effect persisted into the following day. The same group of researchers extended this study to investigate possible antidepressant efficacy in a double-blind RCT (J. Cole et al., 2022). Patients partook 100mg D-cycloserine or placebo 1-2 hours before each treatment session in the first 2 weeks of a 4-week iTBS course. Significantly better treatment outcomes were seen in the D-cycloserine group with comparable

acceptability and safety as the group treated with iTBS alone. Interestingly, the combined approach may have additional cognitive benefits in both objective and subjective cognitive measures. In a later analysis, patients who received adjunctive D-cycloserine significantly improved on the 1-back working memory task as well as scores on the “Perceived Difficulties Questionnaire” after 2 weeks (DeMayo et al., 2024). There was no significant difference between their 1-back measures to healthy controls. Taken together, compared to iTBS alone, D-cycloserine-enhanced iTBS may lead to better antidepressant effects with possible additional procognitive benefits.

Priming by cognitive/ psychological interventions

Capitalising on the state-dependency of TMS, a more receptive brain state may be achieved by pre-treatment cognitive-psychological activities which functionally target specific neural regions implicated in depression (Luber et al., 2007; Sack et al., 2024). For instance, increased pre-treatment activity of the rACC (or its scalp reflection of EEG-measured frontal theta) has been associated with greater antidepressant efficacy likely because of its hub position in the DMN (Pizzagalli, 2011; Pizzagalli et al., 2003). Li et al. (2016) developed a cognitive task (RECT) to boost rACC activity 10min before each stimulation session. Compared to using rTMS alone, the cognitive-priming approach led to significantly better antidepressant responses with higher frontal theta observed in responders but not non-responders. In other words, improved treatment efficacy after RECT-modulated rTMS may be directly linked to increased pre-treatment rACC or frontal theta activity. However, this method is limited by its high cognitive demand that may be difficult to meet in real-world clinical populations. Transcranial alternating current stimulation (tACS), another non-invasive neuromodulation technique, may act as an alternative based on its ability to mimic natural brain oscillatory activities. Briley, Boutry, et al. (2024) peak-synchronised iTBS with 5Hz tACS over the left dlPFC. Compared to using iTBS or tACS alone, this dual technique led to longer-lasting and greater increase in frontal theta power and higher levels of positive shift in the emotional bias measured 20min after stimulation, suggesting a promising link between enhanced frontal theta activity and better antidepressant effects. An ongoing pilot study was subsequently developed to test its performance in a patient group with mild-to-moderate depression (see Chapter 2 of this thesis).

Along this line of research, psychotherapy combined with rTMS also seems a feasible treatment modality with the likelihood of better treatment outcomes (Donse et al., 2018). An early case study reported the practicality of combining cognitive-behavioural therapy (CBT)

with rTMS, which led to more rapid remission (39 sessions) compared to the patient's previous course (59 sessions) possibly through the engagement of the regulatory circuit from the prefrontal cortex to dorsal raphe nucleus (Vedeniapin et al., 2010). Interestingly, the CBT involved the reactivating of negative thoughts and experiences but with a subsequent focus of reinterpreting and restructuring them in a more positive framework. This may explain the lack of effect in Isserles et al. (2011), where negative emotions were reactivated in some patients before each stimulation session and induced the worst treatment outcomes, as "reactivation" may not be the key but the following "restructure" or "reinterpretation".

In summary, pre-treatment cognitive or psychological tasks are promising priming techniques for improving subsequent rTMS effects. Initial evidence favoured the use of RECT while theta tACS may be an alternative to account for its cognitive burden. In addition, future research should examine the use of psychotherapeutic modalities involving restructuring of negative experiences as an augmentative method for rTMS.

1.4.3 Augmentation as standard practice: targeting method and number of sessions

Among the augmentation interventions reviewed here, anatomical MRI-based neuronavigation and the use of additional sessions stand out as standard practices in other studies where either was used in both control and experimental conditions. It is of clinical interest to further inspect into their effectiveness given the additional financial and time cost entailed.

Neuronavigation

Anatomical MRI-based neuronavigation registers each patient's structural MRI to a standard head template and guides the coil placement to individual anatomical locations, as an attempt to account for variations in brain anatomy (Mylius et al., 2013). The common practice is to target the dlPFC over the border between the "anterior and middle thirds of the middle frontal gyrus", an area cytoarchitecturally defined as the junction between the BA 9 and 46 (Rajkowska & Goldman-Rakic, 1995). It was used as a standard targeting method in approximately 20% of the studies included here (N = 11). However, the 2 RCTs showed inconsistent results comparing it to surface-based methods. Fitzgerald et al. (2009) demonstrated its superiority over the 5cm method which tends to target too posterior to be the proper range of dlPFC. Conversely, no significant difference was found in comparison to the F3 method (Hebel et al., 2021). There might be a "ceiling effect" in Hebel et al. (2021) where TMS was used as an "add-on" treatment alongside with standard care in an inpatient setting,

likely making any further improvement by the neuronavigation method clinically trivial. Despite this, such mixed results highlight the need for further evidence to support the routine use of neuronavigation, especially given its high costs.

2 recent systematic reviews reported no significant advantage of neuronavigated over non-neuronavigated rTMS even after controlling for the variations in stimulation doses (Terao & Kodama, 2025; Valter et al., 2024). Several explanations have been put forward. First, induced electrical field is characterised by non-linearity relative to the geometric mean of the coil. This means that a more precise targeting approach may not generate higher electrical field at the intended stimulation site. As in Hebel et al. (2021), stimulation targeted by MRI or F3 method led to comparable electrical fields in the prefrontal cortical areas, suggesting that higher anatomical precision may not translate to clinically meaningful factor for better treatment results. Second, there is still uncertainty surrounding the precise cortical target for optimal treatment effects in depression. Lastly, there may be minimal deviations between neuronavigation and some surface-based methods. For example, the Beam F3 method (based on an algorithm using simple scalp measurements) approximates MRI-based neuronavigation with discrepancies of < 0.65 cm in 50% of participants, < 0.99 cm in 75%, and < 1.36 cm in 95% (Mir-Moghtadaei et al., 2015). Nevertheless, neuronavigation itself, within any given method (MRI-based or not), might still be a superior coil placement practice. In Caulfield et al. (2022), neuronavigation-based targeting led to significantly smaller deviations regarding distance and angle from the scalp target, less inter-operator differences and higher induced electric field in targeted areas compared to cap-based targeting, which may facilitate optimal engagement of intended neural circuits. A future head-to-head trial was warranted for a direct comparison regarding therapeutic effects.

Additional sessions

As part of standard practice in some trials, patients who did not achieve adequate response after 15 sessions were offered an additional 15 sessions (Blumberger et al., 2016; Blumberger et al., 2012; Fitzgerald et al., 2012). This issue of whether increasing numbers of treatment sessions can lead to enhanced effects has been investigated by a subset of studies using a range of rTMS protocols. Improved outcomes regarding both response and remission rates were reported when treatment was continued for non- or partial responders to an acute course of 10Hz HFL (Fitzgerald et al., 2018; McDonald et al., 2011) or 18Hz dTMS (Yip et al., 2017) or when an additional daily session was included (Mielacher et al., 2020). Importantly, simply extending the treatment course using the same protocol seems to achieve comparable results as providing

additional, alternative forms of rTMS with higher technological demands such as SBL and fMRI-based targeting. Currently, the optimal number of treatment sessions is still under debate with the general recommendation of at least 20-30 sessions for consistent results (McClintock et al., 2018). To address this issue, Hutton et al. (2023) examined a large patient registry (N = 7215) across 105 sites. A strong correlation between higher session numbers and better treatment outcomes was reported as patients who received fewer than 30 sessions had reduced benefits than those who received more. Of note, similar distribution patterns of symptom improvement were observed across groups, suggesting that inferior endpoint effectiveness was more likely attributed to premature termination than other reasons (Hutton et al., 2023). Even though the naturalistic nature of the study disconfirms a causal interpretation, these results, alongside with the above-mentioned findings, indicate that patients may benefit from additional sessions if meaningful symptom relief is not achieved following an initial acute course.

1.4.4 Combining TMS with medications

Consistent with real clinical settings, 84% of studies (N = 48) included in this review enrolled patients who continued on suboptimally effective medications, 63% of which (N = 30) required stable doses weeks before and during the treatment course. 1 trial (Hausmann, Kemmler, et al., 2004; Hausmann, Pascual-Leone, et al., 2004) started various antidepressants in drug-free patients on the same day of the first rTMS session. 7 studies examined adjunctive or subsequent pharmacological treatment as augmentation including antidepressants (N = 3), ketamine (N = 2), pramipexole (N = 1), and D-cycloserine (N = 1, discussed under the section of “priming techniques”).

Given that both pharmacotherapy and rTMS modulate synaptic responses as part of their therapeutic mechanisms, their combined application may produce synergistic or additive effects, leading to additional benefits than either treatment method alone (Rakesh et al., 2024; Sohn et al., 2024; Zaidi et al., 2024). Recent meta-analyses evidenced that using rTMS as an “add-on” strategy for ongoing medication regimes or concurrently initiating rTMS with a medication can produce better treatment outcomes than using these medications alone, without increasing risks of adverse events (Kochanowski et al., 2024; Rakesh et al., 2024; Zaidi et al., 2024). Interestingly, such effects may vary as a function of medication class. Zaidi et al. (2024) suggested that combining TMS with SSRIs had a significant effect on enhancing antidepressant effects, but not with venlafaxine, an SNRI. Albeit limited by the heterogeneity of study design and patient populations, these reviews highlight the criticality of considering the strategies for combining rTMS with pharmacotherapy for better treatment results.

In Briley, Webster, Lankappa, et al. (2024), trajectories of improvement during a 4-week rTMS course were analysed based on a single-item measure recorded at each treatment session. An exploratory analysis identified concurrent antidepressants as a significant predictor for both “strong improvers” (who showed consistent improvement from early in the treatment) and “delayed improvers” (who started showing improvement only from halfway through the treatment), compared with absence of concurrent antidepressants as significant predictor for “non-improvers”. Concurrent antipsychotic use was a significant predictor for non-improvement over strong improvement. Hunter et al. (2019) conducted a retrospective chart study to investigate relationships between concurrent medication categories and clinical outcome to a 6-week rTMS course and found that psychostimulants were associated with greater improvement across the treatment course. Therefore, types of pharmacotherapies may lead to more rapid onset of action and enhanced clinical effectiveness when combined with rTMS, possibly as an augmentation strategy for rTMS treatment. Here, we focus on three categories of medications based on their targeting sites at synapses including norepinephrine and serotonin neurotransmission, dopamine release, and glutamate levels (see “priming by D-cycloserine” for a separate discussion).

Firstly, some antidepressant medications work by modulating the availability of synaptic monoamines such as norepinephrine and serotonin, which may overlap with rTMS mechanisms at the level of monoamine neurotransmitters, suggesting a possibility of synergistic effects when combining the two together (Anttila & Leinonen, 2001; Dubin, 2017; Sheffler et al., 2023). One example is mirtazapine, an atypical antidepressant with comparable effectiveness as first-line treatments such as SSRIs (Jilani et al., 2024). Schüle et al. (2003) observed that subsequent use of mirtazapine may be useful in stabilising clinical effects of rTMS and converting non-responders to responders. Similarly, some non-responders were converted after concurrent use of SSRIs (Tendler et al., 2018). In contrast, in a large, double-blinded RCT, LF to the right dlPFC with and without venlafaxine (150-225 mg/day) led to statistically similar antidepressant effects (Brunelin et al., 2014). This is consistent with Zaidi et al. (2024) where SNRI did not generate additional benefits when combined with rTMS likely due to different synaptic mechanisms on cortical excitability. It is worth noting that this trial reported 12 SAEs. Despite a general good safety profile reported in recent reviews, this raises some concerns over the potential side effects when combining antidepressants with rTMS. Another study reported the occurrence of generalized tonic-clonic seizure in a patient on high doses of antidepressants including venlafaxine, mianserine and mirtazapine, and indicated that the combined medications may have increased their vulnerability (Isserles et al., 2011). However, there is

currently no definite answer to contraindications related to antidepressants apart from avoiding those that will likely lower seizure thresholds such as bupropion and imipramine (Rakesh et al., 2024; Stultz et al., 2020).

Secondly, augmenting rTMS with medications may lead to domain-specific improvements. Decreased dopamine signalling and reduced dopamine concentration in key brain regions are associated with the pathophysiology of depression (Dunlop & Nemeroff, 2007). There is increasing evidence that pramipexole, a dopamine agonist traditionally used for treating Parkinson's Disease and restless leg syndrome, is an effective augmentation treatment for antidepressants in TRD with a good safety and tolerability profile (Hori & Kunugi, 2012; Tundo et al., 2022). Such effects are partially explained by its modulations of the induction of LTP-/ LTD-like plasticity (Sohn et al., 2024). Interestingly, a case study shows that pramipexole can alleviate anhedonia symptoms in a partial responder to a course of rTMS (d'Andrea et al., 2023). The authors hence suggested that pramipexole may provide a domain-based solution to boost TMS effects, together forming a “prefrontal-striatal augmentation strategy” that combines neuromodulatory effects on prefrontal regions and pharmacological effects on dopaminergic activity within the striatum (d'Andrea et al., 2023).

Lastly, synergistic effects may be obtained by combining rTMS and ketamine, with both treatments relying on neuroplasticity for therapeutic effectiveness (Debowska et al., 2023). While the exact mechanism of action of ketamine is still under debate, most hypotheses focus on its impact on neuroplasticity through antagonism of NMDA-R, specifically concerning its preferential inhibition of GABAergic interneurons leading to increased glutamatergic neurotransmission and a net gain in AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) activation associated with the upregulation of neurotrophic factors (Zanos & Gould, 2018). A mixed picture was shown in the 2 studies included here. While subsequent use of IV ketamine converted 19% of rTMS non-responders to responders (Payette et al., 2023), dual infusions of ketamine administered during the course of rTMS did not produce additional benefit (Shanok et al., 2024). The latter study used a “joint dTMS protocol” that stimulates both “the left frontal and mid-frontal regions” with higher remission and response rates of 39.64% and 76.92% than traditional protocols, which suggests that any additional benefits from ketamine may be clinically negligible. It is worth noting that these 2 studies deviated from the more commonly used rTMS-ketamine protocol wherein ketamine is simultaneously delivered during a session of high-intensity, low-frequency rTMS targeting the medial prefrontal region involving the ACC (Arubuolawe et al., 2024; Debowska et al., 2023). Preliminary evidence mostly from case studies demonstrates its potential effectiveness for non-

responders to antidepressant medications and/ or rTMS or ketamine alone (Arubuolawe et al., 2024; Debowska et al., 2023). Particular benefits were indicated in cases of complex psychiatric comorbidities (e.g., substance use disorder, anxiety, anorexia nervosa, OCD) with sustained remission for a minimum of 1 year (Arubuolawe et al., 2024). An important consideration for implementing rTMS–ketamine treatment in real-world clinical settings is to address potential patient biases, as Shanok et al. (2024) reported that many expressed concerns about the use of psychedelic anaesthetic drugs.

In summary, pharmacotherapy may augment the antidepressant effectiveness of rTMS. However, current evidence shows high heterogeneity regarding study design even within a single medication category, making it difficult to generalise study results. There is also a lack of RCTs comparing rTMS with and without tested medications even though increasing evidence in the other direction suggests the usefulness of rTMS as an “add-on” therapy to ongoing medications. For future research, more studies are needed to investigate parameter-related factors such as the optimal timing to initiate medications and rTMS in concurrent regimes and the optimal dosage to use as well as potential side effects.

1.4.5 Alternative therapies

Bright light therapy

Bright light therapy (BLT) has proven efficacy for non-seasonal depressive disorders with a possible advantage of rapid symptom relief (Menegaz de Almeida et al., 2025). It works by signal projections from “intrinsically photosensitive retinal ganglion cells” to neural circuits implicated in depression, involving structures such as the suprachiasmatic nucleus, lateral habenula, and the amygdala (Menegaz de Almeida et al., 2025; Wang et al., 2020). A possible synergistic or additive effect of combining BLT and TMS was first reported by Mania and Kaur (2019) that, in the 6 patients with TRD, a course of simultaneous BLT during dTMS led to high response and remission rates of 100% and 50% respectively. In a rater-blinded RCT, Barbini et al. (2021) further compared the treatment effect of dlPFC TMS with and without BLT (delivered in separate sessions). Despite higher degrees of clinical improvement found in the overall sample, this significant result was invalidated when bipolar patients were excluded. One possibility is that bipolar patients are more likely to benefit from BLT. A recent study investigated properties of “sleep and circadian rhythms” as potential biomarkers to distinguish between unipolar and bipolar depressive episodes (Leseur et al., 2024). Compared to unipolar patients, bipolar patients reported significantly higher levels of hypersomnia (excessive

daytime sleepiness) and were objectively observed to have longer sleep duration and motor retardation, leading to the clinical recommendation that BLT may be more relevant in this patient group. This agrees with previous meta-analyses showing consistent evidence of BLT as an effective monotherapy or adjunctive therapy for bipolar depression (Hirakawa et al., 2020; Wang et al., 2020). However, we cannot exclude the possibility that lack of effect on unipolar depression in Barbini et al. (2021) may be due to the suboptimal protocol design (e.g., non-concurrent delivery of the two treatments) and choice of light parameters. A recent review observed comparable treatment efficacy of BLT in unipolar and bipolar patient groups with no difference in either effect size or response (Riedinger et al., 2025). Further research is needed to explore the treatment parameters to optimise the TMS-BLT combination while with the potential efficacy difference in unipolar and bipolar depression in mind.

Acupuncture

Acupuncture is a form of alternative medication involving the insertion of thin needles into chosen sites, known as “acupoints”, on the body. Evidence here generally supported the use of acupuncture as an augmentative approach to rTMS in post-stroke depression (Hu & Li, 2024; Yin et al., 2022) and depression with specific comorbidities of insomnia or anxiety (He et al., 2011; Yan et al., 2023).

In traditional Chinese medicine, depression arises due to disruptions in the flow of “qi” (life force or vital energy), which manifested as stuck emotions linked to deficiencies in liver and kidney functions (Y. Yang et al., 2024). Acupuncture targets the key acupoints on the head and limbs along main “meridians”, or channels through which qi flows (Yang et al., 2022). Recent meta-analyses supported its superiority over treatment as usual alone and its effectiveness as an adjunctive approach for the treatment of depressive disorders (Armour et al., 2019; Xiao et al., 2024). Noticeably, acupuncture combined with rTMS demonstrated the highest probability of being the most effective antidepressant regime, compared to acupuncture combined with other pharmacological or non-pharmacological approaches (Lam Ching et al., 2023). Synergistic effects may be obtained as both approaches can exert “multi-target antidepressant effects” involving modulations of neurotrophic factors, neurotransmission systems, neuronal connectivity, and inflammatory responses (Armour et al., 2019; Xu et al., 2025; Yang et al., 2022). In Wang et al. (2016), in female patients with MDD, 8 weeks of verum acupuncture plus fluoxetine increased resting-state functional connectivity between the left amygdala and subgenual/ pregenual ACC, compared to sham acupuncture plus fluoxetine, which was significantly correlated with the decrease in depressive scores. This suggests a limbic-regulated

antidepressant mechanism of acupuncture, which result nevertheless may be restrained by gender-specific factors. In addition, a single session of acupuncture on its own may be sufficient to induce neuroplastic. T. Zhang, J. Zhang, et al. (2021) measured prefrontal activity in MDD patients before and after a single session of acupuncture targeting the “Baihui” acupoint located at the middle of the crown. The effects varied with symptom severity that no effect was observed in patients with mild-to-moderate symptoms, yet a trend towards high levels of frontopolar activity was shown in patients with severe symptoms. In addition, there was a significant correlation between depression severity and dlPFC activation following acupuncture but only in patients with severe symptoms. These findings suggest that acupuncture may activate the prefrontal areas in MDD as a function of symptom severity. In summary, acupuncture appears a promising approach to boost TMS effects by targeting multimodal cellular and molecular systems for enhanced antidepressant responses. However, most trials included in the current and previous reviews were conducted in China. It is therefore unclear if the findings are generalisable outside the Chinese populations.

1.4.6 Limitations and clinical implications

Limitations

Firstly, scoping review has its inherent limitation as a descriptive approach. No meta-analysis was conducted here to evaluate the strength of evidence. However, our goal was to map out the available types of interventions with a focus on breadth rather than depth, making scoping review the most appropriate tool for this objective.

Secondly, we only included peer-reviewed full-text reports. Considering the conceivably available range of interventions, our focus was on those that have been trialled in a fully reported study where sufficient information was available regarding efficacy and acceptability/tolerability. However, it is acknowledged that, by excluding pre-prints, dissertations, abstracts, protocols and posters, we might have missed some relevant approaches and compromised the breadth of this scoping review.

Thirdly, limitations were revealed by a review of quality assessment results. This review included 38 RCTs. However, data on adherence, and reference to a pre-published analysis protocol was not common, particularly in older studies. The remaining 20 studies (34.5%) did not use an RCT design with 5 non-randomised controlled studies, 12 non-controlled experimental studies and 3 single-case studies. None of these studies had patients nor outcome assessors blinded. In addition, caution is especially needed when interpreting the latter 2

categories where it is hard to account for the carry-over effects from the previous course, making the source of additive benefits unclear. For all study types, most studies were inadequately powered, indicating that most cannot be seen as definitive regarding efficacy. Furthermore, it is acknowledged that most studies adopted the optimal rTMS protocol at the time of trial, yet recent updates have suggested some inadequacy in older studies. In this aspect, the risk-of-bias summary showed a general trend among augmentation categories that (1) most studies only included a single follow-up timepoint shortly following the end of course (< 1 week); (2) most studies included non-augmented TMS with insufficient treatment duration (< 20 sessions); (3) most studies did not include a sham condition for augmentative intervention. Fourthly, within the same category, there are significant discrepancies in methodologies (e.g., the TMS protocol used, parameters of augmentation intervention, control methods for concurrent medications, and criteria for response and/ or remission), making it difficult to reach consistent conclusions about the specific use of any augmentative method. Some studies included in this review deviated from the more common clinical parameters using TMS or the combined modalities. For example, the 2 ketamine studies applied ketamine and TMS in separate sessions while these were more commonly administered concurrently (see above discussion of ketamine). In addition, several studies used 20Hz HF to the left dlPFC as the control condition, which is not a common clinical practice for depression treatment. Such deviations make it difficult to generalise to and link with a wider literature.

Finally, it is acknowledged that multimodal therapies in the field of neuromodulation such as TMS are limited by a poor understanding of underlying treatment mechanisms (National Academies of Sciences & Medicine, 2016). There is still insufficient evidence of optimal TMS parameters to use or the optimal brain state for maximal benefits. This is further complicated by a similar lack of consensus regarding many of the augmentation interventions reviewed here (e.g., acupuncture and bright light therapy). In the current review, we only included quantified measures of depressive symptoms as outcomes. However, it is possible that changes can occur at a sub-behavioural level and are only measurable with more sensitive brain techniques such as neuroimaging.

Clinical implications

PPI contribution

We presented the initial results to the NEAT PPI group. The discussion surrounded the acceptability of TMS and potential augmentation approaches as well as possible barriers to their implementation in real-world clinical settings. The following points were proposed:

- Simultaneously combining rTMS with another technique (e.g., acupuncture, bright light therapy) may be helpful in improving the acceptability of rTMS itself likely due to reduced fear and anxiety when patients are “distracted” from scalp sensations.
- The acceptability of different augmentation methods can vary as a function of stages of depression.
- A general potential barrier against applying combined/ augmented approach to rTMS is longer waiting lists and higher clinical costs.
- Barriers to specific types may include the following: (1) acupuncture: a clash between eastern and western medical concept in populations from different cultural backgrounds; (2) D-cycloserine: unfamiliarity with this medicine in the general public, combined with its lack of regulation in the UK, leading to increased concerns over potential side effects; (3) bright light therapy: concern over adherence to using light therapy at home and if daily tracking of usage will lead to extra patient burden.

Future directions

We suggest here a list of augmentative interventions with early-evidence efficacy for rTMS in depression:

- SBL treatment (1Hz LF to the right dlPFC followed by 10Hz HF to the left dlPFC) for older patients above 60 years old.
- Priming techniques including:
 - Priming by neuromodulation with tested protocols including (1) 1Hz LF to the right dlPFC primed by 6Hz HF to the right dlPFC at 80-90% of rMT, (2) 10Hz HF to the left dlPFC primed by iTBS to the left dlPFC at 80-90% of rMT, and (3) iTBS to the left dlPFC primed by high-definition tDCS with cathode at F3 at 2mA.
 - iTBS primed by D-cycloserine.
 - rTMS primed by cognitive-psychological interventions such as rACC-engaging cognitive task (an alternative approach may involve theta tACS to reduce cognitive burden).
- Novel antidepressant options, including ketamine and pramipexole, combined with rTMS concurrently or subsequently.
- Bright light therapy potentially with better effects for bipolar depression.
- Acupuncture.

In general, RCTs with larger sample sizes, adequate treatment length, and longer follow-up periods are needed for interventions with early-evidence efficacy. These should be supported by mechanism-of-action studies investigating the interaction of chosen combinations. We suggest here a list of suggestions for future research and methodological improvements:

- Studies should report changes in rTMS stimulation intensity and numbers of sessions as an indication of treatment adherence.
- Studies should generally include adequately powered sample size and at least 20 sessions of rTMS as standard care, and at least 1-week follow-up period.
- Studies in controlled designs are needed to test the effects of switching rTMS treatment target and adding additional sessions using the same protocol.
- Future research is needed to see if the additional benefit of SBL treatment for older patients is attributed to the bilateral protocol per se or higher dosages used.
- Future research is needed to test if priming rTMS with psychological interventions with a focus on restructuring negative thoughts and/ or experiences can lead to additional benefits.
- Future research is needed to test rTMS with and without acupuncture in patients with more diverse ethnical and cultural backgrounds.

Chapter 2. Feasibility pilot study of a dual neuromodulation approach

2.1 Introduction

2.1.1 Background: Capitalising on state dependency of TMS

The clinical effect of rTMS is a combined result of the stimulation and the “brain state” at the time of stimulation (G. Schiena et al., 2020; Silvanto & Pascual-Leone, 2008). Such state-dependency has been studied at the levels of brain oscillations, cognitive activity, and recent brain state history (Sack et al., 2024). This study will focus on the subset of brain oscillations, or the rhythmic electrical activity of neurons, to explore its influence on rTMS-induced neural effects. Neuronal groups act as oscillators whose membrane potentials change via the fast process of action potentials and the slower process of post-synaptic potentials (Ward, 2003). Neural oscillations reflect the timing of neuronal spikes at the microscopic level and cyclic changes in the brain excitability at the network level (Buzsaki, 2006). This dynamic “coupling and uncoupling” of brain regions forms the basis of functional networks that support a range of computational and communicative processes underlying specific perceptual and cognitive states (Buzsaki & Draguhn, 2004; Hanslmayr et al., 2019; Sack et al., 2024; Thut et al., 2012). Large-scale oscillatory activity can be non-invasively measured by EEG at frequency bands including delta (< 4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (30-100 Hz) (Teplan, 2002). EEG measures are increasingly used as a probe for aberrant neurophysiological processes underlying psychiatric disorders (Basar, 2013; McLoughlin et al., 2014).

Frontal theta rhythm: the electrophysiological correlate of rTMS antidepressant effects

The ACC links the “emotional limbic system” and the “cognitive prefrontal cortex” (Stevens et al., 2011). It forms part of an interactive functional network responsible for emotion processing and regulation and shows size differences in mood disorders and schizophrenia (Ertl et al., 2013; Ibrahim et al., 2022; Torrico & Abdijadid, 2019). Although not directly stimulated, the ACC is primarily modulated by rTMS protocols stimulating the dlPFC. Increased grey matter volume in the ACC was reported in MDD patients after a course of standard 10Hz rTMS (10Hz rTMS to the left dlPFC) and was correlated with improvement of depressive symptoms (Lan et al., 2016). Moreover, based on a whole-brain resting-state network approach to 20

common resting state networks, it was found that only the network including the ACC was influenced by the rTMS procedure (Tik et al., 2017). This suggests a potential role of neuroplastic effects on the ACC as an antidepressant mechanism behind rTMS treatment modalities.

There appears to be a division between subgenual ACC (sgACC) and rostral ACC (rACC) in the pathophysiology of depression (Bush et al., 2000; Ge et al., 2020). Higher baseline functional connectivity between sgACC and dlPFC as well as hyperactivity within sgACC are associated with higher levels of depression severity and less clinical responsiveness but might be normalised following successful rTMS application (Cash et al., 2021; E. J. Cole et al., 2022; Oathes et al., 2023; Oathes et al., 2021). In contrast, there is a strong relationship between higher neuronal activity in the rACC before treatment and improved antidepressant response across treatment types including rTMS to the dlPFC (Pizzagalli, 2011). This is possibly due to the hub position of rACC in the DMN where it supports “adaptive self-focused processing” (e.g., mindfulness practices, reframing negative thoughts, problem-solving strategies) and recalibrates the relationship between the DMN and the “task-positive network” (Pizzagalli, 2011; Takano & Tanno, 2009). The relationship still appeared robust after controlling for various clinical and demographical factors associated with treatment outcomes (Pizzagalli et al., 2018).

At the scalp level, rACC activity can be translated into an EEG biomarker of task-related frontal theta activity (Asada et al., 1999; Cavanagh & Frank, 2014; Ishii et al., 2014; Phouthavong & Thorkelson, 2021). Theta oscillations represent one of the most prominent rhythms of the brain that is mainly localised in the hippocampus, prefrontal areas, and sensory cortices (Colgin, 2013; Karakas, 2020). Generally, slower oscillations including the theta rhythm synchronise distinct neuronal ensembles to facilitate specific cognitive functions (Buzsaki & Draguhn, 2004). During wakefulness, human theta rhythm is primarily distributed along the frontal midline, which is strongly associated with higher-order cognitive and executive processes such as decision making (Lavín et al., 2023; Rajan et al., 2018), cognitive reappraisal as part of emotion regulation (Ertl et al., 2013), cognitive control facing uncertainty (Cavanagh et al., 2012; Cavanagh & Frank, 2014), and working memory maintenance and manipulation (Herweg et al., 2020; Itthipuripat et al., 2013; Jensen & Tesche, 2002). Bailey and colleagues conducted a series of studies exploring the usefulness of frontal theta activity as a predictive biomarker of rTMS-induced antidepressant effects (Bailey et al., 2018, 2019; Bailey et al., 2021). Compared to non-responders to standard 10Hz rTMS, responders showed significantly higher frontal-midline theta power and connectivity measured during a working memory task

both at baseline and repeated after one week of treatment (Bailey et al., 2018). This was concurrent with greater cognitive improvement (measured as shorter reaction time during the task) and mood improvement observed in responders at week 1, but not in non-responders. The authors argued that enhanced frontal-midline theta activity reflects increased metabolic function of the ACC and indicates a better ability to suppress rumination due to better attention control in responders. However, this effect might be restricted to task-related measures. A later finding of increased resting frontal-parietal theta connectivity in responders at baseline and week 1 did not replicate in a larger independent clinical sample where a reversed pattern was detected (Bailey et al., 2019; Bailey et al., 2021). In addition, enhanced resting theta power was observed in non-responders compared to responders (Arns et al., 2012). This suggests that resting theta activity might not be a generalisable biomarker and highlights the functional difference between theta activity at rest and that originating from the ACC for cognitive performance.

In addition to being a predictive biomarker, change in frontal theta activity following rTMS treatment for depression is related to treatment efficacy (Nakamura-Palacios et al., 2023). Noda et al. (2013) compared EEG and clinical outcomes measured in patients with TRD before a two-week treatment course of standard 10Hz rTMS and 3 hours after the last session. Long-lasting potentiation effects of the stimulation were mainly observed in the delta, theta, and low-alpha frequency bands. Specifically, prefrontal theta power significantly increased over time, which correlated with improved cognitive performance measured as higher numbers of preserved items and lower error rates during the Wisconsin Card Sorting Test. The authors believed that such theta power increase had its origin from the ACC due to its dense connection with the stimulation site of dlPFC (Noda et al., 2013). Furthermore, functional connectivity of theta band along the anterior midline was enhanced after 6 weeks of standard 10Hz rTMS, which was significantly correlated with cognitive improvement measured by the Colour Stroop Test (Mitoma et al., 2022). These findings suggest that frontal theta rhythm may be an electrophysiological neural correlate of cumulative effects of rTMS in depression. Although the exact mechanism behind it remains unknown, rTMS is likely to achieve distributed effects beyond the stimulation target by modulating cortical oscillatory activity across connected regions (Fox et al., 2012; Kricheldorff et al., 2022; Leuchter et al., 2013).

Similarly, frontal theta activity also seems closely related to antidepressant effects of prefrontal TBS protocols. A sham-controlled PET study observed that TBS protocols primarily modulated the frontal-cingulate circuit involving the ACC and the medial PFC instead of the stimulation site of the dlPFC (C. T. Li et al., 2018). Alongside the finding that enhanced

metabolism in the hippocampus, another area where strong theta signals can be observed, was associated with better treatment effectiveness, the authors hypothesized that theta rhythm may be a key antidepressant mechanism of TBS. This was consistent with findings from an earlier study that short-term changes induced by TBS protocols were primarily detected on the theta band in the prefrontal regions where TMS-evoked theta activity was increased following iTBS and decreased following cTBS (Chung et al., 2017). Furthermore, Tsai et al. (2022) conducted a sham-controlled, double-blind randomized trial to investigate brain oscillations as neural correlates of rTMS effects. They accounted for analytical limitations of previous studies by adopting the Holo-Hilbert spectral analysis, a high-dimensional approach sensitive to nonlinear and nonstationary data. EEG measures were compared before and after a 2-week course of rTMS treatment. For responders to iTBS, but not non-responders, significant increases in the log power of “theta-alpha amplitude modulation frequency” (a measurement of theta amplitudes as modulated by the coupling alpha waves) were observed over the frontal and occipital regions. This was directly related to the degree of recovery. In contrast, increased alpha power over the frontal-central region was observed in both responders and non-responders to standard 10Hz rTMS but not correlated with antidepressant effects, suggesting different mechanisms underlying these two protocols (Tsai et al., 2022).

In sum, frontal theta activity is a promising EEG biomarker for depression. The antidepressant efficacy of rTMS can be both predicted and indexed by frontal theta oscillations (Y. C. Tsai et al., 2023). Higher task-related frontal-midline theta activity, with its main origin from the ACC, distinguishes responders from non-responders to standard 10Hz rTMS, although further evidence is needed for other rTMS protocols. In addition, theta oscillations might be a key mechanism behind the antidepressant effects of rTMS. This is particularly relevant to TBS protocols which primarily modulate theta-prominent areas and show a correlation between frontal theta rhythm and clinical outcomes beyond cognitive aspects.

State-dependent dual neuromodulation protocols

In Hunter et al. (2013), a stronger relationship between rACC activity and treatment response was observed when measured closer to the start of treatment. They argued that rACC theta represents a changeable “state” marker of antidepressant effectiveness, suggesting the possibility of manipulating pre-treatment rACC state for better treatment outcomes (Arns et al., 2015; Hunter et al., 2013). In other words, it is likely to create a pre-treatment brain environment of high rACC activity, or high frontal theta, to augment rTMS. This was first tested by Li et al. (2016) who conducted an RCT to examine antidepressant effects of pre-

rTMS modulations of frontal theta activity by an rACC-engaging cognitive task (“RECT”). Three study groups were included for comparison: (1) RECT-rTMS group where participants completed a 10-min RECT exercise before each rTMS session, (2) rTMS-only group with sham RECT, and (3) RECT-only group with sham rTMS. It was found that RECT-modulated frontal theta activity, which was highly correlated with the glucose uptake of rACC measured by PET, can predict antidepressant responses to rTMS with sensitivity of 83.3% and specificity of 77.3%. A later study further confirmed its usefulness as a predictive biomarker for rTMS but not iTBS in a different cohort (C. T. Li et al., 2021). More importantly, the RECT-rTMS group showed the best antidepressant effect with a remission rate of 41.6%, compared to 16.6% in the rTMS-only group, while using RECT alone did not achieve clinically significant improvement. This cooccurred with enhanced frontal theta power in the responders of the combined group, but not in the rTMS-only group. This study provided initial evidence that the antidepressant efficacy of rTMS can be boosted by enhancing frontal theta activity before treatment. However, due to high cognitive and motivation requirements, it can be difficult for individuals with more severe depression to complete tasks like RECT in real-life clinical settings (Li et al., 2016).

Transcranial alternating current stimulation (tACS) applies to the scalp sinusoidal electrical currents that simulate naturally occurring rhythmic patterns of brain oscillations, allowing selective manipulation of oscillatory activity at a given frequency (Elyamany et al., 2021; Herrmann et al., 2016). There is still a lack of understanding as to the exact mechanism by which tACS modulates cortical activity (Fertonani & Miniussi, 2017; Pozdniakov et al., 2021). Some studies suggest that tACS can synchronise brain oscillatory activity to an externally imposed frequency, a process known as “entrainment” where large neuron populations show phase-alignment and amplitude increase at specific frequency bands during and after the stimulation (Thut et al., 2012; Thut et al., 2011). However, this view has been criticised as “oversimplified” (Fertonani & Miniussi, 2017). In Vossen et al. (2015), intermittent tACS at individual alpha frequency was applied with phase continuity either maintained or changed between successive trains. When measured post-stimulation, the EEG results showed a lack of offline entrainment effects, that is, alpha power enhancement occurred irrespective of conditions of phase continuity and peaked at spontaneous alpha-peak frequency rather than the driven frequency. It was thus proposed that (1) online tACS-entrainment effects may not be strong enough to sustain after the stimulation; (2) offline tACS effects on brain oscillations are more likely attributed to short-term plasticity in the driven frequency band, although successful online entrainment might be a prerequisite (Klink et al., 2020; Veniero et al., 2015; Vossen et

al., 2015). Many other studies similarly reported post-stimulation power enhancement at the stimulation frequency without phase alignment (Kasten et al., 2016; Wischnewski et al., 2019; D. Yang et al., 2024; Zaehle et al., 2010). Nevertheless, theta tACS can still be a useful alternative to RECT by enhancing pre-treatment frontal theta power without the need for task performance.

Developing a dual approach

To address the issue of high variability of TMS effects, Guerra and colleagues conducted a series of studies exploring how the concurrent use of tACS at the gamma frequency can modulate TBS-induced plasticity in the primary motor cortex (M1) (Andrea Guerra et al., 2020; Guerra et al., 2019; Guerra et al., 2018). Motor-evoked potential (MEP) is an established measure of corticospinal excitability by sending suprathreshold single TMS pulses over a specific part of M1 where plastic changes can be conveniently quantified as facilitation or suppression of MEPs (Parmigiani et al., 2023). Replicated in different cohorts, their main finding was that gamma-tACS, but not beta-tACS or sham-tACS, boosted iTBS-induced LTP-like plasticity (measured as greater MEP facilitation) and reversed cTBS-induced LTD-like plasticity (measured as MEP facilitation rather than expected suppression). Importantly, these results could not be explained by the add-on effect of gamma-tACS as it alone did not change the corticospinal excitability. The authors proposed the mechanism of “rhythm-dependent plasticity” that tACS-enhanced synchronisation of M1 neurons at the gamma frequency leads to a shift in thresholds for synaptic plasticity whereby the threshold for LTP-like plasticity is reduced while that for LTD-like plasticity is increased (Andrea Guerra et al., 2020; Guerra et al., 2019; Guerra et al., 2018). This technique may hold promise for rehabilitation interventions in Parkinson’s disease with initial evidence showing the usefulness of gamma-tACS in restoring iTBS-induced plasticity that is reduced in the patient group (A. Guerra et al., 2020; Guerra et al., 2023). Based on these studies, Maiella et al. (2022) extended the protocol of concurrent tACS-iTBS to test over the dlPFC. Healthy participants underwent three separate stimulation sessions using iTBS with gamma-tACS, theta-tACS, and sham-tACS respectively. Single TMS pulses were delivered with simultaneous EEG recordings to directly examine changes in cortical oscillations of a specific brain area (Kricheldorff et al., 2022). Compared to baseline, gamma activity (measured as both power enhancement and connectivity improvement) was significantly boosted following iTBS combined with gamma-tACS, but not other tACS conditions. Such effects were restricted to the local plasticity of the stimulation site.

In addition, no modulation of resting-state theta oscillations was observed across stimulation conditions.

However, one of the main limitations of the above studies is their phase-independency, meaning that rTMS was delivered in ignorance of the tACS phase, which might explain the lack of modulatory effects by stimulation at lower frequencies. This issue was first tested by Goldsworthy et al. (2016) who time locked cTBS to the peak or the trough of alpha-tACS in M1. Greater MEP suppression (indicating augmented LTD-like plasticity) was observed when stimuli were delivered to the trough, but not the peak, of the applied current. Based on this preliminary finding, another group of researchers synchronised rTMS to peak or trough phases of alpha-tACS, beta-tACS and sham tACS in separate conditions to explore the modulatory effects on M1 (Nakazono et al., 2021; Ogata et al., 2021). Different effects were observed for different rTMS protocols. For repetitive paired-pulse TMS (a facilitatory protocol involving the repeated application of a paired pulse at 0.2Hz), beta-tACS enhanced the LTP-like plastic response at the peak phase, while no effect was observed following beta-tACS trough condition or both alpha-tACS conditions (Nakazono et al., 2021). For iTBS, LTP-like plasticity was suppressed following both beta-tACS conditions and alpha-tACS peak condition but not alpha-tACS trough condition (Ogata et al., 2021). This suggests that tACS-induced oscillatory activity can determine the direction and/ or range of rTMS-induced aftereffects in a frequency- and phase-specific manner.

Hosseinian and colleagues went further to explore the possibility of developing synchronised tACS-rTMS as a technique to externally “enhance and stabilise” a target frequency in brain regions critical for cognitive functions such as the dlPFC (Hosseinian, Yavari, Biagi, et al., 2021; Hosseinian, Yavari, Kuo, et al., 2021). rTMS and tACS both can modulate oscillatory patterns and have proven therapeutic potentials in the clinical setting (Lee et al., 2023; Leuchter et al., 2013; Noda et al., 2013). However, these techniques depend on different neurophysiological mechanisms and thereby have distinct effects as well as limitations. rTMS represents a “pulsed form of rhythmic stimulation” that reset oscillatory phases through the induction of action potentials within the local networks (Hanslmayr et al., 2019; Thut et al., 2011). It can lead to frequency-specific modulation, but such effects typically do not last beyond the stimulation period (Leuchter et al., 2013). In comparison, tACS utilises a “continuous form of rhythmic stimulation” that changes neuronal membrane potentials in an oscillatory manner (Thut et al., 2011). Using subthreshold intensity, tACS modulates endogenous brain activity by altering the probability of a neuron generating action potentials (Elyamany et al., 2021). Such effects can sustain longer time courses but are largely limited by

the degrees of mismatch between the target stimulation frequency and the spontaneous oscillatory frequency. By combining these two techniques, it is possible to induce oscillatory activity at a given frequency (via rTMS) and achieve subsequent long-lasting stabilisation of this activity (via tACS) (Hosseinian, Yavari, Biagi, et al., 2021; Hosseinian, Yavari, Kuo, et al., 2021).

To test the feasibility of this method, Hosseinian, Yavari, Biagi, et al. (2021) first combined and synchronised 10Hz rTMS and 10Hz alpha-tACS over the bilateral dlPFC where endogenous alpha activity was observed to be low in the healthy human brain. Following the stimulation, resting alpha power over frontal and parietal regions increased the most when rTMS was peak synchronised to tACS, compared to uncombined protocols (rTMS alone and tACS alone) and compared to sham, which effect lasted up to 30 min after the end of stimulation. In contrast, no effect was observed when rTMS was trough synchronised to tACS, suggesting a criticality of phase-dependency in such protocols. In addition, such effects were interpreted as an interplay between the two techniques as each stimulation alone only produced transient increase in the 10Hz power measured 1min after the end of stimulation. In a later study (Hosseinian, Yavari, Kuo, et al., 2021), they turned to the theta frequency band and its cognitive correlates as a function of the combined stimulation. It was found that resting prefrontal theta power (at 6Hz) was enhanced to the largest degree when 6Hz rTMS was peak synchronised to 6Hz tACS, compared to the double-sham condition, with the effect persisting up to 60 min after the end of stimulation. However, when compared to single protocols, the dual approach was only significantly better than using rTMS alone, but not tACS alone. The second part of this study was designed to test the effect on cognitive processes by using n-back tasks, an established working memory task where, presented with a sequence of stimuli, participants need to determine if the current item is the same as the one shown “n” trials ago. EEG was recorded simultaneously during the task performance. No significant difference in task performance was observed for the 1-back task, while the combined protocol improved performance relative to sham for the 3-back task. Significant increases in the task-related theta power over the frontal and parietal regions were observed immediately following combined stimulation or 6Hz tACS alone, though not after rTMS alone, for both 1-back and 3-back working memory tasks.

Phase-synchronising rTMS and tACS thus is likely to “induce and stabilise” oscillatory activity at a given frequency, which can, in turn, modulate cortical plasticity and cognitive functions. More recently, Briley, Boutry, et al. (2024) peak-synchronised iTBS with 5Hz-tACS over the left dlPFC (termed as “tsiTBS”) and investigated the potential value of this technique as an

augmentation strategy for treating depression. Different from the single post-stimulation measurement in Hosseinian Yavari, Kuo, et al. (2021), frontal theta power was measured during a 2-back task at multiple time points (1 minute, 8 minutes, and 15 minutes) after the stimulation. At the 8-minute time point, change in theta power (compared to the pre-treatment baseline measurement) was significantly greater than double sham following tsiTBS and tACS alone with no difference between the two conditions. At the 15-minute time point, theta power was significantly increased in all active conditions compared to double sham with the greatest effect in the tsiTBS condition. Importantly, different trajectories of effect were observed for the stimulation protocols. At the 8-minute time point, tACS on its own elicited a numerically greater change in theta power than the tsiTBS, but this effect subsequently declined by the last measurement point. In comparison, the increase in theta power following the tsiTBS was steeper and did not yet reach its peak at the 15-minute time point. This suggested that the long-lasting effect on the frontal theta after the combined stimulation could not be accounted for by tACS alone. In this way, tsiTBS may be useful in creating a high frontal theta brain state which provides an optimal neuronal context for iTBS treatment. Furthermore, this study measured emotional bias, involving tasks where judgments are needed for emotionally ambiguous facial expressions, 20 minutes after the end of all stimulation conditions. Depression is characterised by a cognitive bias towards negative information (Bourke et al., 2010; Elliott et al., 2011). This can be especially prominent for facial expressions that depressed patients tend to interpret neutral faces to be sad (Liu et al., 2012; Raes et al., 2006). Evidence shows that reduced depressive severity is associated with an improved ability to positively interpret ambiguous information, possibly involving enhanced brain serotonin functions (Bhagwagar et al., 2004; Harmer et al., 2003; Suddell et al., 2023). In this study, the result was most positive following tsiTBS compared to all other stimulation types, suggesting that enhanced theta activity indicates antidepressant effectiveness and that this dual approach likely has potential clinical application in depression (Briley, Boutry, et al., 2024).

In all, enhanced and prolonged responses can be achieved by synchronising rTMS with tACS in a frequency- and phase-specific manner. By accounting for the oscillatory activity at the time of stimulation, phase-synchronised tACS-rTMS holds promise to augment the antidepressant effects induced by rTMS alone (Janssens & Sack, 2021).

2.1.2 Present feasibility pilot study

This study aimed to test the feasibility and acceptability of multi-session “tsiTBS” as developed by Briley, Boutry, et al. (2024) in a patient group with mild-to-moderate depression and to test

its potential usefulness as an antidepressant modality. Abnormal oscillatory activities across frequency bands have been observed in depressive disorders for which effective treatments are associated with the restoration of regular oscillatory patterns (De la Torre-Luque & Bornas, 2017; Leuchter et al., 2013). It is of interest for the current study to investigate whether similar results can be replicated in depression which is characterised by different brain environments from healthy subjects. In line with the non-patient study (Briley, Boutry, et al., 2024), we measured resting-state and task-related EEG activities before and after the stimulation but extended post-stimulation timepoints up to 36min in order to capture longer trajectories of EEG effect. We additionally measured multi-timepoint functional near-infrared spectroscopy (fNIRS) to assess the concentration changes of oxygenated-hemoglobin and deoxygenated-hemoglobin in the frontal cortex. The fNIRS data will be separately analysed and presented in a future report and will only be described here for methodological purposes. In addition to the emotional bias task (EBT), we obtained measures from the THINC-it battery to gain insights into alterations of cognitive functions which constitute a central component in depression (Hammar et al., 2022). Furthermore, we conducted a semi-structured interview at the end of the study period to better understand the acceptability and tolerability of the dual neuromodulation approach. Neuromodulation techniques generally have a high level of acceptability, but it is still unclear concerning the safety and tolerability profile of combined use of techniques (H. Li et al., 2021).

The primary goal of this study was to test the practicality of methods and procedures in delivering multiple sessions of tsiTBS in patients with depression, and to refine protocol in preparation for future larger-scale studies. It was not adequately powered to enable conclusive assessment of therapeutic synergy of the dual approach. With this in mind, some hypotheses were nonetheless proposed based on the previous findings by Briley, Boutry, et al. (2024): compared to iTBS plus sham tACS, following tsiTBS, (1) task-related frontal theta oscillatory power will show significant enhancement, (2) resting-state frontal theta oscillatory power will show significant increase, (3) emotional bias values will be significantly higher (more positive), and (4) performance will show significant improvement as measured in cognitive tasks.

2.2 Methods

2.2.1 Overview of study

We conducted a randomised, sham-controlled pilot study, examining the feasibility and acceptability, as well as the mechanism of action of a dual neuromodulation approach for people with mild-to-moderate depression. Participant feedback and researcher insight were used to update the experiment procedure twice, initially after the first 6 participants and again after the 9th participant. The final study design is summarised in Figure 2.1, and a list of changes is given in Table 2.1. Please also see the appendix B.1 for summary of the 2 older versions.

Baseline session

Participants were pre-screened by questionnaire-based telephone assessment and those potentially eligible were invited to attend a baseline session. PHQ-9, GAD-7, WSAS, EQ-5D-5L questionnaires (Herdman et al., 2011; Kroenke et al., 2001; Mundt et al., 2002; Spitzer et al., 2006) were completed before attending the session. Written, informed consent was obtained at the start of the baseline session and study eligibility was determined by an outcome assessor using SCID-5-RV and MADRS scores. Originally, the baseline session did not contain any further measurements. However, to shorten the study length and reduce participants' traveling burden, we extended this session to include components in study day 1 of version 1.0 if the eligibility was confirmed.

In version 2.0, participants subsequently completed two variants of the emotional bias task (EBT) (CANTAB® [Cognitive assessment software]. Cambridge Cognition (2023). All rights reserved. <https://cambridgecognition.com/>) and the Choice Reaction Task (CRT), or "Spotter" task in the THINC-it cognitive battery. It is worth noting that CRT was included after the 2nd participant based on their feedback of difficulty in concentration following stimulation sessions. fNIRS assessment was then completed, during which a verbal fluency task and an emotional Go/ No-Go task were conducted sequentially as participants sat comfortably in a well-lit room. Following practices of a short, practice version of 2-back working memory task, resting motor threshold (rMT) was identified, and the stimulation procedure was demonstrated.

In the final version 3.0, we again shortened the baseline session by removing the baseline fNIRS measurement and rescheduling rMT measurement to study day1. This was to minimise participant burden and cognitive load considering that the extended baseline as in version 2.0 could be overwhelming as an introductory session.

Modification	Details
Add in choice reaction task (CRT)	Based on the account of x002 that they experienced reduced concentration for a short while following stimulation sessions, we decided to add in CRT to examine potential impact on cognitive functions.
Changes in the baseline session	In the version 2.0, the baseline session was extended to include clinical interview, EBT, CRT, fNIRS, and TMS motor threshold measurement. In the final version 3.0, the baseline session was again shortened by removing baseline fNIRS measures and moving motor threshold measurement to the start of study session 1.
Changes in fNIRS timepoints	Compared to version 1.0 where fNIRS was measured at baseline and follow-up, the later versions included fNIRS on study session 2 before and after stimulation.
Extended stimulation sessions	Compared to older versions where 2 stimulation sessions were given per day for 2 days (totalling 4 sessions), the final version changed to 1 stimulation session per 5 for 5 days totalling 5 sessions.
tACS electrode application	Applied tACS electrodes with saline-moistened sponges instead of conductive paste for quicker set-up.

Table 2.1. Modifications of experimental procedures across protocol versions.

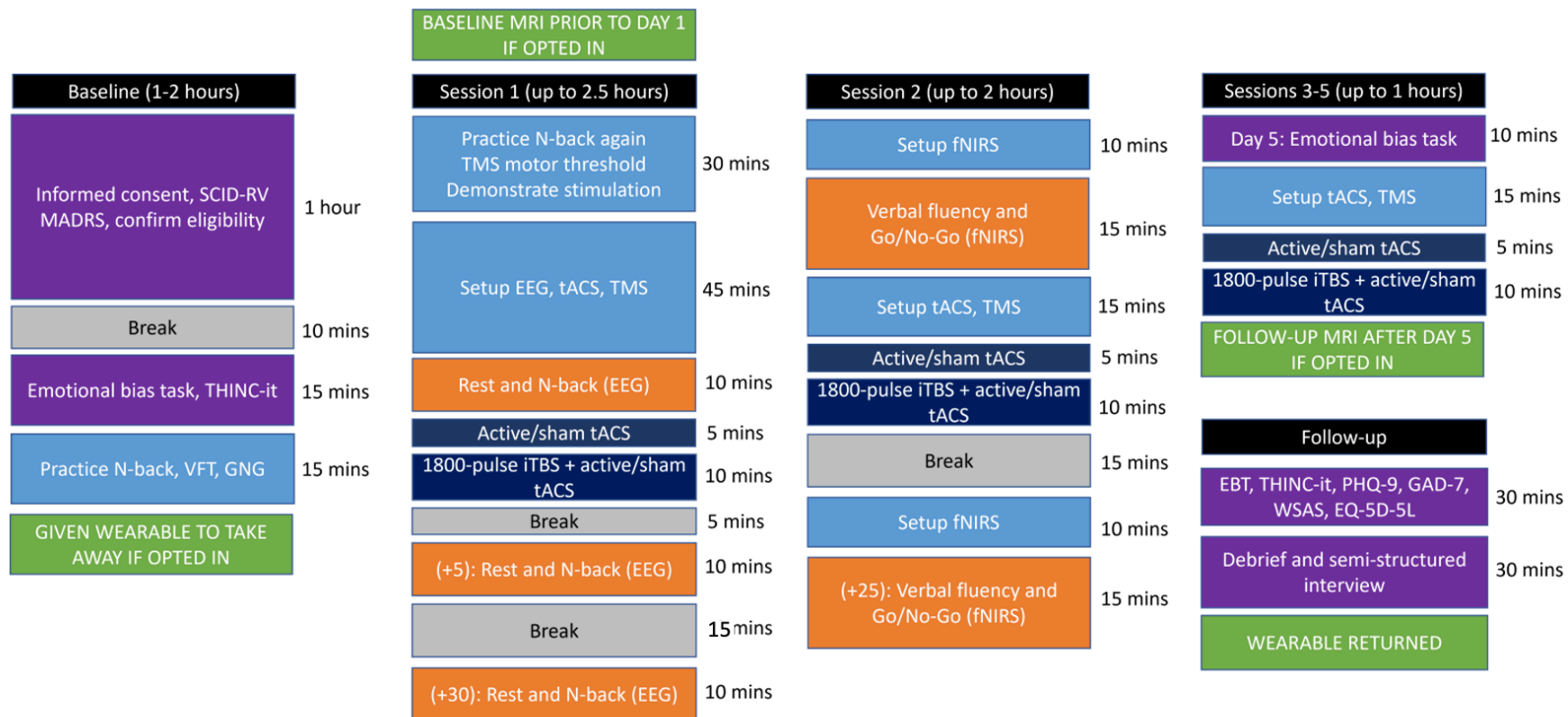


Figure 2.1. Overall experimental procedure (version 3.0). The final version of study protocol includes a baseline session, 5 study days with 1 stimulation session per day (maximum 1 day in between sessions), and a follow-up session. On study day 1, EEG measures were recorded during resting states or n-back working memory task before, 5 minutes and 30minutes after stimulation. On study day 2, fNIRS measures were recorded during a verbal fluency test and an emotional Go/ No-Go task before and 25 minutes after stimulation. Study sessions should start within 28 days following baseline and be followed by the follow-up session within a week.

Study sessions

For the first 9 participants, the main experiment consisted of 2 testing days scheduled with 2-3 days of interval in between. Participants completed 4 stimulation sessions (2 on each day), EEG measurements (day1), and, for x007 and x009, fNIRS measurements (day2). Participants then attended a follow-up day within the same week of study day2 to complete repeated measures from baseline session and a semi-structured interview. For the later participants (x010-x012), the main experiment consisted of 5 days scheduled with a maximum of 1 day in between. Participants completed 5 stimulation sessions (1 on each day), EEG measurements (day1), and fNIRS measurements (day2). Despite the changes in experimental procedure, no change was made in terms of stimulation parameters or task procedures. The following description applies to the latest version. At the start of study day1, screening questionnaire was reviewed to detect any changes in participant eligibility. rMT was measured and stimulation was demonstrated. tACS, TMS and EEG were then set up. With room lights switched off, EEG was recorded during the resting state (including eye-closed and eye-open conditions) and then the 2-back task. The researchers then delivered the stimulation which lasted 15min in total. After a short break, further runs of resting-state and n-back were obtained at the 5- and 30-mins and 11-min and 36min post-stimulation timepoints respectively. The EEG cap and tACS electrodes were then removed and a side-effects questionnaire was completed. On study day2, fNIRS was measured before and 25 minutes after the stimulation using the same protocol as day1. The side-effects questionnaire was then completed upon completion. Study day 3-5 included 1 stimulation session per day using the same protocol as day1 and the completion of side-effects questionnaires post-stimulation. On the follow-up day, participants again completed PHQ-9, GAD-7, WSAS, EQ-5D-5L questionnaires. They then completed the EBT and CRT tasks following the same procedure as the baseline session. Following a short break, a semi-structured interview was conducted by researchers to discuss about the experience of taking part in the study, the acceptability and tolerability of the dual approach, and suggestions to improve study protocol.

2.2.2 Participants

A total of 12 participants with mild-to-moderate unipolar depression, aged between 18 and 59, were recruited. Exclusion criteria included: currently under the care of a mental health Crisis Team or Intensive Home Treatment team; current or past diagnosis of bipolar or psychotic disorder, substance abuse or dependence, dementia or mild cognitive impairment; PHQ-9 scored above 19 or below 5; suicidal ideation or behaviour within the past 3 months; any skin or allergy condition in which tACS electrodes or EEG gel cannot be applied; contraindications to receiving TMS. The study was approved by the Research Ethics Committee of the University of Nottingham Faculty of Medicine and Health Sciences (Ethics Reference Number FMHS 288-0523), and written informed consent was obtained from all participants. Participants were compensated with a £100 Amazon shopping voucher for sessions completed (pro rata if not all sessions were completed).

2 dropped out before the first study session, 1 for no given reason and 1 due to not tolerating discomfort during iTBS demonstration. We tested 10 participants in total (9 females; mean age $\pm$ SD, 29 ± 12.57 yrs; 5 reported ethnicities other than white). 1 was classed as ambidextrous and the remainder as right-handed by the criteria of Oldfield (1971). Participants were randomised to the following stimulation conditions by the MinimPy software (<http://minimpy.sourceforge.net/>): sham tACS + iTBS (or “iTBS-only”; N = 6) and active tACS + iTBS (or “tsiTBS”; N = 4). MinimPy is a free, open-source, desktop minimisation program where we randomly allocated participants to one of the two stimulation conditions, with minimisation on baseline PHQ-9 score (low: 5-11, or high: 12-19), using the “biased coin” probability method, base probability of 0.7, and the “marginal balance” distance method.

6 participants provided data for all outcome measures including questionnaire scores before and after the study, CRT task measures before and after the study, EBT scores before and after the study, EEG measures for resting state (before, 5min and 30min after stimulation) and n-back (before, 11min and 36min after stimulation) at all timepoints, adverse effects (measured after each study day) and interview data. Despite differences in the protocol versions used, all the above-mentioned outcomes were consistently measured and analysed across all participants. CRT was not tested for the first 2 participants. For 3 participants, EEG and n-back measures were not included due to failure of the EEG system (N = 1) or faults with trigger recording (N = 2). An interview was conducted with the participant who withdrew due to discomfort. Number of participants included for each measure is summarised in Table 2.2.

Outcome measures	Number of included datapoints
Questionnaire scores	10 (iTBS, N = 6; tsiTBS, N = 4)
CRT task	8 (iTBS, N = 5; tsiTBS, N = 3)
EBT scores	10 (iTBS, N = 6; tsiTBS, N = 4)
EEG measures	7 (iTBS, N = 3; tsiTBS, N = 4)
N-back measures	7 (iTBS, N = 3; tsiTBS, N = 4)
Adverse effects	10 (iTBS, N = 6; tsiTBS, N = 4)
Interview	11 (iTBS, N = 6; tsiTBS, N = 4)

Table 2.2. Number of participants included for each outcome measure.

2.2.3 Neuromodulation

Transcranial magnetic stimulation (TMS)

TMS was delivered using a Magstim Rapid2 Plus with a D70mm Air Film Coil. Throughout the stimulation, participants wore foam earplugs to attenuate noise and a neck pillow to help minimise the head movement, while a researcher wearing ear covers stood nearby monitoring coil drift. rMT was assessed at the baseline session, by visual monitoring of the resting right thumb. rMT was defined as the lowest stimulation intensity required to elicit a thumb twitch on 50% of trials. Stimulation consisted of 1800 pulses of iTBS (10mins) delivered at 80% rTMS intensity involving 60 cycles of triplet 50Hz pulses, repeated at 5Hz, 2s on and 8s off. The stimulation target was localised at F3, which is a commonly used approximate of the left dlPFC based on the International 10-20 system (Herwig et al., 2003). The coil was placed tangentially to the scalp over F3, with handle angled 45° backwards relative to the midline. The F3 electrode was removed to optimise the contact distance between coil and scalp.

In the “tsiTBS” condition, each iTBS cycle was initiated by the Nurostym tES system, which sent a trigger pulse through a BNC cable to the Magstim Stimulator Interface Module. In the “iTBS-only” condition, the entire sequence of 60 iTBS cycles was triggered at once. The same course of iTBS was delivered in the two stimulation conditions.

Transcranial alternating current stimulation (tACS)

tACS was delivered using a Nurostym tES system (Neuro Device Group S.A., Poland) using sponge-covered electrodes placed at F3 (anode) and TP9 (cathode), the same locations used by Briley, Boutry, et al. (2024), Hosseinian, Yavari, Biagi, et al. (2021), and Hosseinian, Yavari, Kuo, et al.

(2021) (note that Hosseinian and colleagues used bilateral targets). For the first participant, 9 cm² square carbon silicone rubber electrodes were used with conductive paste. However, for subsequent participants, 25 cm² electrodes were enclosed in sponges moistened with saline, which facilitated lower impedance and faster setup. Care was taken to ensure that electrode sponges maintained full contact with the scalp, hair was moved to the side and EEG cap was used to keep the electrodes in place.

Electrodes were placed prior to fitting the EEG cap with the anode located using the Beam F3 algorithm (Beam et al., 2009) and the cathode located behind the left ear. Impedance was kept below 15 kOhms. The stimulation involved an alternating current at 5Hz with 1 mA peak-to-peak amplitude. It ramped on over 2s, remained at the full intensity for 5 mins, after which the Nurostym device sent pulses to trigger each iTBS cycle. In the “tsiTBS” condition, iTBS pulse was timed in the way that the middle pulse of each triplet occurred at the tACS (anode) waveform peaks. tACS continued for the 10 minutes of the iTBS cycle, then faded off over 2 seconds. In the “iTBS-only” condition, pulse after the tACS had reached its peak intensity, it then faded out across 10 seconds.

2.2.4 Electroencephalography (EEG)

Data acquisition

22-channel EEG recordings were obtained with Ag/AgCl electrodes mounted in an appropriately sized cap, arranged according to the 10-5 international system. The F3 electrode, and surrounding electrode holders, were removed to reduce the distance of TMS coil to the scalp. The TP9 was also removed as it was located on top of the tACS cathode. Signals were online referenced to Common Mode Sense, located left and posterior of the vertex, amplified with a BioSemi Active Two system, online filtered between 0.16 and 100 Hz, sampled at 2048 kHz, and stored for offline analysis.

Resting-state and n-back tasks

All task procedures were implemented in PsychoPy (v2022.2.5). Event triggers were sent by PsychoPy to the EEG amplifier and stored alongside the EEG recordings. The resting states were guided by an audio cue that instructed participants to close their eyes (for 100s) and then open their eyes viewing a fixation cross on a grey background (for 100s). The 2-back task was identical to that used in Briley, Boutry, et al. (2024). In 2-back blocks, stimuli consisting of capital letters “A” to “J” were presented one at a time (for 500ms) in the centre of the screen, interspersed by 1-s fixation periods. Participants were instructed to press a button as soon as they saw a letter that appeared two

letters before. After the first two stimuli, the target probability on each trial was 25%, with the constraint that targets were not allowed to occur consecutively. 130 trials were presented during each 2-back run.

Data pre-processing

Data were pre-processed using the EEGLAB toolbox v2022.1 (Delorme & Makeig, 2004) with Matlab (R2022b, The Mathworks, Natick, MA). Data were first band-pass filtered between 0.5 and 40 Hz. Bad channels were then detected and removed if kurtosis exceeded the threshold of ± 5 standard deviations. To avoid capturing eye movement responses, the first 10 seconds and last 5 seconds of each resting-state period were discarded. Resting-state data were segmented into 3-second non-overlapping epochs, and task data were segmented into 3-second overlapping epochs around non-target stimuli. Epochs containing outliers were removed. Then, resting-state epochs were concatenated with alternate task epochs (in order to prevent overlapping) and subjected to independent component analysis (ICA) using the Infomax extended algorithm (Anemuller et al., 2003; Bell & Sejnowski, 1995; Lee et al., 1999). Components were identified and removed from scalp topographies and time courses if prominent sources of noise such as eye movements. ICA component weights and rejections were then applied to the full overlapping set of non-target task data epochs. Data were re-referenced to average reference, then time-frequency analysis was performed with complex Morlet wavelet across 1 to 30 Hz (at 1Hz steps) using the mfeeg toolbox (Wu et al., 2015). For task data, this focused on the frontal midline AFz and Fz electrodes. Mean power across the electrodes at theta (4–8 Hz) frequencies during the 1-second inter-stimulus fixation intervals following non-target trials (excluding incorrect responses) was extracted for each time point and stimulation condition. Consistent with Briley, Boutry, et al. (2024), non-target trials were analysed since targets could be confounded by motor-related brain activity, and inter-stimulus periods were analysed based on the hypothesis that theta is generally the strongest during the information maintenance stage (inter-stimulus periods). Since the main aim was to assess changes in maximal theta following stimulation, rather than within-trial modulations of theta power, task-related frontal theta power was calculated as each post-stimulation time point in decibels relative to pre-stimulation measurements. As our primary hypotheses did not concern resting-state, we ran exploratory analyses for that dataset, with power also extracted for beta (13–30 Hz) frequencies (including the full beta range, low beta at 13-20Hz, and high beta at 21-30Hz) and alpha (9–12 Hz) frequencies, all at the frontal central electrodes (Az and Fz). Similar to task data, resting power for

each post-stimulation time point, frequency band, and condition (eyes open or closed) was expressed in decibels relative to pre-stimulation resting power for that frequency band and condition.

2.2.5 Emotional bias task (EBT)

Task description

Participants completed two variants of the CANTAB emotional bias task (Cambridge Cognition, Cambridge, UK), presented on a compatible iPad (Apple, Cupertino, CA) at the baseline session and the follow-up session. Following a brief explanation, the task contains a series of images of faces that are morphed between two emotions of varied intensities. Two variants included faces covering spectrums from “happy” to “sad”, and from “happy” to “disgusted”. Each face was presented for 150ms followed by a black-and-white noise mask. The participant then selected the perceived emotion by pressing a label, after which a central fixation cross appeared before the next face. Each variant consisted of two practice trials and 45 main assessed trials. The primary outcome measure from each variant was the “bias point”, which was calculated as the proportion of faces identified as “happy”, scaled from 0 and 15, where 7.5 represents an equal number of happy and the relevant negative emotion responses.

2.2.6 Choice response task

Task description

Participants completed the CRT (“Spotter”) task twice under the THINC-It tool, presented on a laptop screen, at both the baseline session and the follow-up session. The CRT is a choice reaction time test of attention. Following a brief explanation, the task contains a series of arrows facing either left or right. Participants were required to press the left or right button as soon as possible depending on the direction of the arrow. Each arrow may either appear on the same side of the screen as the direction to which it points (“congruent” trials) or it may appear on the opposite side of the screen to its direction (“incongruent” trials). The participant’s response triggered the next arrow to appear.

2.2.7 Semi-structured interview

A semi-structured interview was conducted with participants on the last study day to explore the barriers and facilitators to engaging in the current research project and the acceptability of the dual neuromodulation approach as a potential treatment for depression. Interview questions focused on

the initial impression before participation, positive and negative aspects of the experience, and opinions on combining tACS and TMS as a dual neuromodulation approach (see Appendix B.2. for a full list of interview questions and prompts). Responders also indicated the level of acceptability of the dual approach on a 1-to-5 rating scale. Interviews were audio-recorded and transcribed verbatim, then were analysed using an inductive content analysis approach (Graneheim et al., 2017). One researcher (Y.P) familiarised with the data by multiple readings of the transcripts and coded for common themes. The themes were then discussed and consolidated by an external qualitative expert who was not part of the research team.

2.2.8 Statistical analysis

All analyses were conducted in R (version 4.4.0, <https://www.R-project.org/>). Analyses used all available data from each participant (Table 2.5) with no extreme outlier detected for any measure. All analyses were two tailed with a significant threshold of .05. All analyses included the interaction effect between independent factors wherever applicable. For analyses using mixed ANOVA, all were conducted following tests confirming normality (Shapiro-Wilk's test) and homogeneity of variance (Leven's test) (all $p > .05$).

Differences in baseline PHQ-9, baseline MADRS, and side-effect scores between stimulation conditions (tsiTBS and iTBS-only) were examined using two sample t-tests. The assumption of normality was confirmed by the Shapiro-Wilk's test ($p = .3$, $p = .83$, and $p = .08$ respectively). The baseline difference of age was examined using Kruskal-Wallis test due to violation of normality by Shapiro-Wilk's test ($p = .005$).

For questionnaire scores, effects were examined comparing each questionnaire score before and after study by stimulation conditions. For n-back task performance, analyses were conducted separately on accuracy measures (D-prime, correct responses to targets and non-targets) and mean target reaction time. For CRT data, analyses were conducted separately on mean reaction time in congruent and incongruent conditions. For task-related theta activity, change in frontal theta power was measured as post-stimulation theta power at each timepoint minus pre-stimulation theta power. For resting-state activity, analyses were conducted on changes in theta, alpha, beta, low-beta, and high-beta relative to pre-stimulation power respectively. Two-way mixed ANOVA was conducted on each above measure with independent factors defined as stimulation conditions and measured timepoints (questionnaire/ CRT: pre-stimulation and post-stimulation; n-back/ task-related theta: pre-stimulation, +11min and +36min; resting-state measures: pre-stimulation, +5min and +30min).

For emotional bias data, a three-way mixed ANOVA was conducted to examine whether emotional bias points differed with stimulation condition, task variant (happy-sad and happy-disgusted), and/or measured timepoint (pre-stimulation and post-stimulation).

2.3 Results

2.3.1 Completion of sessions

Overall, 12 participants were recruited and 10 completed the study (version 1.0, N = 6; version 2.0, N = 2; version 3.0, N = 2). For one participant (x005), iTBS was stopped midway during one stimulation session due to loosened trigger cable, while the participant was not made aware of the fault. One participant (x010) was originally allocated to the tsiTBS condition, but, due to issues with the tACS cable or electrode, they were switched to the iTBS-only condition. Their data were analysed per protocol (iTBS-only). Please see Table 2.3 for a summary of completed sessions by protocol versions for each participant.

Protocol version	ID	Stimulation condition	Completed stimulation sessions
Version 1.0	x001	Sham	4
	x002	Active	4
	x003	Active	4
	x004	Sham	4
	x005	Active	3
	x006	Sham	4
Version 2.0	x007	Sham	4
	x008	N/A	N/A
	x009	Sham	4
Version 3.0	x010	Sham	5
	x011	N/A	N/A
	x012	Active	5

Table 2.3. Summary of completed stimulation sessions for each participant. Sham = sham tACS + iTBS (“iTBS-only”). Active = active tACS + iTBS (“tsiTBS”). 2 participants (x008 and x011) withdrew before the first stimulation session. All apart from x005 completed all stimulation sessions. Participant x010 was switched from the active group to sham due to technical faults.

2.3.2 Demographic characteristics and clinical variables

There was no significant group difference in baseline PHQ-9, baseline MADRS, or age (all $p > .05$) (Table 2.4). Numerically, the tsiTBS group had higher numbers of mental health diagnoses and psychiatric medications. Overall, in terms of questionnaire scores, the tsiTBS group displayed higher levels of variability and higher medians at both measured timepoints, while the iTBS group displayed

a more prominent trend of decrease in scores after study (Figure 2.2). The health questionnaire scale (EQ-5D-5L scale) showed a significantly higher (better perceived health) baseline score in the tsiTBS group ($p = .047$). No other significant difference in questionnaire scores was reported (all $p > .05$).

	tsiTBS	iTBS-only	Statistical comparison
Age (years) mean $\pm$ SD	37.25 $\pm$ 16.32	22.33 $\pm$ 3.83	$t[3.22]=1.76$ $p = .17$
Gender	4 females	5 females, 1 male	
Mental health diagnoses	cPTSD (N = 3) Depression (N = 3) GAD (N = 2) Social anxiety (N = 1) Eating disorder (N = 1)	Mixed anxiety and depressive disorder (N = 1) Depression (N = 1) GAD (N = 1) Autism (N = 1)	
Psychiatric medications	Diazepam 2mg PRN (N = 1) Quetiapine (N = 1) Zopiclone (N = 2) Escitalopram (N = 1)	Sertraline (N = 1) Propranolol (N = 1)	
Baseline MADRS mean $\pm$ SD	20.25 $\pm$ 2.75	22.67 $\pm$ 3.78	$t[7.84]=-1.7$ $p = .28$
Baseline PHQ-9 mean $\pm$ SD	12 $\pm$ 4.83	11.67 $\pm$ 3.72	$t[5.34]=0.12$ $p = .91$

Table 2.4. Summary of demographic and clinical characteristics of participants by stimulation condition. cPTSD = complex post-traumatic stress disorder. GAD = generalised anxiety disorder. Some participants had more than one diagnoses and/ or took multiple medications.

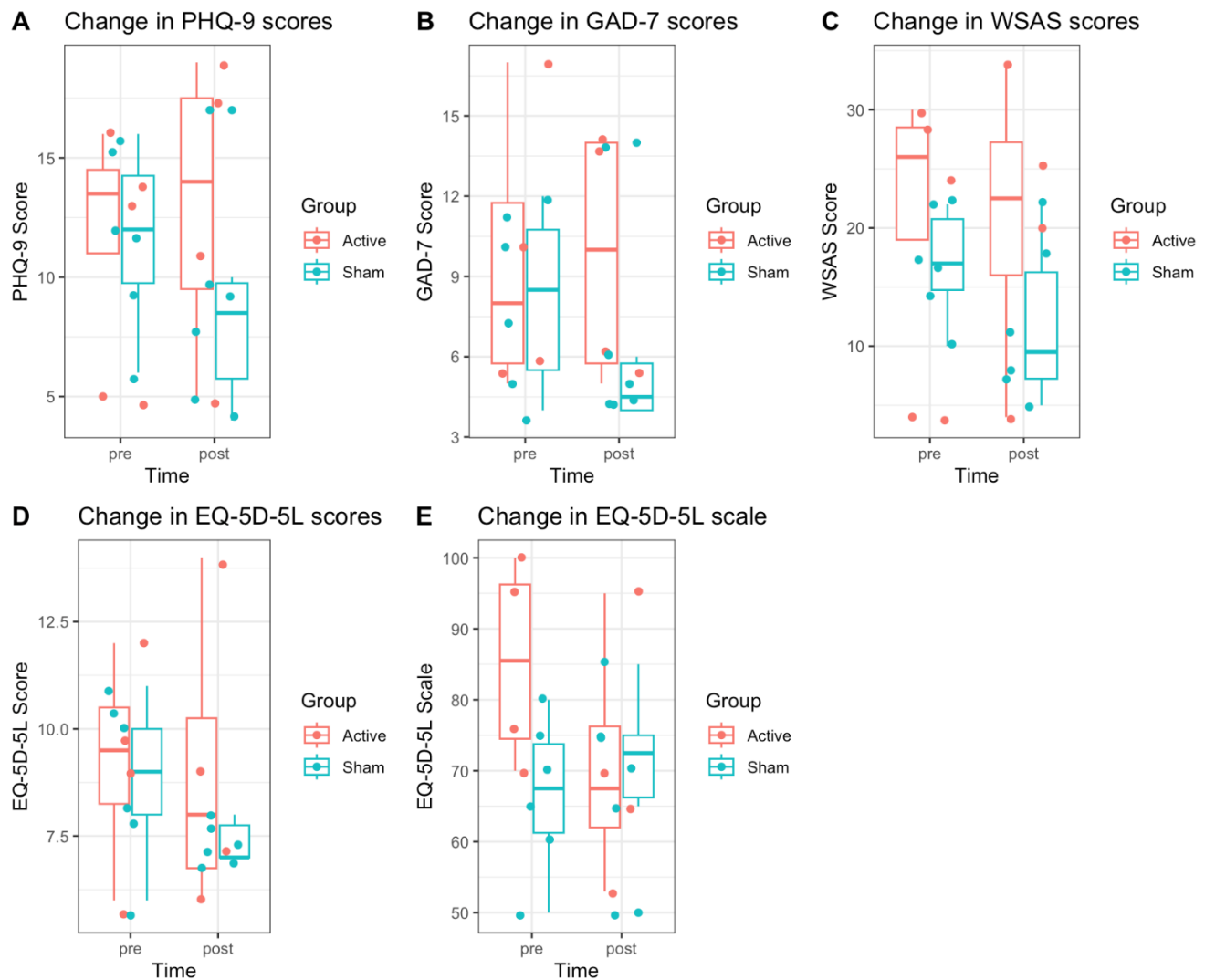


Figure 2.2. Comparison of questionnaire scores before and after study between stimulation conditions. Each circle represents a participant. Boxplots show quartiles. PHQ-9 = Patient Health Questionnaire-9. GAD-7 = General Anxiety Disorder-7. WSAS = work and social adjustment scale. EQ-5D-5L, a health questionnaire including index scores and a rating scale.

2.3.3 N-Back task performance

In all, responses were correctly made to 77.6 ± 12.12 percent of targets and were correctly withheld to 96.69 ± 2.79 percent of non-targets (Table 2.5). D-prime, a sensitivity measure of signal detection, was calculated by subtracting z-scores of false alarms (incorrect response to non-targets) from z-scores of hits (correct responses to targets). No significant effect was observed for any measure (all $p > .05$). Responses were made to targets at 73.3 ± 14.52 milliseconds. Similar to accuracy measures, no significant effect on reaction time was observed of either stimulation condition or measured timepoints (all $p > .05$).

	Pre-stimulation	+11 min	+36 min
tsiTBS	96.1% $\pm$ 3.68%	96.8% $\pm$ 2.14%	96.5% $\pm$ 4.37%
iTBS-only	96.9% $\pm$ 3.71%	96% $\pm$ 2.19%	97.9% $\pm$ 0.903%
A. correct responses to non-targets			
	Pre-stimulation	+11 min	+36 min
tsiTBS	81.1% $\pm$ 16.6%	76% $\pm$ 16%	84.2% $\pm$ 11.3%
iTBS-only	74.4% $\pm$ 10.7%	71.8% $\pm$ 11.6%	78% $\pm$ 9.22%
B. correct responses to targets			
	Pre-stimulation	+11 min	+36 min
tsiTBS	0.039 $\pm$ 2.69	-0.134 $\pm$ 2.1	0.461 $\pm$ 2.58
iTBS-only	-0.232 $\pm$ 1.84	-0.788 $\pm$ 1.49	0.448 $\pm$ 0.832
C. D-prime			

Table 2.5. Summary statistics for n-back accuracy measured as percentage of correct responses to non-targets (A) and targets (B) and D-prime scores (C) (all reported as Mean $\pm$ SD). Post-stimulation timepoints were measured at 11min and 36min following the end of stimulation.

2.3.4 EBT scores

Emotional bias was measured before and after study with two task variants of happy-sad (HS) and happy-disgusted (HD). Figure 2.3A shows the emotional bias measures compared between stimulation conditions for each task variant, with higher points suggesting higher degrees of positivity. There were significant two-way interactions between stimulation condition and time [$F(1,8) = 6.511$, $p = .034$, $\eta^2_g = .04$] and between task variant and time [$F(1,8) = 7.383$, $p = .026$, $\eta^2_g = .02$], but no significant three-way interaction was found [$F(1,8) = 0.237$, $p = .639$, $\eta^2_g < .001$]. More specifically, baseline emotional bias points were generally higher for HD (8.17 ± 1.23) than HS (6.67 ± 1.37), $p = .002$. There also showed higher (more positive) emotional bias points in the “tsiTBS” group (8.54 ± 1.14) than the “iTBS-only” group (7.11 ± 1.53) measured after stimulation sessions, $p = .0374$ (Figure 2.3B).

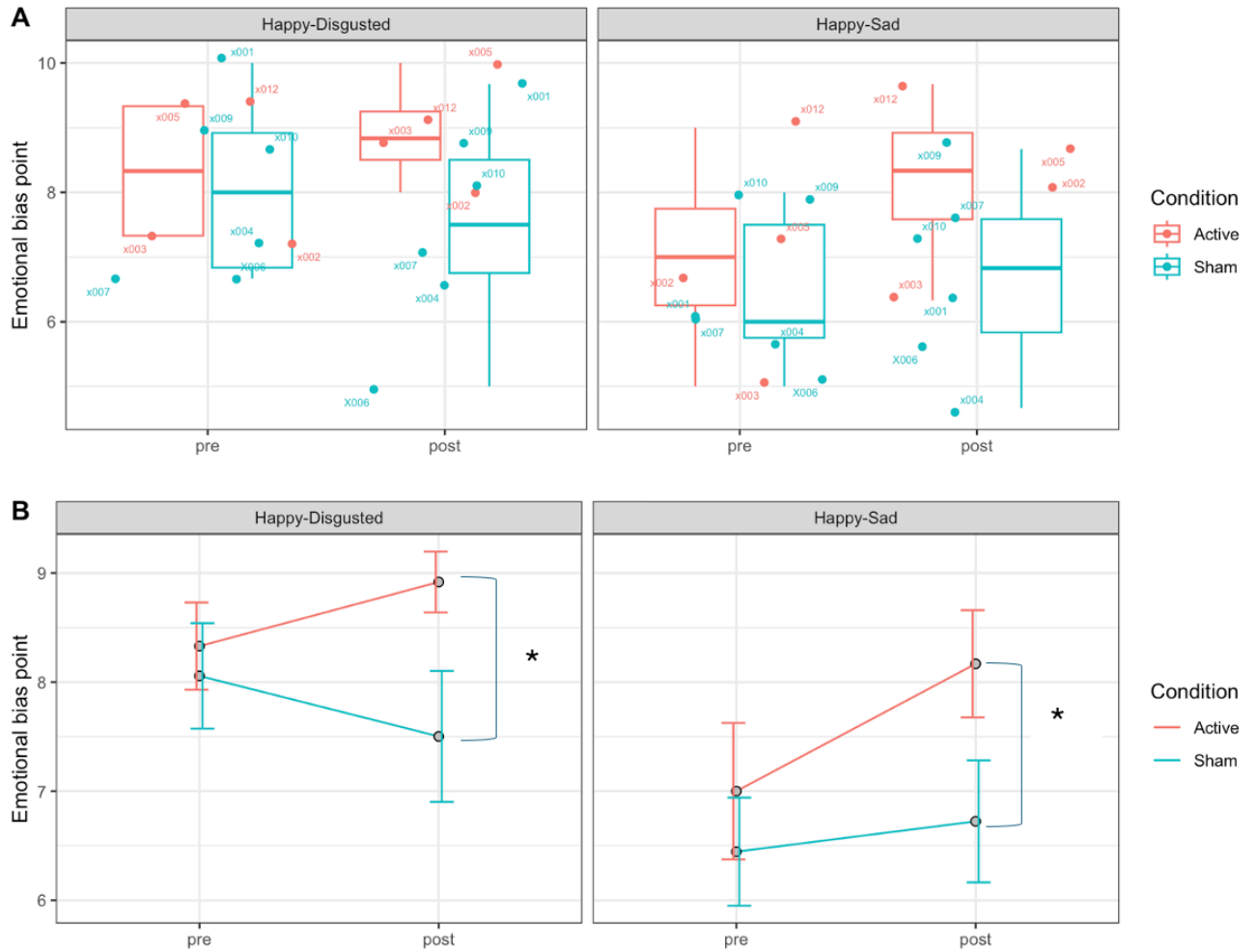


Figure 2.3. Comparison of emotional bias points before and after study between stimulation groups. A. Labels indicate individual participants. B. Error bars are mean $\pm$ standard error. Black asterisks indicate, for both task variants, significant differences in post-study scores between tsiTBS and iTBS-only groups ($p = .0374$).

2.3.5 Task-related frontal theta power

Figure 2.4 shows the change in frontal midline theta power, as compared to pre-stimulation measures, during the 2-back task at 11min and 36min post-stimulation timepoints. Opposite patterns were observed in the two stimulation conditions, with a greater variability following iTBS alone. Following the tsiTBS, frontal theta initially dropped at 11min timepoint but slightly increased at 36min timepoint. Following iTBS alone, frontal theta initially increased at 11min timepoint but fell by the 36min timepoint. However, these trends were only numerical as no significant effect of stimulation condition [$F(1,5) = 0.13$, $p = .73$, $\eta^2_g = .011$], measured timepoints [$F(1,5) = 0.11$, $p = .75$, $\eta^2_g = .013$], or their interaction [$F(1,5) = 0.55$, $p = .49$, $\eta^2_g = .06$] was revealed.

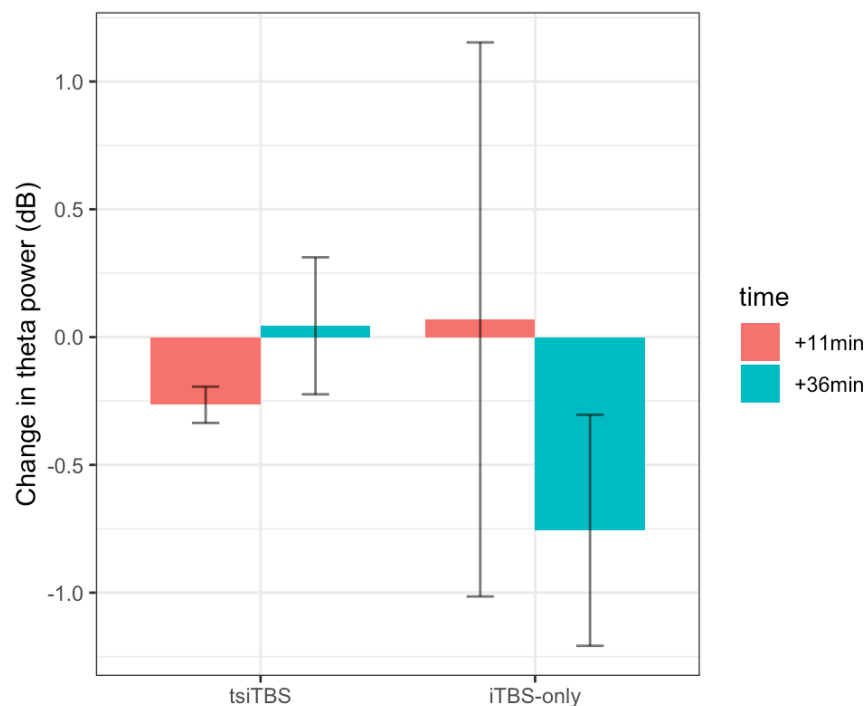


Figure 2.4. Change in frontal theta power (in decibels, relative to pre-stimulation measures) during 2-back task 11min and 36min post-stimulation. Error bars are mean $\pm$ standard error.

2.3.6 Resting-state oscillatory power

Figure 2.5 shows change in resting-state frontal theta power, as compared to pre-stimulation measures, at 5min and 30min post-stimulation timepoints in eyes-closed (A) and eyes-opened (B) conditions. Noticeably, greater variability was observed following iTBS alone, similar to task-related measures. No significant effect was observed for stimulation condition, measured timepoints, or their interaction for either condition (all $p > .05$). Resting-state analyses were also conducted for alpha (9-

12 Hz), beta (13-30 Hz), low-beta (13-20Hz), and high-beta (21-30 Hz) frequencies. There was a significant main effect of stimulation condition for low-beta in the eyes-open condition [$F(1,5) = 9.711$, $p = .026$, $\eta^2_g = .6$]. Changes in frontal-central beta at lower range were greater for the tsiTBS than iTBS alone ($p = .001$) across post-stimulation timepoints (Figure 2.5C). No other significant effect was detected.

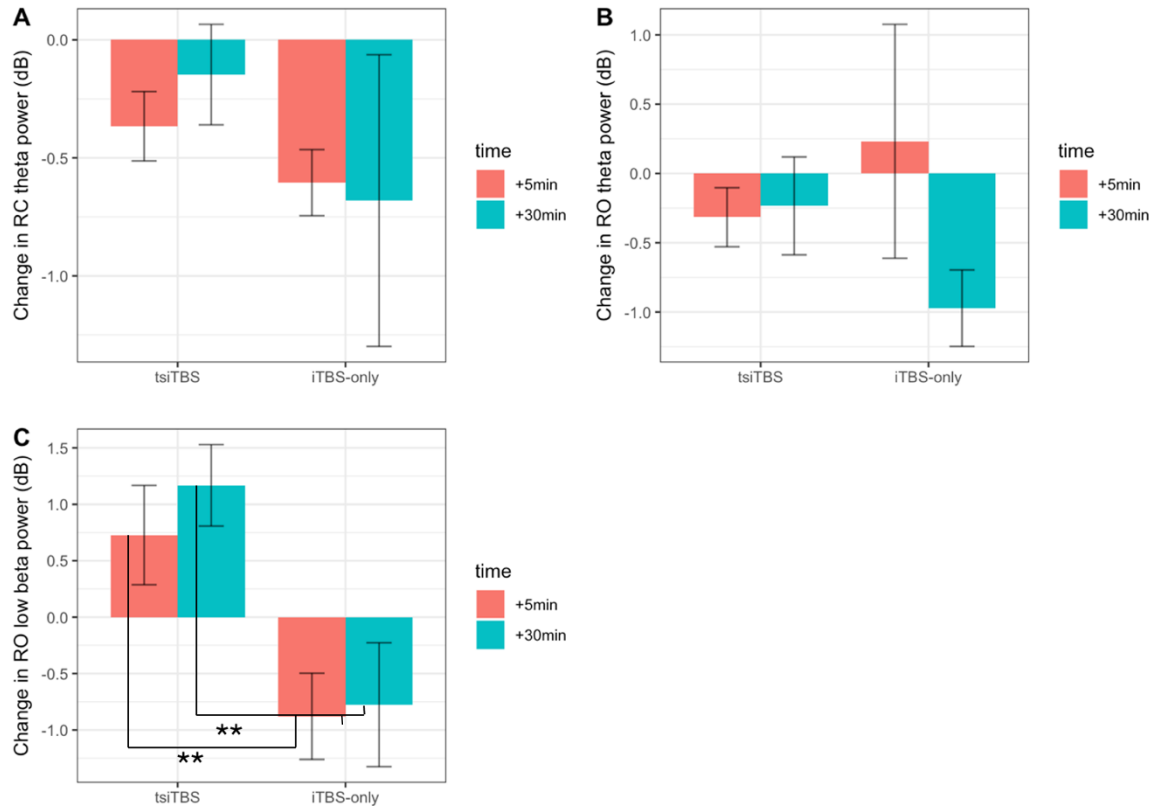


Figure 2.5. Change in frontal theta power measured in resting eyes-closed (A) and eyes-opened (B) conditions and change in frontal low beta power measured in resting eyes-opened condition (C), at 5min and 30min post-stimulation timepoints. Values are decibels relative to pre-stimulation measurements. Errors bars are mean $\pm$ standard error. Black asterisks indicate significantly greater changes in lower beta frequencies following tsiTBS than iTBS alone ($p = .001$).

2.3.7 CRT performance

Participants completed the CRT (“Spotter”) task before and after the study (Table 2.6). For either congruent or incongruent conditions, reaction time did not vary between stimulation groups or between measured timepoints (all $p > .05$).

	tsiTBS		iTBS-only	
	Pre	Post	Pre	Post
Congruent (msec, Mean $\pm$ SD)	413.06 $\pm$ 58.50	430.85 $\pm$ 90.41	432.65 $\pm$ 85.11	418.36 $\pm$ 81.18
Incongruent (msec, Mean $\pm$ SD)	513.84 $\pm$ 146.13	514.66 $\pm$ 173.67	495.55 $\pm$ 124.41	472.42 $\pm$ 144.36

Table 2.6. Summary statistics of reaction time in congruent (arrow appears at the same side of the screen where it points to) and incongruent conditions by stimulation group.

2.3.8 Adverse effects

No serious adverse effect was reported in this study. Fatigue/ drowsiness was rated as “severe” in one tsiTBS session with symptoms “gone by the evening” as reported by the participant. Including symptoms rated as “mild”, participants reported a mean of 3.75 and 2.33 adverse effects in the tsiTBS and iTBS conditions with no significant difference in between ($p = .52$). The most reported adverse effects were fatigue/ drowsiness (40% of sessions), scalp discomfort (30% of sessions), and visual changes (25% of sessions), and the remaining adverse effects were reported on fewer than 10% of sessions (Table 2.7).

	Number of cases reported			
	Mild	Moderate	Severe	Total (%)
Scalp discomfort	3	3	0	6 (30%)
Headache	2	0	0	2 (10%)
Neck pain	2	0	0	2 (10%)
Jaw ache	1	1	0	2 (10%)
Dizziness	0	2	0	2 (10%)
Nausea	1	0	0	1 (5%)
Fatigue/ drowsiness	7	0	1	8 (40%)
Visual changes	5	0	0	5 (25%)
Watering eyes	1	0	0	1 (5%)
Tinnitus	0	0	0	0
Taste change	0	0	0	0

Table 2.7. Number of cases reported for each side effect by rated severity. The percentage indicated the percentage of sessions with reported side effect including all severity levels.

2.3.9 Semi-structured interview

4 main themes (initial engagement, experience of participation, feelings about brain stimulation techniques after participation, and recommendations for future study) were identified using an inductive content analytic approach. Tables containing code unites (under each subtheme) were first presented, with percentage of participants (total N = 11) to indicate frequency of occurrence, followed by descriptions and example references.

Initial engagement

Previous knowledge and expectations	Limited knowledge (73%)
	Confused with brain scan (9%)
	Had TMS before (9%)
	No expectation (36%)
	Expectation of side effects (9%)
Initial impressions	Interesting (45%)
	Cool (9%)
	Unusual (18%)
	Difficult and complicated (9%)
	Wanted to know more (27%)
	No concerns (55%)
	Concerns related to ECT (9%)
Motivations for participation	Interesting (45%)
	Potential benefits to own self (27%)
	Potential benefits to research (64%)
	Potential alternative to ECT (9%)
	Opportunity to try the techniques (27%)
	Own clinician supported the techniques (9%)
	Have free time (9%)
	Inconvenience allowance (18%)
	Convenient location (9%)

Previous knowledge and expectations

Most participants had no or limited knowledge of the brain stimulation techniques used in this study. One participant confused the techniques with a brain scan. One participant took part in a TMS study before but never had the dual approach. There were mixed expectations based on the information sheet. While many did not expect any side effects or effects on mood or depressive symptoms, some expected sustained side effects, or uncomfortable sensations associated with stimulation, for example:

"I knew that it wasn't going to be harmful, in the way it was described. (x005, tsiTBS)"

"I thought that would be more intense...and I think I expected a greater amount of discomfort. (x012, tsiTBS)"

Initial impressions

Some general first impressions included feeling the study to be "interesting", "cool", "unusual", or "difficult and complicated". Some participants expressed interest in learning more about aspects of the study, for example:

"I had questions about, obviously, because it's a fairly new area of research, I had questions about how successful it would be...to see whether having this treatment would make a marked difference in outcome. (x010, iTBS-only)"

Most participants did not have concerns about brain stimulation or side effects. However, one participant (x002, tsiTBS) expressed specific concerns due to the perceived similarity of TMS to ECT, considering possible induction of seizures, and wanted to know if researchers had done it themselves:

"A little bit concerning but because it's on the ECT end of the spectrum... I think the TMS felt closer to ECT than the tACS. With it being lots of repeated pulses... [it] felt like something that was more likely to induce a seizure. Because I know that ECT is intentionally induced seizures, there was a bit there...The first thing was I wanted to know if the people on the team had had it done to them with concerns around ECT."

Motivations for participation

There were a range of motivations behind participants' decisions to take part including study being interesting, potential benefits to own self, potential benefits to research, an opportunity to try the technologies, and the use of such technologies supported by own clinician, for example:

"...it linked in with my own self-interest in mental health, my own personal health conditions and seeing whether it would benefit me. (x005, tsiTBS)"

"I mean it was a good incentive...it goes into research which at the end of the day will either help people or determine that this is not helpful for people. (x011, iTBS-only)"

"... [my community psychiatric nurse] was very pro it, and anything that she is kind of very pro, I'm always kind of interested in it because she likes some newer stuff. (x012, tsiTBS)"

One participant (x002, tsiTBS) brought up the prospect of such techniques as an alternative to ECT, "if I can be part of a trial that possibly stops people existing with [ECT], experiencing that, then

that's something worth doing". Some practical facilitators included having free time, inconvenience allowance, and convenient location.

Experience during participation

Rapport with researchers	Professional (45%)
	Trustworthy (18%)
	Nice (27%)
	Good communication (36%)
	Responsive to feedback (9%)
	Able to accommodate needs (18%)
	Perceived collaboration (9%)
Stimulation induction	Difficulty with tACS impedance test (18%)
	TMS motor threshold measuring was unpleasant (9%)
	TMS motor threshold measuring was unusual but not uncomfortable (9%)
	Negative affective impact from tACS pad slipping (9%)
	Fear and concern after TMS induction (9%)
Physical sensations during stimulation	Comfortable (9%)
	No discomfort (64%)
	Uncomfortable but not painful (9%)
	TMS too uncomfortable to tolerate (9%)
	Mild sensations (27%)
	Better after coil adjustment (9%)
	A gradual adaptation (55%)
	Different sensations between sessions (18%)
	Different sensations between tACS locations (9%)
Side effects	No side effect (45%)
	Watering eye on one side (9%)
	Slight drowsiness (9%)
	Cloudy vision (9%)
	Dizziness (9%)
	Loss of concentration (9%)
	Mild headache (27%)
	Side effects gone by evening (9%)
	Side effects explained by external factors (18%)

Rapport with researchers

Many participants expressed having a good rapport with researchers. Some mentioned that one of the facilitating factors of retention was due to their trust and confidence in researchers' professionalism, for example:

"The fact that the two of you were open and professional but approachable. You both seem very trustworthy which was a big part of it. (x002, tsiTBS)"

During the study period, many participants felt able to build good communication with the research team who clearly explained the study procedure, attended to feedback, and accommodated participants' needs, and felt the research team to be "nice". One participant (x005, tsiTBS) described the stimulation process as "kind of like a collaboration" that, "[researchers] put stuff on my head and let it monitor my whatever and I'm also taking part and doing something to help [them] understand what I'm going through".

Stimulation induction

Some participants experienced difficulties associated with tACS impedance testing. With one participant (x005, tsiTBS), the tACS sponge slipped, which created a spark. This experience had a negative impact on the rest of the session:

"...that was really invasive in the sense of feeling more- Feeling the electric, like it went wrong a bit, didn't it?... I saw sparks and felt the spark so that was a bit surprising...that set the pattern for how I'd feel about the rest of the time there."

Several participants commented on the procedure of establishing TMS motor threshold. One participant (x002, tsiTBS) found the experience "unpleasant" due to facial muscle twitches, which induced "fear and concern" before the first stimulation session.

Physical sensations during stimulation

Most participants found the stimulation without discomfort and, for example, described that:

"...it's like the doctor doing the knee jerk thing...it's just a reaction [x001, iTBS-only]."

"...it was being tapped on the head with the rubber end of a pencil repeatedly [x002, tsiTBS]."

"...personally, I feel like there's someone massaging very tired muscles [x006, iTBS-only]."

Some found the process "uncomfortable but not painful" which can be improved by adjusting the coil position (x005, tsiTBS). Mild sensations were reported mostly in hair or face. One participant (x012, tsiTBS) found the stimulation "comfortable" and described the experience that, "almost kind of went into like a sleepy state...just kind of go with it... I think there's a rhythm to it... You get into

a flow with it". One participant (x011) withdrew before the first stimulation session due to discomfort from the iTBS. They described the sensations of being too uncomfortable to stay long, which did not improve over time:

"... if it was going to be sustained for like 10 minutes, it was like, no, that's too uncomfortable. If you're tapping on your head or if something was on your scalp, you could tell that it was actually more internal than sort of like it wasn't on my skin, obviously. It was like it was actually in my skull. It hurt every time. Like I say, it didn't increase or decrease. It just seemed be like it was the same sensation every time it happened."

Many participants reported a gradual adaptation:

"But after actually that first wave, I'm okay with the rest so kind of relaxed [x006, iTBS-only]."

"I think you kinda get used to it...it was just intimidating at first that you don't really know what that supposed to feel like, but after you got used to everything, it was quite okay [x009, iTBS-only]."

Noticeably, two participants from the tsiTBS condition reported more dramatic differences between sessions. One (x005) reported "more penetrative" sensation in the second session:

"... in the first one, the first day, it felt like it was going to induce a migraine, a headache but it didn't...but the second one I felt it was like too penetrative...it was penetrative as in, I knew it wasn't going to pierce into my skin or anything. It felt like I had that spot [the fontanel] and it was pressing too hard."

The other (x002) specifically commented on experiences with tACS that stinging sensations were worsened and prolonged in the second session:

"It was significantly worse than the first stimulation day but like bee stings, like antiseptic, it was quite strong for, I don't know, 30 seconds and then it died down. but then unlike the first stimulation day, it came back that day."

This participant also reported different sensations associated with stimulation sites that "the tACS mainly stung at the front one [the forehead]" but "more just like pins and needles rather than anything [behind the ear]".

Side effects

Most participants did not experience side effects or pain during or after the stimulation. One participant (x007, iTBS-only) experienced "cloudy vision" during some parts of the study but did not specify if it's related to stimulation per se. Some side effects including watering eye and

drowsiness were reported to occur during the session but did not sustain afterwards. Mild headache after stimulation was reported by several participants. One participant (x002, tsiTBS) reported changes in experienced side effects that “a little bit of dizziness more so the second time than the first time” and “more significant loss of concentration after the first session than the second session”. Some participants attributed experienced side effects to causes outside of the experiment (e.g., “insomnia”) and described them as “gone by the evening”.

Feelings about brain stimulation techniques after participation

Perceived effectiveness	No difference (45%)
	Felt better (9%)
	Improved sleep (9%)
Thoughts about dual neuromodulation as future treatment option	Perceived future promise (27%)
	A good treatment option (9%)
	Safe (9%)
	Willing to have as treatment (64%)
	Unwilling to use unless necessary (9%)
	Happy to recommend to others (9%)
	Rated 5 (45%)
	Rated 4 (36%)
	Rated 2 (9%)
	Set-up can be tricky (9%)
	TMS motor threshold measuring can be an issue (9%)
	Different from other treatments for depression (18%)
	Better than ECT (9%)

Perceived effectiveness

Many participants did not feel much difference after the study. One participant (x006) from the iTBS-only group expressed feeling better:

“...the physical thing that I could evidence with how I felt was before I have taken part in the trial, I have had a personal struggle, challenges that have affected my mental health and so on a daily basis I feel like there’s some heaviness in my chest but after the first session it was actually light, surprisingly.”

This participant also theorised that “it works because...just part of my brain when it was the magnetic waves, I don’t know, it shakes something inside” and it led to “instant relief”. Another participant (x012) from the tsiTBS group noticed improved sleep following the last session, "Friday night I had the best night’s sleep I’ve had in weeks". They wondered “if that’s just like an accumulation of other thing that’s going on”.

Thoughts about dual neuromodulation as future treatment option

Some participants expressed overall positive thoughts about the techniques:

“I feel intrigued into what the future will be of it being used and together [x004, iTBS-only].”

“I think that it came across as a very safe way of doing it [x010, iTBS-only].”

“I think it’s a great treatment option [x012, tsiTBS].”

Many expressed willingness to have it as treatment if effectiveness is proven or if offered as an available option:

“If it actually works and it’s going to get rolled out on the NHS or wherever or privately then I’d pay for it [x005, tsiTBS].”

“I think I feel really positive about it, to the point that I would like to speak to my GP if, in future, I could have this kind of treatment because I feel like it has benefited me [x006, iTBS-only].”

“I would be open to trying it if it proved that it would help. I don’t see problems with it [x009, iTBS-only].”

One participant (x002, tsiTBS) felt that they would only have it if their clinician thought of it as necessary, “I’m not going to be running to my GP to ask for a course of TMS or similar unless they really start to think that you need it”. When asked to rate on a scale of 1 to 5 where 1 is very unacceptable and 5 very acceptable to use the dual neuromodulation approach, five participants rated 5 and three rated 4. The participant who withdrew rated 2, associating it with discomfort. Some identified certain barriers for its use including TMS motor threshold measurement (e.g., “difficult...and painful to find the right spot”) and “tricky” set-up.

When comparing the acceptability of tsiTBS to other antidepressant treatments, some participants noted the differences between the approaches:

“Because medication, like CBT and what not, it’s very different [x001, iTBS-only].”

“... it’s a totally different thing, like the way the body reacts [x012, tsiTBS].”

One participant (x002, tsiTBS) specifically pointed out its advantage over ECT, “if combining them means fewer people experience ECT, that’s a good thing.” One participant (x012, tsiTBS) highlighted the experience of “no pressure to do anything” unique to the neuromodulation approach, “It’s like it’s helping myself but without having to be asked to do more, dig deeper, try harder, think your way out of it...and just be open to whatever may or may not come.”

Recommendations for future study

No recommendation (27%)
Promote the study on a wider scale (9%)
Information sheet was overdetailed (9%)
Information sheet had unusual wording (9%)
Formatting information sheet for easier reading (9%)
Distinguish techniques from ECT in information sheet (9%)
Detail steps involved in the study in information sheet (9%)
Lab room was better (18%)
Distractions due to environmental factors (9%)
Testing in the ECT clinic was off-putting (9%)
Having something pleasant to look at can help with stillness (9%)
Inconvenience with EEG gel (36%)
Easier to pick out EEG when dry (9%)
Face database needed more diversity (18%)
Baseline session was a good introduction (27%)
Good to have adequate breaks (18%)
Add in feedback after each session (9%)
Use sponges rather than paste for tACS (9%)
Add in countdown before TMS starts (18%)
Inform of the remaining time midway through stimulation (9%)

Recommendations were made based on participants' experiences of participation. It was suggested that the study should be promoted on a wider scale for a more diverse range of participants such as libraries, service centres, and Facebook community pages. When it comes to information sheet, one participant (x005, tsiTBS) found it "overdetailed" with "unusual" wording that might confuse the lay audience. It was suggested that the formatting should be designed so that it is easier to read, for example, by incorporating emboldened headings and bullet points. With the similarity to more invasive methods such as ECT in mind, distinctions should be made clearly. In addition, explicit information should be provided as to steps of the study (e.g., the length of each session).

Some suggestions were also made regarding the testing environment. Some participants expressed preference of the smaller lab room over the larger testing room at the hospital. Reasons included emotional stress associated with the setting within an ECT clinic, and distractions due to environmental factors such as the window view and peripheral movement and noises. In addition, one participant (x002, tsiTBS) suggested that having something pleasant to look at can help with the stillness required during the stimulation session.

Several participants mentioned about the inconvenience associated with the EEG gel:

“When I tried to wash it [gel]...it’s just gloopy [x002, tsITBS].”

“The gel, it took a lot of time to get out [x004, iTBS-only].”

“The gel was quite annoying...I had to soak in the shower for so long to get everything out [x009, iTBS-only].”

One advised that it was easier to “pick it out when dry” instead of washing it.

Several participants commented on the lack of diversity regarding the face database used in the emotional GNG and the EBT tasks:

“The one thing that really hit me with those, all the people were very, very white...On the computer, it's really like these are all [white]. [x002, tsITBS]”

“... the examples were all primarily of white people of a particular age. [x010, iTBS-only]”

Regarding the structure of study sessions, it was overall perceived as well-organised with specific advantages associated with arranging study sessions in consecutive days, reasonable session length, and enough time to have breaks and/ or discussions, for example:

“The structure of how it went was good. I felt like there were enough breaks and there was enough talking about what things would be like. [x004, iTBS-only]”

In particular, several participants mentioned that the baseline session was a “good introduction” and provided “a bit of foresight” into the study. One participant (x004, iTBS-only) particularly mentioned the demonstration of TMS pulses on arm as a good way to “know what it would feel like”.

One suggestion about experimental components was to add in feedback after each session.

Finally, recommendations were made regarding the stimulation procedure. One participant (x002, tsITBS) preferred sponge covers to rubber electrodes when having tACS, “... I was getting stinging behind my ear quite strongly that we didn’t get when we used the sponges”. Several participants were surprised by the first TMS pulse, and it was suggested that countdown should be added before it started. In addition, considering the length of stimulation, it was suggested to inform participants of the remaining time midway through.

2.4 Discussion

Depression is characterised by aberrant prefrontal EEG activity possibly as a reflection of dysfunctional neuroplastic processes, which is associated with different responses between patients and healthy participants to rTMS treatment (De la Torre-Luque & Bornas, 2017; Deng et al., 2023). Based on Briley, Boutry, et al. (2024), this pilot study showed the feasibility of conducting multi-session tsiTBS in a patient group of mild-to-moderate depression who reported overall good acceptability of the dual approach. Some of the key outcomes were reported as comparable to Briley, Boutry, et al. (2024): the tsiTBS group showed a numerically similar trajectory of frontal theta power rise post-stimulation (despite no improvement in cognitive performance) and significantly more positive emotional bias compared to the iTBS-only group after stimulation (despite no improvement in questionnaire scores). A list of recommendations was proposed, based on participant feedback and researcher insight, for further study improvement.

2.4.1 Changes in brain oscillatory power

In Briley, Boutry, et al. (2024), changes in frontal theta power were measured during n-back task at multiple post-stimulation timepoints (1min, 8min and 15min) in healthy participants. Following an initial drop at 1min, a steep rise in theta was observed following the tsiTBS without plateauing at the end of measurement, with a similar trajectory (although smaller effect) following iTBS alone. It was thereby suggested that brain stimulation may not directly enhance theta but, instead, induce a process of theta enhancement over time as part of offline effects (Briley, Boutry, et al., 2024). The current study extended the stimulation duration (1800 pulses iTBS compared to 600 pulses before) and measured later timepoints at 11min and 36min post-stimulation. There showed a numerically but non-significantly similar trajectory following the tsiTBS that theta decreased at 11min but slightly increased at 36min, while a reversed and more inconsistent pattern was displayed following iTBS alone.

With the small sample size in mind, the delayed and decreased boosting effect following the dual approach may additionally be explained by altered brain activity associated with altered working memory functions in depression. According to a recent systematic review, patients with depression showed prolonged response times and lower accuracy for n-back tasks across different levels of cognitive load (i.e., varied “n”) than healthy controls, suggesting prefrontal inefficiency linked to working memory subprocesses including maintaining, retrieving and updating information (Nikolin

et al., 2021). In this aspect, altered frontal theta activity, reflecting changes in limbic-cortical regions, has been proposed as a neurophysiological correlate of impaired executive functions in depression (Pizzagalli et al., 2010; Fingelkurts et al., 2015; Tsai et al., 2023). In Murphy et al. (2019), frontal midline theta was measured during a verbal working memory task in patients with depression and healthy controls with matched demographic features and baseline task performance. Theta activity was significantly reduced in patients during encoding and maintenance phases albeit comparable task performance between groups. Regarding the lack of significant effect in this study, it is speculated that it may be harder to induce theta power rise in patients with depression after just one stimulation session. It may also be that depression is characterised by much more delayed rise in theta than healthy participants, which failed to be captured by the timepoints used here.

In resting-state analyses, frontal-midline low beta (13-20Hz) significantly increased following the tsiTBS compared to iTBS alone. Beta oscillations have been linked with aspects of depression such as ruminative thinking (Forner-Phillips et al., 2020) and anxiety traits (Sporn et al., 2020), with lower beta activity specifically implicated in visual-spatial working memory processes (Heinrichs-Graham & Wilson, 2015; Proskovec et al., 2018). Two independent studies measuring prefrontal EEG with a “pervasive three-electrode system” (Fp1, Fp2, and Fpz) indicated that beta may outperform other frequency bands as a diagnostic biomarker for depression (Cai et al., 2016; Shen et al., 2017). However, the role of resting-state beta activity (specifically frontal low beta here) in depression remains inconclusive, considering high heterogeneity of task conditions and electrode set-up reported in the current literature.

2.4.2 Emotional bias task

Consistent with Briley, Boutry, et al. (2024), the current study found significantly more positive emotional bias following sessions of tsiTBS than iTBS alone, suggesting promising antidepressant implications of the dual approach. According to Beck’s cognitive theory, depression is characterised by a systematic negative bias in information processing, which can be attributed to interactions between neurobiological and psychological factors contributable to the development of depressive symptoms (Beck, 2008). Particularly, patients with depression tend to evaluate facial expressions with reduced sensitivity to positive emotions and increased bias towards negative interpretations (Bourke et al., 2010; Elliott et al., 2011; Krause et al., 2021; Liu et al., 2012; Raes et al., 2006). This has been associated with dysfunctions of the amygdala, the prefrontal cortex, the ACC, and their connections (Stuhrmann et al., 2011). Such negative emotional bias is responsive to antidepressant

treatment. Acute administration of a single dose of antidepressant medication showed effectiveness in normalising facial processing bias, despite no change in subjective mood and anxiety symptoms (Harmer et al., 2017; Harmer et al., 2009; Suddell et al., 2023; Wells et al., 2014; Zhang et al., 2020). It was thereby proposed that effects on emotional information processing may be a key mechanism for antidepressant treatments (Suddell et al., 2023; Wells et al., 2014; Zhang et al., 2020).

It was hypothesised that synchronised tACS promoted the propagation effects of iTBS, leading to more prominent effects on emotional processes (Briley, Boutry, et al., 2024). Increasing evidence shows that therapeutic effects of rTMS rely on its effects beyond the stimulation site into deeper brain regions implicated in the limbic system and the DMN (Deng et al., 2023; Philip et al., 2018). In particular, the propagation of TMS-evoked activity from the target site of the dlPFC to the sgACC has been proposed as a key mechanism for clinical improvement (Downar et al., 2024; Liston et al., 2014). Some suggest that this process may be modifiable by accounting for underlying oscillatory activities (Vink et al., 2018). Particularly, theta oscillations are critical for the interaction between prefrontal areas and the amygdala in regulating emotional behaviour (Domic-Siede et al., 2024; Sperl et al., 2019). Synchronised tACS may boost the propagation effect of rTMS by capitalising on the role of theta oscillation in regulating these connected regions. Different from Briley, Boutry, et al. (2024), EBT was measured at a later timepoint at least 24 hours after the last stimulation session. Even though the increase in post-stimulation theta only showed a numerical trend following the tsiTBS, it is possible that the effects on EBT arose from a delayed theta enhancement beyond the 36min post-stimulation timepoint or an accumulated effect of multiple sessions.

2.4.3 Acceptability of the stimulation techniques

The theoretical framework of acceptability (TFA) highlights the temporal dynamics of emotional and cognitive responses before, during and after the treatment intervention (Sekhon et al., 2017). For post-intervention assessments, acceptability can be measured as experienced acceptability and anticipated acceptability, with a special focus for feasibility pilot studies on possible modifications in preparation for a full-scaled trial (Sekhon et al., 2017). Several key components of the TFA were particularly relevant to the content analysis findings here and are discussed below. A list of recommendations will be included in the following section.

Firstly, “intervention coherence” refers to one’s understanding of the intervention and how it works (Sekhon et al., 2017). In the current study, most participants had very limited previous knowledge of brain stimulation, while some expressed concerns associated with more invasive techniques such

as ECT. The current literature in perceptions about non-invasive neuromodulation techniques has highlighted a need for clear and explicit information about how they work, safety, and administration indications, considering the lack of familiarity in the general public (Atkinson-Clement et al., 2025; Beaumont et al., 2025; Stillianesis et al., 2022). For instance, a recent survey reported increased optimism and decreased negativity after information was provided about a range of non-invasive neuromodulation techniques (Atkinson-Clement et al., 2025). In this regard, some good practices include a well-designed information sheet, an accessible baseline session and clear instructions from researchers throughout the study (also see below “list of recommendations”). Additionally, one participant highlighted “trust” as a critical factor as the fact that researchers had used the techniques on themselves made a difference. Compared to other antidepressant options such as medications, non-invasive neuromodulation has the advantage that researchers can also personally experience the intervention, which should be leveraged when introducing the study.

“Affective attitude” refers to how one feels about the intervention and “ethicality” refers to if the intervention aligns with one’s values (Sekhon et al., 2017). Most participants approached this study with a positive attitude, which may be related to the motivational factors such as a general interest in the study content, potential benefits to own self, and potential benefits to research. A good rapport with researchers, as reported by many, may be a key factor for maintaining the positivity through study. However, there were some difficulties reported about the stimulation induction process such as problems with impedance test and unpleasant sensations from motor threshold measurements. It is important to address such issues properly by the research team as such experiences induced negative feelings that impacted the rest of the study. Following the study, many participants felt positive towards the dual approach and expressed willingness to have it as a treatment option. Among eight completers who answered the question, five rated the tsiTBS as “5” (“very acceptable”) with two from the tsiTBS group, and three rated “4” with one from the tsiTBS group.

“Self-efficacy” refers to one’s confidence in their ability to engage in the behaviours required for the intervention (Sekhon et al., 2017). Here it is associated with the tolerability factors of physical sensations during stimulation and side effects. Apart from one participant who withdrew before the first stimulation session due to pain reactions to iTBS, the stimulation was generally not painful. Noticeably, in the tsiTBS group, two participants reported the second session to be more intense, with one specifically associated with sensations from tACS. With interindividual variability in mind, it may be that the dual approach induced more varied sensational responses between sessions or increased sensitivity over time. Self-reported side effects were generally mild with no difference

between groups. The most commonly reported adverse effects were fatigue or drowsiness during stimulation and mild headache following stimulation. In addition, in response to the report of reduced concentration by the second participant, we incorporated reaction time measures (CRT, or “Spotter” task) thereafter to assess impact on cognitive functions. No significant difference was found between groups or between measured timepoints, suggesting that the stimulation was not associated with changes in cognition.

2.4.4 Protocol development and recommendations

The study protocol underwent two main updates based on participant feedback and researcher insights. The final version included 5 study days with 1 stimulation session per day. This, compared to the original setting of 2 stimulation sessions per day for 2 study day plus relevant brain activity measures (EEG or fNIRS), reduced participant burden and mimicked real-life clinical scheduling. No difficulty was identified by participants or researchers particularly related to protocol changes. However, some issues stood out in terms of experimental set-up. For 1 participant, one stimulation session failed due to loosened trigger cable. For 1 participant, stimulation condition had to switch from active to sham due to faults with tACS cable/ electrode. For 2 participants, EEG data were excluded due to faults with recorded triggers, which could have been avoided by checking triggers prior to the start of EEG recording. These warranted a more careful and comprehensive checking procedure before the session. Moving forward, this study will inform the development of future trials. Here is a list of recommendations for consideration.

Recruitment methods	The study should be promoted on a wider scale to target a diverse range of potential participants. Most participants were recruited via posters in this study, but digital platforms should also be considered in future studies.
Accessible introduction to study and techniques used	Information sheet. Use accessible language and formatting (e.g., bullet points and emboldened headings) to help with understanding of techniques used, safety and administration indications. It should clearly explain steps involved in participating the study, the form of inconvenient allowances (where applicable), and study locations. In addition, it can help build trust in participants by mentioning researcher’s own experience of having the stimulation.

	Baseline session can be a good introduction by demonstrating stimulation protocols.
Testing environment	Efforts should be made to reduce distractions during testing, for example, by hiding cables from surface areas and minimising peripheral noises or movements. Many participants preferred a lab environment to hospital settings.
Experimental set-up	A comprehensive pre-session checklist should be made to ensure smooth running of experiments. Some aspects highlighted from this study included checking cable connections, checking EEG triggers, making sure all devices are sufficiently charged, and testing if there is any fault with experimental devices.
Stimulation induction	Instructions should be made not only about main stimulation procedures but the induction process. Some participants experienced unpleasant sensations during TMS motor threshold measuring or tACS impedance test, which could have affectively negative impact on the rest of the study.
Specific study components	EEG gel. Many participants had trouble with washing out EEG gel. One possible solution is to pick it out when dry instead of washing it immediately.
	Face database. It was recommended to increase the ethnic diversity of face database used in tasks wherever possible.
	tACS sponges. We found that using saline-soaked sponge covers facilitated impedance testing, compared to applying inductive gel over electrodes. The second participant reported that it also reduced stinging sensation.
	TMS timing reminders. It was recommended to add in countdowns before the first TMS pulse and to inform participants of the remaining time midway through.
	Feedback. It was recommended to add in feedback after each study session.

2.4.5 Limitations

This feasibility pilot study has several limitations. Firstly, the interpretation of outcomes is limited by the pilot nature of this study. We included a small sample size with only one male participant. Previous studies have differentiated antidepressant responses to rTMS between men and women possibly as a function of female hormones (Adamson et al., 2022; Hanlon & McCalley, 2022; Huang et al., 2008). It thus requires future adequately powered trials, with comparable proportions of participants from both sexes, to determine the generalisability of these preliminary findings. Moreover, with protocol development as one of the main objectives, three versions of protocols were used, resulting in different numbers and/ or frequencies among participants. It remains unknown if version difference had any influence on observed effects. Secondly, as discussed in Briley, Boutry, et al. (2024), it is still unclear whether similar results can be achieved by simply delivering the two techniques together without synchronisation. However, the effects of rTMS demonstrated phase-dependency when combined with tACS, that is, the direction or range of rTMS-induced aftereffects was largely determined by whether it was synchronised to peak or trough of tACS (Goldsworthy et al., 2016; Hosseinian, Yavari, Biagi, et al., 2021; Hosseinian, Yavari, Kuo, et al., 2021; Nakazono et al., 2021; Ogata et al., 2021). Thirdly, as a mechanism-of-action study, a maximum of 5 stimulation sessions were included, while it is generally recommended to include 20-30 rTMS sessions for consistent results (McClintock et al., 2018). To compare the clinical effectiveness of tsiTBS and iTBS requires future trials incorporating an extended study period. Finally, there are general limitations to the understanding of mechanisms of non-invasive neuromodulation, for example, how they interact with the underlying brain activity, what parameters to use for optimal effects, and what factors contribute to intra- and/ or inter-individual variability (Thut, et al., 2017). Future trials should be developed to test on various stimulation parameters and measured timepoints of brain activity.

Concluding remarks

Depression is a common, disabling, and costly condition high in risks of relapse and comorbidity. TMS is a non-invasive neuromodulation technique with proven clinical efficacy for the management of depression and its refractory cases. There is an urgent need to address its treatment limitations as not all patients can achieve adequate response. As reviewed in Chapter 1, a range of augmentation strategies has been identified as attempts to boost TMS effects for treating unipolar depression. In total, 56 studies tested additional interventions, including additional non-invasive neuromodulation techniques (including additional TMS) and non-neuromodulation treatments, given alongside a standard course of TMS. However, the interpretation of results was limited by the descriptive approach of scoping review, insufficient study designs (lack of power, lack of long-term follow-up, lack of sham and inadequate TMS-course duration), heterogeneity of treatment interventions even within the same category, and a generally limited understanding of multimodal therapy in the field of neuromodulation. With this mind, some augmentation strategies nonetheless stood out with early-evidence efficacy, warranting further investigation: bilateral treatment for older patients, priming techniques, novel antidepressant options, and alternative therapies such as bright light therapy and acupuncture. As also highlighted in the scoping review, the clinical effect of TMS is state-dependent, or is a combined result of the stimulation and the neural context at the time of stimulation. In Chapter 2, a dual neuromodulation approach was tested peak-synchronising iTBS to tACS (tsiTBS), based on the hypothesis that higher pre-treatment frontal theta activity is associated with better TMS treatment outcomes for depression. This pilot study confirmed the feasibility of multi-session tsiTBS in patients with depression who reported an overall good tolerability of the dual approach. Although not adequately powered for conclusive assessments, some preliminary findings align with the prior study testing tsiTBS in healthy participants (Briley, Boutry, et al., 2024), that is, a numerically similar trajectory of frontal theta power rise post-stimulation and a more positive bias in evaluating ambiguous facial expressions. Based on participant feedback and researcher insight, a list of recommendations was generated to inform future trials regarding recruitment methods, accessible introduction to brain stimulation, testing environment, experimental set-up, stimulation induction, and specific study components.

Appendices

Appendix A: scoping review

A.1 Search strategy

Searches were conducted in August 2024.

PubMed

Search	Actions	Details	Query
#4	...	>	Search: ((transcranial magnetic stimulation OR TMS OR theta burst stimulation) AND (depression OR major depression)) AND (augmentation OR combination OR priming OR optimis* OR personali* OR individuali* OR adjunct*)
#3	...	>	Search: augmentation OR combination OR priming OR optimis* OR personali* OR individuali* OR adjunct*
#2	...	>	Search: depression OR major depression
#1	...	>	Search: transcranial magnetic stimulation OR TMS OR theta burst stimulation

Web of Science

Query Preview

((ALL=("transcranial magnetic stimulation" OR "TMS" OR "theta burst stimulation")) AND ALL=("depression" OR "major depression")) AND ALL=("augmentation" OR "priming" OR "combination" OR "optimis*" OR "individuali*" OR "personali*" OR "adjunct*")

PsycINFO

▲ Searches

1	("transcranial magnetic stimulation" or "TMS" or "theta burst stimulation").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2	("depression" or "major depression").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
3	("augmentation" or "priming" or "combination" or "optimis*" or "individuali*" or "personali*" or "adjunct*").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
4	1 and 2 and 3

EMBASE

▲ Searches

1	("transcranial magnetic stimulation" or "TMS" or "theta burst stimulation").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
2	("depression" or "major depression").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3	("augmentation" or "priming" or "combination" or "optimis*" or "individuli*" or "personali*" or "adjunct*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
4	1 and 2 and 3

Cochrane Central Register of Controlled Trials

—	Title Abstract Keyword ▼	"transcranial magnetic stimulation" OR "TMS" OR "theta burst stimulation"
—	AND ▼	Title Abstract Keyword ▼ "depression" OR "major depression"
—	AND ▼	Title Abstract Keyword ▼ "augmentation" OR "combination" OR "priming" OR "optimise" OR "individualise" OR "personalise" OR "adjunct"

(Word variations have been searched)

A.2 Data extraction instrument

Study title, authors, year, journal	Country	Type of study	Sample characteristics (size, age, sex, diagnosis, meds, co-morbidities)	Experimental design (control condition)	Experimental design (augmentation)	Reported depression outcomes	Reported side effects or acceptability of intervention	Limitations	Any further information (including potential new references)

Note. Experimental design (including control condition and augmentation condition) followed the Template for Intervention Description and Replication (TIDieR) checklist wherever applicable (Hoffmann et al., 2014).

A.3 Quality assessment tool by type

A.3.1 Randomised controlled studies

Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Was the treatment allocation concealed (so that assignments could not be predicted)?	Were participants and outcome assessors blinded to group assignment?	Was there similarity of groups at baseline	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Was there high adherence to the intervention protocols for each treatment group?	Were other interventions avoided or similar in the groups	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Were outcomes and subgroups identified before the analysis was conducted?	Did they use an intention-to-treat analysis?
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A.3.2 Non-randomised controlled studies

Clearly stated research question or objective	clearly specified and defined study population	at least 50% of participation rate	Groups recruited from the same population and uniform eligibility criteria	Was a sample size justification, power description, or variance and effect estimates provided?	For augmentation that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (dose-response relationship as per Bardford Hill criteria)	Were the augmentation approach (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
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A.3.3 Non-controlled experimental studies

Was the study question or objective clearly stated?	Were eligibility/selection criteria for the study population prespecified and clearly described?	Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Were all eligible participants that met the prespecified entry criteria enrolled?	Was the sample size sufficiently large to provide confidence in the findings?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	If the intervention was conducted at a group level (did the statistical analysis take into account the use of individual-level data to determine effects at the group level)?
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A.3.4 Single-case studies

Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the results well-described?
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A.4 All-group traffic light figures

Bilateral vs. Unilateral

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Hausmann, Kemmler, 2004	+	-	X	X	+
	Hausmann, □ Pascual-Leone, 2004	+	-	X	X	+
	Rybak, 2005	+	-	X	X	+
	Mi, 2022	-	X	X	X	-
	Cristancho, 2019	X	X	X	X	X
	Prentice, 2023	X	X	-	X	X
	Tadayonnejad, 2023	X	X	-	X	X
	Blumberger, 2012	+	X	+	X	-
	Blumberger, 2016	+	X	+	X	-
	Trevizol, 2019	+	X	+	X	-
	Fitzgerald, 2012	+	-	X	X	+
	Allen, 2024	-	X	+	X	X
	Fitzgerald, 2011	+	-	-	X	+
	Fitzgerald, 2018	+	X	X	X	+
	Li, 2014	+	X	X	+	+
	Chen, 2016	+	X	X	+	+
	Aaronson, 2022	-	X	-	X	X
	Lee, 2020	-	X	+	X	X
	Zhang, 2021	+	X	+	X	+

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
X High
- Some concerns
+ Low

Non-neuromodulation (total)

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Payette, 2023	X	X	?	X	X
	Shanock, 2024	-	X	+	X	-
	Tendler, 2018	X	X	+	X	-
	d'Andrea, 2023	X	X	-	+	-
	Brunelin, 2014	+	+	+	X	+
	Cole, 2022	+	+	-	X	+
	Schüle, 2003	X	X	X	X	+
	Li, 2016	+	+	X	X	+
	Isserles, 2011	+	X	-	X	+
	Adu, 2023	+	X	+	X	X
	He, 2011	+	X	X	X	X
	Yan, 2023	+	X	+	X	X
	Yin, 2022	+	X	-	X	-
	Hu, 2024	+	X	-	X	-
	Barbini, 2021	+	X	X	X	-
	Ross, 2023	+	X	-	X	+

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
X High
- Some concerns
+ Low
? Unclear

Personalised TMS

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Fitzgerald, 2009	+	×	×	×	+
	Hebel, 2021	+	+	-	×	×
	Paillère, 2010	+	×	×	×	+
	Jha, 2016	-	×	-	×	-
	Poydasheva, 2019	+	×	-	×	×
	Zhang, 2021	+	×	×	-	+
	Price, 2010	+	×	-	×	+
	George, 2023	+	×	+	×	+

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
 High
 Some concerns
 Low

Switch target

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Mielacher, 2020	+	+	+	+	×
	Fettes, 2017	×	×	+	+	-
	Feffer, 2018	×	×	+	-	+
	Fitzgerald, 2006	×	×	×	×	+
	McDonald, 2011	×	×	+	×	+
	Fitzgerald, 2018	+	×	×	×	+
	Prentice, 2023	×	×	-	×	×

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
 High
 Some concerns
 Low

Priming

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Fitzgerald, 2008	+	-	×	×	+
	Vidya, 2024	+	+	×	-	+
	Lee, 2021	×	×	+	×	-
	Lee, 2020	-	×	+	×	×

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
 High
 Some concerns
 Low

Additional sessions

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Yip, 2017	×	×	-	×	+
	McDonald, 2011	×	×	+	×	+
	Fitzgerald, 2018	+	×	×	×	+
	Mielacher, 2020	+	+	+	+	×

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

Judgement
 High
 Some concerns
 Low

non-TMS neuromodulation

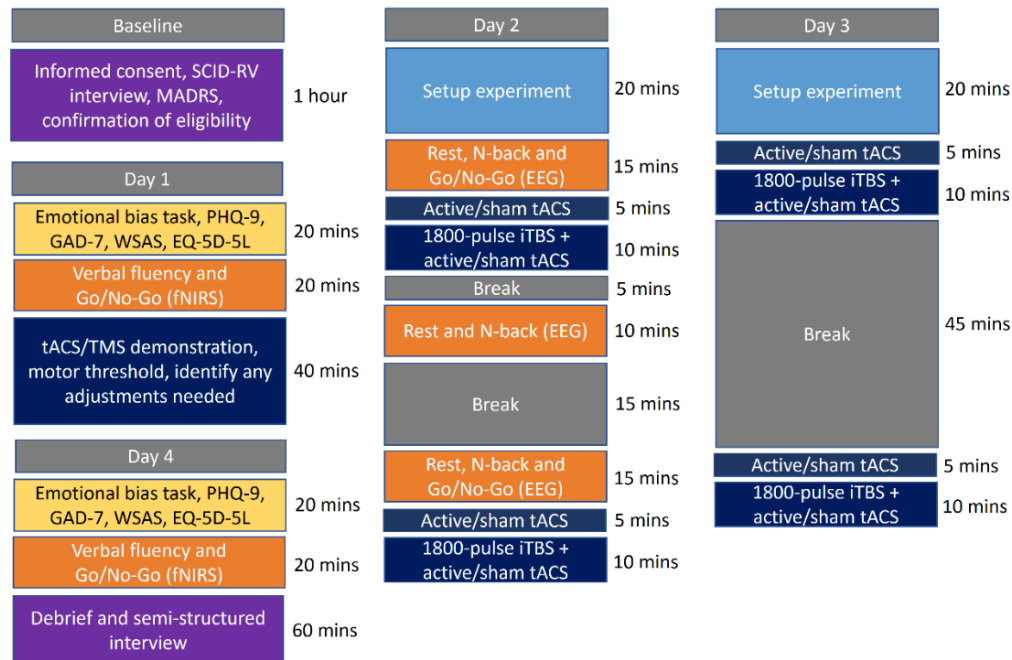
		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Li, 2024	+	+	×	×	+
	Zhou, 2024	+	+	+	-	+
	Jaiswal, 2024	+	-	×	×	×
	Seemann, 2023	×	×	+	+	×

Domains:
D1: Study Design adequacy.
D2: Sham adequacy.
D3: TMS adequacy.
D4: Follow-up adequacy.
D5: Confounding control.

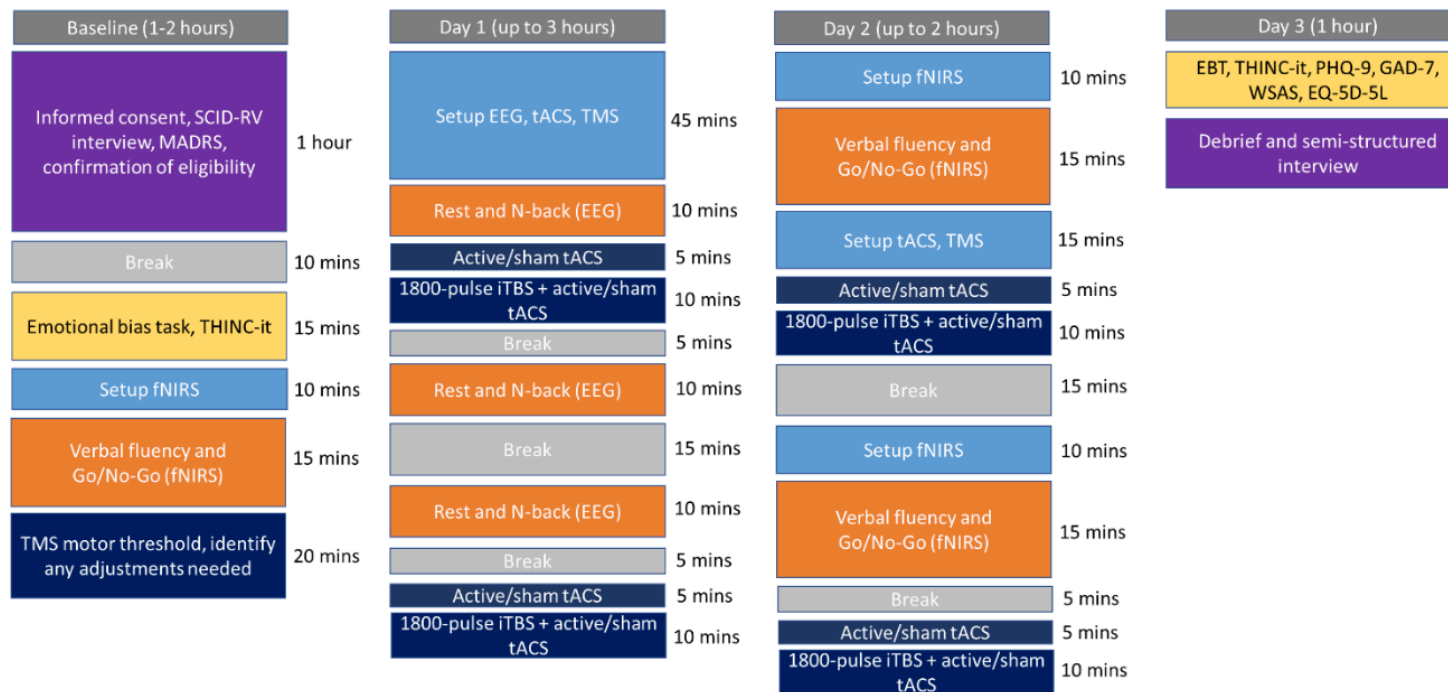
Judgement
 High
 Some concerns
 Low

Appendix B: feasibility pilot study

B.1 older versions of study protocol



Overall experimental procedure (version 1.0). The first version of study protocol includes a baseline session, 2 study days with 2 stimulation session per day, and a follow-up session. Different from the final version, the baseline session was shorter only including the screening interview. Brain activity was measured only on study day2 including EEG measures before, and 5min and 30min post-stimulation, and fNIRS measures before and 30min post-stimulation. fNIRS was also measured on baseline and follow-up sessions.



Overall experimental procedure (version 2.0). The second version of study protocol includes a baseline session, 2 study days with 2 stimulation session per day, and a follow-up session. The baseline session was longer including the screening interview, cognitive tasks, fNIR measures and TMS motor threshold measurement. Brain activity measures including both EEG and fNIRS used the same timings as the final version.

References

- Aaronson, S. T., Carpenter, L. L., Hutton, T. M., Kraus, S., Mina, M., Pages, K., Shi, L., West, W. S., & Sackeim, H. A. (2022). Comparison of clinical outcomes with left unilateral and sequential bilateral Transcranial Magnetic Stimulation (TMS) treatment of major depressive disorder in a large patient registry. *Brain Stimul*, 15(2), 326-336. <https://doi.org/10.1016/j.brs.2022.01.006>
- Abraham, W. C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nat Rev Neurosci*, 9(5), 387. <https://doi.org/10.1038/nrn2356>
- Adamson, M., Hadipour, A., Uyulan, C., Erguzel, T., Cerezci, O., Kazemi, R., Phillips, A., Seenivasan, S., Shah, S., & Tarhan, N. (2022). Sex differences in rTMS treatment response: A deep learning-based EEG investigation. *Brain and Behavior*, 12(8), e2696.
- Adu, M. K., Shalaby, R., Eboreime, E., Sapara, A., Lawal, M. A., Chew, C., Daubert, S., Urchuck, L., Surood, S., Li, D., Snaterse, M., Mach, M., Chue, P., Greenshaw, A. J., & Agyapong, V. I. O. (2023). Apparent Lack of Benefit of Combining Repetitive Transcranial Magnetic Stimulation with Internet-Delivered Cognitive Behavior Therapy for the Treatment of Resistant Depression: Patient-Centered Randomized Controlled Pilot Trial. *Brain Sci*, 13(2). <https://doi.org/10.3390/brainsci13020293>
- Allen, R. M., Scanlan, J. M., & Gama-Chonlon, L. (2024). Bilateral rTMS Shows No Advantage in Depression nor in Comorbid Depression and Anxiety: A Naturalistic Study. *Psychiatric Quarterly*, 95(1), 107-120.
- Anemuller, J., Sejnowski, T. J., & Makeig, S. (2003). Complex independent component analysis of frequency-domain electroencephalographic data. *Neural Netw*, 16(9), 1311-1323. <https://doi.org/10.1016/j.neunet.2003.08.003>
- Anttila, S. A., & Leinonen, E. V. (2001). A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev*, 7(3), 249-264. <https://doi.org/10.1111/j.1527-3458.2001.tb00198.x>
- Armour, M., Smith, C. A., Wang, L.-Q., Naidoo, D., Yang, G.-Y., MacPherson, H., Lee, M. S., & Hay, P. (2019). Acupuncture for depression: a systematic review and meta-analysis. *Journal of clinical medicine*, 8(8), 1140.
- Arns, M., Drinkenburg, W. H., Fitzgerald, P. B., & Kenemans, J. L. (2012). Neurophysiological predictors of non-response to rTMS in depression. *Brain stimulation*, 5(4), 569-576.
- Arns, M., Etkin, A., Hegerl, U., Williams, L. M., DeBattista, C., Palmer, D. M., Fitzgerald, P. B., Harris, A., deBeuss, R., & Gordon, E. (2015). Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? *Eur Neuropsychopharmacol*, 25(8), 1190-1200. <https://doi.org/10.1016/j.euroneuro.2015.03.007>
- Arubulawe, O. O., Folorunsho, I. L., Busari, A. K., Ibeneme, C., Diala, A. B., Afolabi, V. I., Harry, N. M., Anona, K., Obitulata-Ugwu, V. O., Kuye, O. A., & Anugwom, G. O. (2024). Combination of Transcranial Magnetic Stimulation and Ketamine in Treatment-Resistant Depression: A Systematic Review. *Cureus*, 16(7), e64712. <https://doi.org/10.7759/cureus.64712>
- Asada, H., Fukuda, Y., Tsunoda, S., Yamaguchi, M., & Tonoike, M. (1999). Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neurosci Lett*, 274(1), 29-32. [https://doi.org/10.1016/s0304-3940\(99\)00679-5](https://doi.org/10.1016/s0304-3940(99)00679-5)

- Atkinson-Clement, C., Junor, A., & Kaiser, M. (2025). Neuromodulation perception by the general public. *Sci Rep*, 15(1), 5584. <https://doi.org/10.1038/s41598-025-89437-8>
- Baeken, C., Brem, A. K., Arns, M., Brunoni, A. R., Filipcic, I., Ganho-Avila, A., Langguth, B., Padberg, F., Poulet, E., Rachid, F., Sack, A. T., Vanderhasselt, M. A., & Bennabi, D. (2019). Repetitive transcranial magnetic stimulation treatment for depressive disorders: current knowledge and future directions. *Curr Opin Psychiatry*, 32(5), 409-415. <https://doi.org/10.1097/YCO.0000000000000533>
- Bailey, N., Hoy, K., Rogasch, N., Thomson, R., McQueen, S., Elliot, D., Sullivan, C., Fulcher, B., Daskalakis, Z., & Fitzgerald, P. (2018). Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. *Brain stimulation*, 11(1), 190-203.
- Bailey, N., Hoy, K., Rogasch, N., Thomson, R., McQueen, S., Elliot, D., Sullivan, C., Fulcher, B., Daskalakis, Z., & Fitzgerald, P. (2019). Differentiating responders and non-responders to rTMS treatment for depression after one week using resting EEG connectivity measures. *Journal of Affective Disorders*, 242, 68-79.
- Bailey, N. W., Krepel, N., van Dijk, H., Leuchter, A. F., Vila-Rodriguez, F., Blumberger, D. M., Downar, J., Wilson, A., Daskalakis, Z. J., Carpenter, L. L., Corlier, J., Arns, M., & Fitzgerald, P. B. (2021). Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression: A non-replication from the ICON-DB consortium. *Clin Neurophysiol*, 132(2), 650-659. <https://doi.org/10.1016/j.clinph.2020.10.018>
- Bajbouj, M., & Padberg, F. (2014). A perfect match: noninvasive brain stimulation and psychotherapy. *Eur Arch Psychiatry Clin Neurosci*, 264 Suppl 1, S27-33. <https://doi.org/10.1007/s00406-014-0540-6>
- Barbini, B., Attanasio, F., Manfredi, E., Cavallini, M. C., Zanardi, R., & Colombo, C. (2021). Bright light therapy accelerates the antidepressant effect of repetitive transcranial magnetic stimulation in treatment resistant depression: A pilot study. *International Journal of Psychiatry in Clinical Practice*, 25(4), 375-377.
- Basar, E. (2013). Brain oscillations in neuropsychiatric disease. *Dialogues Clin Neurosci*, 15(3), 291-300. <https://doi.org/10.31887/DCNS.2013.15.3/ebasar>
- Beam, W., Borckardt, J. J., Reeves, S. T., & George, M. S. (2009). An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul*, 2(1), 50-54. <https://doi.org/10.1016/j.brs.2008.09.006>
- Beaumont, J. D., Goodwin, E., Smith, N. C., Davis, D., Dalton, M., & Barwood, M. J. (2025). "A fear of the unknown": Understanding the perceptions of transcranial electrical stimulation (tES). *Journal of Cognitive Enhancement*, 9(2), 244-255.
- Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry*, 165(8), 969-977. <https://doi.org/10.1176/appi.ajp.2008.08050721>
- Bell, A. J., & Sejnowski, T. J. (1995). An information-maximization approach to blind separation and blind deconvolution. *Neural Comput*, 7(6), 1129-1159. <https://doi.org/10.1162/neco.1995.7.6.1129>
- Bhagwagar, Z., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2004). Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. *American Journal of Psychiatry*, 161(1), 166-168.
- Bhattacharya, A., Mrudula, K., Sreepada, S. S., Sathyaprabha, T. N., Pal, P. K., Chen, R., & Udupa, K. (2022). An Overview of Noninvasive Brain Stimulation: Basic Principles and Clinical Applications. *Can J Neurol Sci*, 49(4), 479-492. <https://doi.org/10.1017/cjn.2021.158>

- Bliss, T. V., & Cooke, S. F. (2011). Long-term potentiation and long-term depression: a clinical perspective. *Clinics (Sao Paulo)*, 66 Suppl 1(Suppl 1), 3-17.
<https://doi.org/10.1590/s1807-59322011001300002>
- Blumberger, D. M., Maller, J. J., Thomson, L., Mulsant, B. H., Rajji, T. K., Maher, M., Brown, P. E., Downar, J., Vila-Rodriguez, F., Fitzgerald, P. B., & Daskalakis, Z. J. (2016). Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled study. *J Psychiatry Neurosci*, 41(4), E58-66. <https://doi.org/10.1503/jpn.150265>
- Blumberger, D. M., Mulsant, B. H., Fitzgerald, P. B., Rajji, T. K., Ravindran, A. V., Young, L. T., Levinson, A. J., & Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J Biol Psychiatry*, 13(6), 423-435. <https://doi.org/10.3109/15622975.2011.579163>
- Blumberger, D. M., Mulsant, B. H., Thorpe, K. E., McClintock, S. M., Konstantinou, G. N., Lee, H. H., Nestor, S. M., Noda, Y., Rajji, T. K., Trevizol, A. P., Vila-Rodriguez, F., Daskalakis, Z. J., & Downar, J. (2022). Effectiveness of Standard Sequential Bilateral Repetitive Transcranial Magnetic Stimulation vs Bilateral Theta Burst Stimulation in Older Adults With Depression: The FOUR-D Randomized Noninferiority Clinical Trial. *JAMA Psychiatry*, 79(11), 1065-1073.
<https://doi.org/10.1001/jamapsychiatry.2022.2862>
- Blumberger, D. M., Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S. H., Lam, R. W., Daskalakis, Z. J., & Downar, J. (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*, 391(10131), 1683-1692. [https://doi.org/10.1016/S0140-6736\(18\)30295-2](https://doi.org/10.1016/S0140-6736(18)30295-2)
- Borrione, L., Bellini, H., Razza, L. B., Avila, A. G., Baeken, C., Brem, A. K., Busatto, G., Carvalho, A. F., Chekroud, A., Daskalakis, Z. J., Deng, Z. D., Downar, J., Gattaz, W., Loo, C., Lotufo, P. A., Martin, M., McClintock, S. M., O'Shea, J., Padberg, F., . . . Brunoni, A. R. (2020). Precision non-implantable neuromodulation therapies: a perspective for the depressed brain. *Braz J Psychiatry*, 42(4), 403-419.
<https://doi.org/10.1590/1516-4446-2019-0741>
- Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in major depression: a review. *Aust N Z J Psychiatry*, 44(8), 681-696.
<https://doi.org/10.3109/00048674.2010.496359>
- Briley, P. M., Boutry, C., Webster, L., Veniero, D., Harvey-Seutcheu, C., Jung, J., Liddle, P. F., & Morriss, R. (2024). Intermittent theta burst stimulation with synchronised transcranial alternating current stimulation leads to enhanced frontal theta oscillations and a positive shift in emotional bias. *Imaging Neuroscience*, 2, 1-14.
- Briley, P. M., Webster, L., Boutry, C., Oh, H., Auer, D. P., Liddle, P. F., & Morriss, R. (2024). Magnetic resonance imaging connectivity features associated with response to transcranial magnetic stimulation in major depressive disorder. *Psychiatry Res Neuroimaging*, 342, 111846. <https://doi.org/10.1016/j.psychresns.2024.111846>
- Briley, P. M., Webster, L., Lankappa, S., Pszczolkowski, S., McAllister-Williams, R., Liddle, P., Auer, D., & Morriss, R. (2024). Trajectories of improvement with repetitive transcranial magnetic stimulation for treatment-resistant major depression in the BRIGHtMIND trial. *npj Mental Health Research*, 3(1), 32.
- Brini, S., Brudasca, N. I., Hodgkinson, A., Kaluzinska, K., Wach, A., Storman, D., Prokop-Dorner, A., Jemiolo, P., & Bala, M. M. (2023). Efficacy and safety of transcranial magnetic stimulation for treating major depressive disorder: An umbrella review and

- re-analysis of published meta-analyses of randomised controlled trials. *Clin Psychol Rev*, 100, 102236. <https://doi.org/10.1016/j.cpr.2022.102236>
- Brunelin, J., Jalenques, I., Trojak, B., Attal, J., Szekely, D., Gay, A., Januel, D., Haffen, E., Schott-Pethelaz, A. M., Brault, C., & Poulet, E. (2014). The efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression: the results from a large multicenter French RCT. *Brain Stimul*, 7(6), 855-863. <https://doi.org/10.1016/j.brs.2014.07.040>
- Brunoni, A. R., Chaimani, A., Moffa, A. H., Razza, L. B., Gattaz, W. F., Daskalakis, Z. J., & Carvalho, A. F. (2017). Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. *JAMA Psychiatry*, 74(2), 143-152. <https://doi.org/10.1001/jamapsychiatry.2016.3644>
- Bulteau, S., Laurin, A., Pere, M., Fayet, G., Thomas-Ollivier, V., Deschamps, T., Auffray-Calvier, E., Bukowski, N., Vanelle, J.-M., & Sébille, V. (2022). Intermittent theta burst stimulation (iTBS) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) to alleviate treatment-resistant unipolar depression: A randomized controlled trial (THETA-DEP). *Brain stimulation*, 15(3), 870-880.
- Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*, 4(6), 215-222. [https://doi.org/10.1016/s1364-6613\(00\)01483-2](https://doi.org/10.1016/s1364-6613(00)01483-2)
- Buzsaki, G. (2006). *Rhythms of the Brain*. Oxford university press.
- Buzsaki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *science*, 304(5679), 1926-1929.
- Cai, H., Sha, X., Han, X., Wei, S., & Hu, B. (2016). Pervasive EEG diagnosis of depression using Deep Belief Network with three-electrodes EEG collector. 2016 IEEE international conference on bioinformatics and biomedicine (BIBM),
- Cappon, D., den Boer, T., Jordan, C., Yu, W., Metzger, E., & Pascual-Leone, A. (2022). Transcranial magnetic stimulation (TMS) for geriatric depression. *Ageing Res Rev*, 74, 101531. <https://doi.org/10.1016/j.arr.2021.101531>
- Cash, R. F. H., Cocchi, L., Lv, J., Fitzgerald, P. B., & Zalesky, A. (2021). Functional Magnetic Resonance Imaging-Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. *JAMA Psychiatry*, 78(3), 337-339. <https://doi.org/10.1001/jamapsychiatry.2020.3794>
- Caulfield, K. A., Fleischmann, H. H., Cox, C. E., Wolf, J. P., George, M. S., & McTeague, L. M. (2022). Neuronavigation maximizes accuracy and precision in TMS positioning: Evidence from 11,230 distance, angle, and electric field modeling measurements. *Brain Stimul*, 15(5), 1192-1205. <https://doi.org/10.1016/j.brs.2022.08.013>
- Cavanagh, J. F., Figueroa, C. M., Cohen, M. X., & Frank, M. J. (2012). Frontal theta reflects uncertainty and unexpectedness during exploration and exploitation. *Cereb Cortex*, 22(11), 2575-2586. <https://doi.org/10.1093/cercor/bhr332>
- Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in cognitive sciences*, 18(8), 414-421.
- Chen, L., Klooster, D. C. W., Tik, M., Thomas, E. H. X., Downar, J., Fitzgerald, P. B., Williams, N. R., & Baeken, C. (2023). Accelerated Repetitive Transcranial Magnetic Stimulation to Treat Major Depression: The Past, Present, and Future. *Harv Rev Psychiatry*, 31(3), 142-161. <https://doi.org/10.1097/HRP.0000000000000364>
- Cheng, C. M., Juan, C. H., Chen, M. H., Chang, C. F., Lu, H. J., Su, T. P., Lee, Y. C., & Li, C. T. (2016). Different forms of prefrontal theta burst stimulation for executive function of medication-resistant depression: Evidence from a randomized sham-controlled

- study. *Prog Neuropsychopharmacol Biol Psychiatry*, 66, 35-40.
<https://doi.org/10.1016/j.pnpbp.2015.11.009>
- Chervyakov, A. V., Chernyavsky, A. Y., Sinitsyn, D. O., & Piradov, M. A. (2015). Possible Mechanisms Underlying the Therapeutic Effects of Transcranial Magnetic Stimulation. *Front Hum Neurosci*, 9, 303. <https://doi.org/10.3389/fnhum.2015.00303>
- Chung, S. W., Lewis, B. P., Rogasch, N. C., Saeki, T., Thomson, R. H., Hoy, K. E., Bailey, N. W., & Fitzgerald, P. B. (2017). Demonstration of short-term plasticity in the dorsolateral prefrontal cortex with theta burst stimulation: A TMS-EEG study. *Clin Neurophysiol*, 128(7), 1117-1126. <https://doi.org/10.1016/j.clinph.2017.04.005>
- Cole, E. J., Phillips, A. L., Bentzley, B. S., Stimpson, K. H., Nejad, R., Barmak, F., Veerapal, C., Khan, N., Cherian, K., Felber, E., Brown, R., Choi, E., King, S., Pankow, H., Bishop, J. H., Azeez, A., Coetzee, J., Rapier, R., Odenwald, N., . . . Williams, N. R. (2022). Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. *Am J Psychiatry*, 179(2), 132-141.
<https://doi.org/10.1176/appi.ajp.2021.20101429>
- Cole, J., Selby, B., Ismail, Z., & McGirr, A. (2021). D-cycloserine normalizes long-term motor plasticity after transcranial magnetic intermittent theta-burst stimulation in major depressive disorder. *Clin Neurophysiol*, 132(8), 1770-1776.
<https://doi.org/10.1016/j.clinph.2021.04.002>
- Cole, J., Sohn, M. N., Harris, A. D., Bray, S. L., Patten, S. B., & McGirr, A. (2022). Efficacy of adjunctive D-cycloserine to intermittent theta-burst stimulation for major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*, 79(12), 1153-1161.
- Colgin, L. L. (2013). Mechanisms and functions of theta rhythms. *Annu Rev Neurosci*, 36, 295-312. <https://doi.org/10.1146/annurev-neuro-062012-170330>
- Conroy, S. K., & Holtzheimer, P. E. (2021). Neuromodulation Strategies for the Treatment of Depression. *Am J Psychiatry*, 178(12), 1082-1088.
<https://doi.org/10.1176/appi.ajp.2021.21101034>
- Cooper, L. N., & Bear, M. F. (2012). The BCM theory of synapse modification at 30: interaction of theory with experiment. *Nature Reviews Neuroscience*, 13(11), 798-810.
- Cristancho, P., Trapp, N. T., Siddiqi, S. H., Dixon, D., Miller, J. P., & Lenze, E. J. (2019). Crossover to bilateral repetitive transcranial magnetic stimulation: a potential strategy when patients are not responding to unilateral left-sided high-frequency repetitive transcranial magnetic stimulation. *The Journal of ECT*, 35(1), 3-5.
- d'Andrea, G., Pettoruso, M., D'Andrea, A., Collecchio, R., Santovito, M. C., Miuli, A., Di Carlo, F., Sensi, S. L., Martinotti, G., & di Giannantonio, M. (2023). Combining Dopamine Agonists With Accelerated Repetitive Transcranial Magnetic Stimulation: A Case of Successful Treatment of Resistant Depression. *The Journal of ECT*, 39(2), 120-121.
- D'Onofrio, V., Manzo, N., Guerra, A., Landi, A., Baro, V., Maatta, S., Weis, L., Porcaro, C., Corbetta, M., Antonini, A., & Ferreri, F. (2023). Combining Transcranial Magnetic Stimulation and Deep Brain Stimulation: Current Knowledge, Relevance and Future Perspectives. *Brain Sci*, 13(2). <https://doi.org/10.3390/brainsci13020349>
- Dalhuisen, I., van Bronswijk, S., Bors, J., Smit, F., Spijker, J., Tendolkar, I., Ruhe, H. G., & van Eijndhoven, P. (2022). The association between sample and treatment characteristics and the efficacy of repetitive transcranial magnetic stimulation in depression: A meta-analysis and meta-regression of sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, 141, 104848.
- De la Torre-Luque, A., & Bornas, X. (2017). Complexity and irregularity in the brain oscillations of depressive patients: a systematic review. *Neuropsychiatry*, 7(5), 466-477.

- Debowska, W., Wiedlocha, M., Debowska, M., Kownacka, Z., Marcinowicz, P., & Szulc, A. (2023). Transcranial magnetic stimulation and ketamine: implications for combined treatment in depression. *Front Neurosci*, 17, 1267647. <https://doi.org/10.3389/fnins.2023.1267647>
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*, 134(1), 9-21. <https://doi.org/10.1016/j.jneumeth.2003.10.009>
- DeMayo, M. M., Cole, J., Sohn, M. N., Bray, S. L., Harris, A. D., Patten, S. B., & McGirr, A. (2024). Procognitive Effects of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation in Major Depressive Disorder: Effets procognitifs de la D-cyclosérine en traitement complémentaire par la stimulation thêta-burst intermittente dans le trouble dépressif caractérisé. *The Canadian Journal of Psychiatry*, 07067437241293984.
- Deng, Y., Li, W., & Zhang, B. (2023). Functional Activity in the Effect of Transcranial Magnetic Stimulation Therapy for Patients with Depression: A Meta-Analysis. *J Pers Med*, 13(3). <https://doi.org/10.3390/jpm13030405>
- Dichter, G. S., Gibbs, D., & Smoski, M. J. (2015). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *Journal of Affective Disorders*, 172, 8-17.
- Domic-Siede, M., Sanchez-Corzo, A., & Guzman-Gonzalez, M. (2024). Brain oscillations during emotion regulation and the two-dimensional model of adult attachment. *Biol Psychol*, 189, 108793. <https://doi.org/10.1016/j.biopsycho.2024.108793>
- Donse, L., Padberg, F., Sack, A. T., Rush, A. J., & Arns, M. (2018). Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study. *Brain Stimul*, 11(2), 337-345. <https://doi.org/10.1016/j.brs.2017.11.004>
- Downar, J., Blumberger, D. M., & Daskalakis, Z. J. (2016). The neural crossroads of psychiatric illness: an emerging target for brain stimulation. *Trends in cognitive sciences*, 20(2), 107-120.
- Downar, J., Siddiqi, S. H., Mitra, A., Williams, N., & Liston, C. (2024). Mechanisms of Action of TMS in the Treatment of Depression. *Curr Top Behav Neurosci*, 66, 233-277. https://doi.org/10.1007/7854_2024_483
- Dubin, M. (2017). Imaging TMS: antidepressant mechanisms and treatment optimization. *Int Rev Psychiatry*, 29(2), 89-97. <https://doi.org/10.1080/09540261.2017.1283297>
- Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*, 64(3), 327-337. <https://doi.org/10.1001/archpsyc.64.3.327>
- El-Hage, W., & Fakra, E. (2016). How to treat and manage unsatisfactory response? *L'encephale*, 42(1 Suppl 1), 1S39-47.
- Elliott, R., Zahn, R., Deakin, J. F., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, 36(1), 153-182. <https://doi.org/10.1038/npp.2010.77>
- Elyamany, O., Leicht, G., Herrmann, C. S., & Mulert, C. (2021). Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. *European Archives of Psychiatry and Clinical Neuroscience*, 271(1), 135-156.
- Ertl, M., Hildebrandt, M., Ourina, K., Leicht, G., & Mulert, C. (2013). Emotion regulation by cognitive reappraisal—the role of frontal theta oscillations. *Neuroimage*, 81, 412-421.
- Feffer, K., Fettes, P., Giacobbe, P., Daskalakis, Z. J., Blumberger, D. M., & Downar, J. (2018). 1 Hz rTMS of the right orbitofrontal cortex for major depression: Safety,

- tolerability and clinical outcomes. *European Neuropsychopharmacology*, 28(1), 109-117.
- Fertonani, A., & Miniussi, C. (2017). Transcranial electrical stimulation: what we know and do not know about mechanisms. *The Neuroscientist*, 23(2), 109-123.
- Fettes, P., Peters, S., Giacobbe, P., Blumberger, D. M., & Downar, J. (2017). Neural correlates of successful orbitofrontal 1 Hz rTMS following unsuccessful dorsolateral and dorsomedial prefrontal rTMS in major depression: A case report. *Brain Stimul*, 10(1), 165-167. <https://doi.org/10.1016/j.brs.2016.11.008>
- Fitzgerald, P. B., Gill, S., Breakspear, M., Kulkarni, J., Chen, L., Pridmore, S., Purushothaman, S., Galletly, C., Clarke, P., & Ng, F. (2022). Revisiting the effectiveness of repetitive transcranial magnetic stimulation treatment in depression, again. *Australian & New Zealand Journal of Psychiatry*, 56(8), 905-909.
- Fitzgerald, P. B., Hoy, K., Gunewardene, R., Slack, C., Ibrahim, S., Bailey, M., & Daskalakis, Z. J. (2011). A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. *Psychol Med*, 41(6), 1187-1196. <https://doi.org/10.1017/S0033291710001923>
- Fitzgerald, P. B., Hoy, K., McQueen, S., Herring, S., Segrave, R., Been, G., Kulkarni, J., & Daskalakis, Z. J. (2008). Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*, 28(1), 52-58. <https://doi.org/10.1097/jcp.0b013e3181603f7c>
- Fitzgerald, P. B., Hoy, K., McQueen, S., Maller, J. J., Herring, S., Segrave, R., Bailey, M., Been, G., Kulkarni, J., & Daskalakis, Z. J. (2009). A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*, 34(5), 1255-1262. <https://doi.org/10.1038/npp.2008.233>
- Fitzgerald, P. B., Hoy, K. E., Elliot, D., McQueen, S., Wambeck, L. E., & Daskalakis, Z. J. (2018). Exploring alternative rTMS strategies in non-responders to standard high frequency left-sided treatment: a switching study. *Journal of Affective Disorders*, 232, 79-82.
- Fitzgerald, P. B., Hoy, K. E., Herring, S. E., McQueen, S., Peachey, A. V., Segrave, R. A., Maller, J., Hall, P., & Daskalakis, Z. J. (2012). A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. *J Affect Disord*, 139(2), 193-198. <https://doi.org/10.1016/j.jad.2012.02.017>
- Fitzgerald, P. B., Huntsman, S., Gunewardene, R., Kulkarni, J., & Daskalakis, Z. J. (2006). A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *International Journal of Neuropsychopharmacology*, 9(6), 655-666.
- Forner-Phillips, N. A., Mills, C., & Ross, R. S. (2020). Tendency to ruminate and anxiety are associated with altered alpha and beta oscillatory power dynamics during memory for contextual details. *Cogn Affect Behav Neurosci*, 20(4), 698-716. <https://doi.org/10.3758/s13415-020-00797-2>
- Forsyth, J. K., Bachman, P., Mathalon, D. H., Roach, B. J., & Asarnow, R. F. (2015). Augmenting NMDA receptor signaling boosts experience-dependent neuroplasticity in the adult human brain. *Proc Natl Acad Sci U S A*, 112(50), 15331-15336. <https://doi.org/10.1073/pnas.1509262112>
- Fox, M. D., Buckner, R. L., White, M. P., Greicius, M. D., & Pascual-Leone, A. (2012). Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological psychiatry*, 72(7), 595-603.

- Ge, R., Downar, J., Blumberger, D. M., Daskalakis, Z. J., & Vila-Rodriguez, F. (2020). Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. *Brain stimulation*, 13(1), 206-214.
- George, M. S., Huffman, S., Dooze, J., Sun, X., Dancy, M., Faller, J., Li, X., Yuan, H., Goldman, R. I., & Sajda, P. (2023). EEG synchronized left prefrontal transcranial magnetic stimulation (TMS) for treatment resistant depression is feasible and produces an entrainment dependent clinical response: A randomized controlled double blind clinical trial. *Brain stimulation*, 16(6), 1753-1763.
- Giron, C. G., Chan, Y. T., Cheung, C. Y., Cheuk, H. Y. C., Cheung, S. W., Choi, Y. Y., & Kranz, G. S. (2023). Surveying efforts to boost the antidepressant effects of repetitive transcranial magnetic stimulation with non-pharmacological adjunct interventions: a systematic scoping review. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 16(1), 390-391.
- Goldsworthy, M. R., Vallence, A. M., Yang, R., Pitcher, J. B., & Ridding, M. C. (2016). Combined transcranial alternating current stimulation and continuous theta burst stimulation: a novel approach for neuroplasticity induction. *Eur J Neurosci*, 43(4), 572-579. <https://doi.org/10.1111/ejn.13142>
- Gonterman, F. (2023). A Systematic Review Assessing Patient-Related Predictors of Response to Transcranial Magnetic Stimulation in Major Depressive Disorder. *Neuropsychiatr Dis Treat*, 19, 565-577. <https://doi.org/10.2147/NDT.S388164>
- Graneheim, U. H., Lindgren, B. M., & Lundman, B. (2017). Methodological challenges in qualitative content analysis: A discussion paper. *Nurse Educ Today*, 56, 29-34. <https://doi.org/10.1016/j.nedt.2017.06.002>
- Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., & Northoff, G. (2008). Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biological psychiatry*, 63(4), 369-376.
- Guerra, A., Asci, F., D'Onofrio, V., Sveva, V., Bologna, M., Fabbrini, G., Berardelli, A., & Suppa, A. (2020). Enhancing Gamma Oscillations Restores Primary Motor Cortex Plasticity in Parkinson's Disease. *Journal of Neuroscience*, 40(24), 4788-4796. <https://doi.org/10.1523/jneurosci.0357-20.2020>
- Guerra, A., Asci, F., Zampogna, A., D'Onofrio, V., Petrucci, S., Ginevrino, M., Berardelli, A., & Suppa, A. (2020). Gamma-transcranial alternating current stimulation and theta-burst stimulation: inter-subject variability and the role of BDNF. *Clinical Neurophysiology*, 131(11), 2691-2699.
- Guerra, A., D'Onofrio, V., Asci, F., Ferreri, F., Fabbrini, G., Berardelli, A., & Bologna, M. (2023). Assessing the interaction between L-dopa and γ -transcranial alternating current stimulation effects on primary motor cortex plasticity in Parkinson's disease. *European Journal of Neuroscience*, 57(1), 201-212. <https://doi.org/10.1111/ejn.15867>
- Guerra, A., Suppa, A., Asci, F., De Marco, G., D'Onofrio, V., Bologna, M., Di Lazzaro, V., & Berardelli, A. (2019). LTD-like plasticity of the human primary motor cortex can be reversed by γ -tACS. *Brain stimulation*, 12(6), 1490-1499.
- Guerra, A., Suppa, A., Bologna, M., D'Onofrio, V., Bianchini, E., Brown, P., Di Lazzaro, V., & Berardelli, A. (2018). Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. *Brain stimulation*, 11(4), 734-742.

- Guo, B., Zhang, M., Hao, W., Wang, Y., Zhang, T., & Liu, C. (2023). Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression. *Transl Psychiatry*, 13(1), 5. <https://doi.org/10.1038/s41398-022-02297-y>
- Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biol Psychiatry*, 78(4), 224-230. <https://doi.org/10.1016/j.biopsych.2015.02.020>
- Hammar, A., Ronold, E. H., & Rekkedal, G. A. (2022). Cognitive Impairment and Neurocognitive Profiles in Major Depression-A Clinical Perspective. *Front Psychiatry*, 13, 764374. <https://doi.org/10.3389/fpsyt.2022.764374>
- Hanlon, C. A., & McCalley, D. M. (2022). Sex/gender as a factor that influences transcranial magnetic stimulation treatment outcome: three potential biological explanations. *Frontiers in Psychiatry*, 13, 869070.
- Hanslmayr, S., Axmacher, N., & Inman, C. S. (2019). Modulating human memory via entrainment of brain oscillations. *Trends in neurosciences*, 42(7), 485-499.
- Harmer, C. J., Bhagwagar, Z., Perrett, D. I., Vollm, B. A., Cowen, P. J., & Goodwin, G. M. (2003). Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology*, 28(1), 148-152. <https://doi.org/10.1038/sj.npp.1300004>
- Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry*, 4(5), 409-418.
- Harmer, C. J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G. M., & Cowen, P. J. (2009). Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry*, 166(10), 1178-1184. <https://doi.org/10.1176/appi.ajp.2009.09020149>
- Hassanzahraee, M., Zoghi, M., & Jaberzadeh, S. (2018). How different priming stimulations affect the corticospinal excitability induced by noninvasive brain stimulation techniques: a systematic review and meta-analysis. *Reviews in the Neurosciences*, 29(8), 883-899.
- Hausmann, A., Kemmler, G., Walpoth, M., Mechtcheriakov, S., Kramer-Reinstadler, K., Lechner, T., Walch, T., Deisenhammer, E., Kofler, M., & Rupp, C. (2004). No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery & Psychiatry*, 75(2), 320-322.
- Hausmann, A., Pascual-Leone, A., Kemmler, G., Rupp, C. I., Lechner-Schoner, T., Kramer-Reinstadler, K., Walpoth, M., Mechtcheriakov, S., Conca, A., & Weiss, E. M. (2004). No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *J Clin Psychiatry*, 65(6), 772-782. <https://doi.org/10.4088/jcp.v65n0608>
- He, J., Tang, Y., Lin, J., Faulkner, G., Tsang, H. W. H., & Chan, S. H. W. (2022). Non-invasive brain stimulation combined with psychosocial intervention for depression: a systematic review and meta-analysis. *BMC Psychiatry*, 22(1), 273. <https://doi.org/10.1186/s12888-022-03843-0>
- He, L., Zheng, Z., Cai, D., & Zou, K. (2011). Randomized controlled trial on comorbid anxiety and depression treated with electroacupuncture combined with rTMS. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*, 31(4), 294-298.
- Hebel, T., Göllnitz, A., Schoisswohl, S., Weber, F. C., Abdelnaim, M., Wetter, T. C., Rupprecht, R., Langguth, B., & Sackmann, M. (2021). A direct comparison of neuronavigated and non-neuronavigated intermittent theta burst stimulation in the treatment of depression. *Brain stimulation*, 14(2), 335-343.

- Heinrichs-Graham, E., & Wilson, T. W. (2015). Spatiotemporal oscillatory dynamics during the encoding and maintenance phases of a visual working memory task. *Cortex*, 69, 121-130. <https://doi.org/10.1016/j.cortex.2015.04.022>
- Helion, C., Krueger, S. M., & Ochsner, K. N. (2019). Chapter 14 - Emotion regulation across the life span. In M. D'Esposito & J. H. Grafman (Eds.), *Handbook of Clinical Neurology* (Vol. 163, pp. 257-280). Elsevier. <https://doi.org/https://doi.org/10.1016/B978-0-12-804281-6.00014-8>
- Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*, 20(10), 1727-1736. <https://doi.org/10.1007/s11136-011-9903-x>
- Herrmann, C. S., Strüber, D., Helfrich, R. F., & Engel, A. K. (2016). EEG oscillations: from correlation to causality. *International Journal of Psychophysiology*, 103, 12-21.
- Herweg, N. A., Solomon, E. A., & Kahana, M. J. (2020). Theta Oscillations in Human Memory. *Trends Cogn Sci*, 24(3), 208-227. <https://doi.org/10.1016/j.tics.2019.12.006>
- Herwig, U., Satrapi, P., & Schonfeldt-Lecuona, C. (2003). Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr*, 16(2), 95-99. <https://doi.org/10.1023/b:brat.0000006333.93597.9d>
- Hirakawa, H., Terao, T., Muronaga, M., & Ishii, N. (2020). Adjunctive bright light therapy for treating bipolar depression: A systematic review and meta-analysis of randomized controlled trials. *Brain Behav*, 10(12), e01876. <https://doi.org/10.1002/brb3.1876>
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S. E., Dixon-Woods, M., McCulloch, P., Wyatt, J. C., Chan, A. W., & Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, 348, g1687. <https://doi.org/10.1136/bmj.g1687>
- Hori, H., & Kunugi, H. (2012). The efficacy of pramipexole, a dopamine receptor agonist, as an adjunctive treatment in treatment-resistant depression: an open-label trial. *The scientific world journal*, 2012(1), 372474.
- Hosseini, T., Yavari, F., Biagi, M. C., Kuo, M. F., Ruffini, G., Nitsche, M. A., & Jamil, A. (2021). External induction and stabilization of brain oscillations in the human. *Brain Stimulation*, 14(3), 579-587. <https://doi.org/10.1016/j.brs.2021.03.011>
- Hosseini, T., Yavari, F., Kuo, M. F., Nitsche, M. A., & Jamil, A. (2021). Phase synchronized 6 Hz transcranial electric and magnetic stimulation boosts frontal theta activity and enhances working memory. *Neuroimage*, 245, 118772. <https://doi.org/10.1016/j.neuroimage.2021.118772>
- Hu, X., & Li, J. (2024). Acupuncture combined with repeated transcranial magnetic stimulation for mild to moderate post-stroke depression: a randomized controlled trial. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*, 44(7), 765-769.
- Huang, C.-C., Wei, I.-H., Chou, Y.-H., & Su, T.-P. (2008). Effect of age, gender, menopausal status, and ovarian hormonal level on rTMS in treatment-resistant depression. *Psychoneuroendocrinology*, 33(6), 821-831.
- Hunter, A. M., Korb, A. S., Cook, I. A., & Leuchter, A. F. (2013). Rostral anterior cingulate activity in major depressive disorder: state or trait marker of responsiveness to medication? *J Neuropsychiatry Clin Neurosci*, 25(2), 126-133. <https://doi.org/10.1176/appi.neuropsych.11110330>
- Hunter, A. M., Minzenberg, M. J., Cook, I. A., Krantz, D. E., Levitt, J. G., Rotstein, N. M., Chawla, S. A., & Leuchter, A. F. (2019). Concomitant medication use and clinical outcome of repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder. *Brain Behav*, 9(5), e01275. <https://doi.org/10.1002/brb3.1275>

- Hutton, T. M., Aaronson, S. T., Carpenter, L. L., Pages, K., Krantz, D., Lucas, L., Chen, B., & Sackeim, H. A. (2023). Dosing transcranial magnetic stimulation in major depressive disorder: relations between number of treatment sessions and effectiveness in a large patient registry. *Brain stimulation*, 16(5), 1510-1521.
- Ibrahim, H. M., Kulikova, A., Ly, H., Rush, A. J., & Sherwood Brown, E. (2022). Anterior cingulate cortex in individuals with depressive symptoms: A structural MRI study. *Psychiatry Res Neuroimaging*, 319, 111420. <https://doi.org/10.1016/j.pscychresns.2021.111420>
- Idlett-Ali, S. L., Salazar, C. A., Bell, M. S., Short, E. B., & Rowland, N. C. (2023). Neuromodulation for treatment-resistant depression: Functional network targets contributing to antidepressive outcomes. *Front Hum Neurosci*, 17, 1125074. <https://doi.org/10.3389/fnhum.2023.1125074>
- Iriarte, I. G., & George, M. S. (2018). Transcranial Magnetic Stimulation (TMS) in the Elderly. *Curr Psychiatry Rep*, 20(1), 6. <https://doi.org/10.1007/s11920-018-0866-2>
- Ishii, R., Canuet, L., Ishihara, T., Aoki, Y., Ikeda, S., Hata, M., Katsimichas, T., Gunji, A., Takahashi, H., Nakahachi, T., Iwase, M., & Takeda, M. (2014). Frontal midline theta rhythm and gamma power changes during focused attention on mental calculation: an MEG beamformer analysis. *Front Hum Neurosci*, 8, 406. <https://doi.org/10.3389/fnhum.2014.00406>
- Isserles, M., Rosenberg, O., Dannon, P., Levkovitz, Y., Kotler, M., Deutsch, F., Lerer, B., & Zangen, A. (2011). Cognitive-emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome. *J Affect Disord*, 128(3), 235-242. <https://doi.org/10.1016/j.jad.2010.06.038>
- Itthipuripat, S., Wessel, J. R., & Aron, A. R. (2013). Frontal theta is a signature of successful working memory manipulation. *Experimental brain research*, 224, 255-262.
- Jaiswal, A., Goyal, N., & Shreekanthiah, U. (2024). High-Definition Transcranial Direct Current Stimulation-Primed Intermittent Theta Burst Stimulation in Treatment-Resistant Depression: A Controlled Study. *J ECT*, 40(1), 41-46. <https://doi.org/10.1097/YCT.0000000000000952>
- Janssens, S. E. W., & Sack, A. T. (2021). Spontaneous Fluctuations in Oscillatory Brain State Cause Differences in Transcranial Magnetic Stimulation Effects Within and Between Individuals. *Frontiers in Human Neuroscience*, 15, Article 802244. <https://doi.org/10.3389/fnhum.2021.802244>
- Jensen, O., & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *Eur J Neurosci*, 15(8), 1395-1399. <https://doi.org/10.1046/j.1460-9568.2002.01975.x>
- Jewett, B. E., & Thapa, B. (2022). Physiology, NMDA receptor. In *StatPearls [Internet]*. StatPearls Publishing.
- Jha, S., Chadda, R. K., Kumar, N., & Bal, C. S. (2016). Brain SPECT guided repetitive transcranial magnetic stimulation (rTMS) in treatment resistant major depressive disorder. *Asian J Psychiatr*, 21, 1-6. <https://doi.org/10.1016/j.ajp.2016.02.003>
- Jilani, T., Gibbons, J., Faizy, R., & Saadabadi, A. (2024). Mirtazapine. *StatPearls*.
- Kar, S. K. (2019). Predictors of Response to Repetitive Transcranial Magnetic Stimulation in Depression: A Review of Recent Updates. *Clin Psychopharmacol Neurosci*, 17(1), 25-33. <https://doi.org/10.9758/cpn.2019.17.1.25>
- Karabanov, A., Ziemann, U., Hamada, M., George, M. S., Quartarone, A., Classen, J., Massimini, M., Rothwell, J., & Siebner, H. R. (2015). Consensus Paper: Probing Homeostatic Plasticity of Human Cortex With Non-invasive Transcranial Brain Stimulation. *Brain Stimul*, 8(5), 993-1006. <https://doi.org/10.1016/j.brs.2015.06.017>

- Karakas, S. (2020). A review of theta oscillation and its functional correlates. *Int J Psychophysiol*, 157, 82-99. <https://doi.org/10.1016/j.ijpsycho.2020.04.008>
- Kasten, F. H., Dowsett, J., & Herrmann, C. S. (2016). Sustained aftereffect of α -tACS lasts up to 70 min after stimulation. *Frontiers in human neuroscience*, 10, 245.
- Klink, K., Paßmann, S., Kasten, F. H., & Peter, J. (2020). The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain Sci*, 10(12). <https://doi.org/10.3390/brainsci10120932>
- Klomjai, W., Katz, R., & Lackmy-Vallee, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med*, 58(4), 208-213. <https://doi.org/10.1016/j.rehab.2015.05.005>
- Kochanowski, B., Kageki-Bonnert, K., Pinkerton, E. A., Dougherty, D. D., & Chou, T. (2024). A Review of Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Combined with Medication and Psychotherapy for Depression. *Harv Rev Psychiatry*, 32(3), 77-95. <https://doi.org/10.1097/HRP.0000000000000396>
- Krause, F. C., Linardatos, E., Fresco, D. M., & Moore, M. T. (2021). Facial emotion recognition in major depressive disorder: A meta-analytic review. *J Affect Disord*, 293, 320-328. <https://doi.org/10.1016/j.jad.2021.06.053>
- Kricheldorf, J., Goke, K., Kiebs, M., Kasten, F. H., Herrmann, C. S., Witt, K., & Hurlemann, R. (2022). Evidence of Neuroplastic Changes after Transcranial Magnetic, Electric, and Deep Brain Stimulation. *Brain Sci*, 12(7). <https://doi.org/10.3390/brainsci12070929>
- Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*, 16(9), 606-613. <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>
- Lam Ching, W., Li, H. J., Guo, J., Yao, L., Chau, J., Lo, S., Yuen, C. S., Ng, B. F. L., Chau-Leung Yu, E., Bian, Z., Lau, A. Y., & Zhong, L. L. (2023). Acupuncture for post-stroke depression: a systematic review and network meta-analysis. *BMC Psychiatry*, 23(1), 314. <https://doi.org/10.1186/s12888-023-04749-1>
- Lan, M. J., Chhetry, B. T., Liston, C., Mann, J. J., & Dubin, M. (2016). Transcranial magnetic stimulation of left dorsolateral prefrontal cortex induces brain morphological changes in regions associated with a treatment resistant major depressive episode: an exploratory analysis. *Brain stimulation*, 9(4), 577-583.
- Lavín, C., Soto-Icaza, P., López, V., & Billeke, P. (2023). Another in need enhances prosociality and modulates frontal theta oscillations in young adults. *Frontiers in Psychiatry*, 14, 1160209.
- Lee, J. C., Corlier, J., Wilson, A. C., Tadayonnejad, R., Marder, K. G., Ngo, D., Krantz, D. E., Wilke, S. A., Levitt, J. G., & Ginder, N. D. (2021). Subthreshold stimulation intensity is associated with greater clinical efficacy of intermittent theta-burst stimulation priming for Major Depressive Disorder. *Brain stimulation*, 14(4), 1015-1021.
- Lee, J. C., Wilson, A. C., Corlier, J., Tadayonnejad, R., Marder, K. G., Pleman, C. M., Krantz, D. E., Wilke, S. A., Levitt, J. G., Ginder, N. D., & Leuchter, A. F. (2020). Strategies for augmentation of high-frequency left-sided repetitive transcranial magnetic stimulation treatment of major depressive disorder. *J Affect Disord*, 277, 964-969. <https://doi.org/10.1016/j.jad.2020.09.011>
- Lee, T. L., Lee, H., & Kang, N. (2023). A meta-analysis showing improved cognitive performance in healthy young adults with transcranial alternating current stimulation. *NPJ Sci Learn*, 8(1), 1. <https://doi.org/10.1038/s41539-022-00152-9>

- Lee, T. W., Girolami, M., & Sejnowski, T. J. (1999). Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Comput*, 11(2), 417-441. <https://doi.org/10.1162/089976699300016719>
- Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipovic, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jaaskelainen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J. P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., . . . Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol*, 131(2), 474-528. <https://doi.org/10.1016/j.clinph.2019.11.002>
- Leseur, J., Boiret, C., Romier, A., Bazin, B., Basquin, L., Stern, E., Pineau, G., Lejoyeux, M., Geoffroy, P. A., & Maruani, J. (2024). Comparative study of sleep and circadian rhythms in patients presenting unipolar or bipolar major depressive episodes. *Psychiatry Res*, 334, 115811. <https://doi.org/10.1016/j.psychres.2024.115811>
- Leuchter, A. F., Cook, I. A., Jin, Y., & Phillips, B. (2013). The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. *Frontiers in human neuroscience*, 7, 37.
- Li, B. J., Friston, K., Mody, M., Wang, H. N., Lu, H. B., & Hu, D. W. (2018). A brain network model for depression: From symptom understanding to disease intervention. *CNS Neurosci Ther*, 24(11), 1004-1019. <https://doi.org/10.1111/cns.12998>
- Li, C. T., Chen, M. H., Juan, C. H., Huang, H. H., Chen, L. F., Hsieh, J. C., Tu, P. C., Bai, Y. M., Tsai, S. J., Lee, Y. C., & Su, T. P. (2014). Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. *Brain*, 137(Pt 7), 2088-2098. <https://doi.org/10.1093/brain/awu109>
- Li, C. T., Chen, M. H., Juan, C. H., Liu, R. S., Lin, W. C., Bai, Y. M., & Su, T. P. (2018). Effects of prefrontal theta-burst stimulation on brain function in treatment-resistant depression: A randomized sham-controlled neuroimaging study. *Brain Stimul*, 11(5), 1054-1062. <https://doi.org/10.1016/j.brs.2018.04.014>
- Li, C. T., Cheng, C. M., Juan, C. H., Tsai, Y. C., Chen, M. H., Bai, Y. M., Tsai, S. J., & Su, T. P. (2021). Task-Modulated Brain Activity Predicts Antidepressant Responses of Prefrontal Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Control Study. *Chronic Stress (Thousand Oaks)*, 5, 24705470211006855. <https://doi.org/10.1177/24705470211006855>
- Li, C. T., Hsieh, J. C., Huang, H. H., Chen, M. H., Juan, C. H., Tu, P. C., Lee, Y. C., Wang, S. J., Cheng, C. M., & Su, T. P. (2016). Cognition-Modulated Frontal Activity in Prediction and Augmentation of Antidepressant Efficacy: A Randomized Controlled Pilot Study. *Cereb Cortex*, 26(1), 202-210. <https://doi.org/10.1093/cercor/bhu191>
- Li, H., Cui, L., Li, J., Liu, Y., & Chen, Y. (2021). Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials. *J Affect Disord*, 287, 115-124. <https://doi.org/10.1016/j.jad.2021.03.019>
- Li, X., Liu, J., Wei, S., Yu, C., Wang, D., Li, Y., Li, J., Zhuang, W., Luo, R. C., Li, Y., Liu, Z., Su, Y., Liu, J., Xu, Y., Fan, J., Zhu, G., Xu, W., Tang, Y., Yan, H., . . . Zhang, X. (2024). Cognitive enhancing effect of rTMS combined with tDCS in patients with major depressive disorder: a double-blind, randomized, sham-controlled study. *BMC Med*, 22(1), 253. <https://doi.org/10.1186/s12916-024-03443-7>
- Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., Voss, H. U., Casey, B. J., Etkin, A., & Dubin, M. J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry*, 76(7), 517-526. <https://doi.org/10.1016/j.biopsych.2014.01.023>

- Liu, W. H., Huang, J., Wang, L. Z., Gong, Q. Y., & Chan, R. C. (2012). Facial perception bias in patients with major depression. *Psychiatry Res*, 197(3), 217-220.
<https://doi.org/10.1016/j.psychres.2011.09.021>
- Luber, B., Balsam, P., Nguyen, T., Gross, M., & Lisanby, S. H. (2007). Classical conditioned learning using transcranial magnetic stimulation. *Exp Brain Res*, 183(3), 361-369.
<https://doi.org/10.1007/s00221-007-1052-7>
- Maiella, M., Casula, E. P., Borghi, I., Assogna, M., D'Acunto, A., Pezzopane, V., Mencarelli, L., Rocchi, L., Pellicciari, M. C., & Koch, G. (2022). Simultaneous transcranial electrical and magnetic stimulation boost gamma oscillations in the dorsolateral prefrontal cortex. *Sci Rep*, 12(1), 19391. <https://doi.org/10.1038/s41598-022-23040-z>
- Mania, I., & Kaur, J. (2019). Bright Light Therapy and rTMS; novel combination approach for the treatment of depression. *Brain Stimul*, 12(5), 1338-1339.
<https://doi.org/10.1016/j.brs.2019.06.002>
- Marx, W., Penninx, B. W., Solmi, M., Furukawa, T. A., Firth, J., Carvalho, A. F., & Berk, M. (2023). Major depressive disorder. *Nature reviews Disease primers*, 9(1), 44.
- McClintock, S. M., Reti, I. M., Carpenter, L. L., McDonald, W. M., Dubin, M., Taylor, S. F., Cook, I. A., O'Reardon, J., Husain, M. M., Wall, C., Krystal, A. D., Sampson, S. M., Morales, O., Nelson, B. G., Latoussakis, V., George, M. S., Lisanby, S. H., National Network of Depression Centers r, T. M. S. T. G., American Psychiatric Association Council on Research Task Force on Novel, B., & Treatments. (2018). Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. *J Clin Psychiatry*, 79(1).
<https://doi.org/10.4088/JCP.16cs10905>
- McDonald, W. M., Durkalski, V., Ball, E. R., Holtzheimer, P. E., Pavlicova, M., Lisanby, S. H., Avery, D., Anderson, B. S., Nahas, Z., Zarkowski, P., Sackeim, H. A., & George, M. S. (2011). Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. *Depress Anxiety*, 28(11), 973-980.
<https://doi.org/10.1002/da.20885>
- McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S. H., Ly-Uson, J., Mansur, R. B., McAllister-Williams, R. H., Murrough, J. W., Nemeroff, C. B., Nierenberg, A. A., Rosenblat, J. D., Sanacora, G., Schatzberg, A. F., . . . Maj, M. (2023). Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry*, 22(3), 394-412.
<https://doi.org/10.1002/wps.21120>
- McLoughlin, G., Makeig, S., & Tsuang, M. T. (2014). In search of biomarkers in psychiatry: EEG-based measures of brain function. *Am J Med Genet B Neuropsychiatr Genet*, 165B(2), 111-121. <https://doi.org/10.1002/ajmg.b.32208>
- Mendlowitz, A. B., Shanbour, A., Downar, J., Vila-Rodriguez, F., Daskalakis, Z. J., Isaranuwatthai, W., & Blumberger, D. M. (2019). Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: A cost analysis. *PLoS One*, 14(9), e0222546. <https://doi.org/10.1371/journal.pone.0222546>
- Menegaz de Almeida, A., Aquino de Moraes, F. C., Cavalcanti Souza, M. E., Cavalcanti Orestes Cardoso, J. H., Tamashiro, F., Miranda, C., Fernandes, L., Kreuz, M., & Alves Kelly, F. (2025). Bright Light Therapy for Nonseasonal Depressive Disorders: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*, 82(1), 38-46.
<https://doi.org/10.1001/jamapsychiatry.2024.2871>

- Mi, Y., Ji, Y., Lou, Z., Hou, Y., & Ruan, L. (2022). Left intermittent theta burst stimulation combined with right low-frequency rTMS as an additional treatment for major depression: A retrospective study. *Indian journal of psychiatry*, 64(4), 364-369.
- Mielacher, C., Schultz, J., Kiebs, M., Dellert, T., Metzner, A., Graute, L., Högenauer, H., Maier, W., Lamm, C., & Hurlmann, R. (2020). Individualized theta-burst stimulation modulates hippocampal activity and connectivity in patients with major depressive disorder. *Personalized Medicine in Psychiatry*, 23-24, 100066. <https://doi.org/https://doi.org/10.1016/j.pmip.2020.100066>
- Mir-Moghtadaei, A., Caballero, R., Fried, P., Fox, M. D., Lee, K., Giacobbe, P., Daskalakis, Z. J., Blumberger, D. M., & Downar, J. (2015). Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain stimulation*, 8(5), 965-973.
- Miron, J. P., Jodoin, V. D., Lesperance, P., & Blumberger, D. M. (2021). Repetitive transcranial magnetic stimulation for major depressive disorder: basic principles and future directions. *Ther Adv Psychopharmacol*, 11, 20451253211042696. <https://doi.org/10.1177/20451253211042696>
- Mitoma, R., Tamura, S., Tateishi, H., Mitsudo, T., Tanabe, I., Monji, A., & Hirano, Y. (2022). Oscillatory brain network changes after transcranial magnetic stimulation treatment in patients with major depressive disorder. *Journal of Affective Disorders Reports*, 7, 100277.
- Moret, C. (2005). Combination/augmentation strategies for improving the treatment of depression. *Neuropsychiatr Dis Treat*, 1(4), 301-309. <https://www.ncbi.nlm.nih.gov/pubmed/18568111>
- Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. H. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry*, 180, 461-464. <https://doi.org/10.1192/bjp.180.5.461>
- Murphy, O. W., Hoy, K. E., Wong, D., Bailey, N. W., Fitzgerald, P. B., & Segrave, R. A. (2019). Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance. *Biol Psychol*, 148, 107766. <https://doi.org/10.1016/j.biopsycho.2019.107766>
- Mutz, J., Vipulanathan, V., Carter, B., Hurlmann, R., Fu, C. H. Y., & Young, A. H. (2019). Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ*, 364, 11079. <https://doi.org/10.1136/bmj.11079>
- Mylius, V., Ayache, S. S., Ahdab, R., Farhat, W. H., Zouari, H. G., Belke, M., Brugieres, P., Wehrmann, E., Krakow, K., Timmesfeld, N., Schmidt, S., Oertel, W. H., Knake, S., & Lefaucheur, J. P. (2013). Definition of DLPFC and M1 according to anatomical landmarks for navigated brain stimulation: inter-rater reliability, accuracy, and influence of gender and age. *Neuroimage*, 78, 224-232. <https://doi.org/10.1016/j.neuroimage.2013.03.061>
- Nakamura-Palacios, E. M., Falçoni Júnior, A. T., Anders, Q. S., de Paula, L. d. S. P., Zottele, M. Z., Ronchete, C. F., & Lirio, P. H. C. (2023). Would frontal midline theta indicate cognitive changes induced by non-invasive brain stimulation? A mini review. *Frontiers in human neuroscience*, 17, 1116890.
- Nakazono, H., Ogata, K., Takeda, A., Yamada, E., Oka, S., & Tobimatsu, S. (2021). A specific phase of transcranial alternating current stimulation at the β frequency boosts repetitive paired-pulse TMS-induced plasticity. *Scientific Reports*, 11(1), Article 13179. <https://doi.org/10.1038/s41598-021-92768-x>
- National Academies of Sciences, E., & Medicine. (2016). Developing multimodal therapies for brain disorders: proceedings of a workshop.

- Nikolin, S., Tan, Y. Y., Schwaab, A., Moffa, A., Loo, C. K., & Martin, D. (2021). An investigation of working memory deficits in depression using the n-back task: A systematic review and meta-analysis. *J Affect Disord*, 284, 1-8. <https://doi.org/10.1016/j.jad.2021.01.084>
- Noda, Y., Nakamura, M., Saeki, T., Inoue, M., Iwanari, H., & Kasai, K. (2013). Potentiation of quantitative electroencephalograms following prefrontal repetitive transcranial magnetic stimulation in patients with major depression. *Neurosci Res*, 77(1-2), 70-77. <https://doi.org/10.1016/j.neures.2013.06.002>
- Oathes, D. J., Duprat, R. J., Reber, J., Liang, X., Scully, M., Long, H., Deluisi, J. A., Sheline, Y. I., & Linn, K. A. (2023). Non-invasively targeting, probing and modulating a deep brain circuit for depression alleviation. *Nature Mental Health*, 1(12), 1033-1042.
- Oathes, D. J., Zimmerman, J. P., Duprat, R., Japp, S. S., Scully, M., Rosenberg, B. M., Flounders, M. W., Long, H., Deluisi, J. A., Elliott, M., Shandler, G., Shinohara, R. T., & Linn, K. A. (2021). Resting fMRI-guided TMS results in subcortical and brain network modulation indexed by interleaved TMS/fMRI. *Exp Brain Res*, 239(4), 1165-1178. <https://doi.org/10.1007/s00221-021-06036-5>
- Ogata, K., Nakazono, H., Ikeda, T., Oka, S. I., Goto, Y., & Tobimatsu, S. (2021). After-Effects of Intermittent Theta-Burst Stimulation Are Differentially and Phase-Dependently Suppressed by α - and β -Frequency Transcranial Alternating Current Stimulation. *Frontiers in Human Neuroscience*, 15, Article 750329. <https://doi.org/10.3389/fnhum.2021.750329>
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9(1), 97-113. [https://doi.org/10.1016/0028-3932\(71\)90067-4](https://doi.org/10.1016/0028-3932(71)90067-4)
- Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature reviews Disease primers*, 2(1), 1-20.
- Paillère Martinot, M.-L., Galinowski, A., Ringuenet, D., Gallarda, T., Lefaucheur, J.-P., Bellivier, F., Picq, C., Bruguière, P., Mangin, J.-F., & Rivière, D. (2010). Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [18F]-fluorodeoxyglucose PET and MRI study. *International Journal of Neuropsychopharmacology*, 13(1), 45-59.
- Parmigiani, S., Ross, J. M., Cline, C. C., Minasi, C. B., Gogulski, J., & Keller, C. J. (2023). Reliability and validity of transcranial magnetic stimulation–electroencephalography biomarkers. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 8(8), 805-814.
- Payette, O., Lespérance, P., Jodoin, V. D., Longpré-Poirier, C., Elkrief, L., Richard, M., Garel, N., & Miron, J.-P. (2023). Intravenous ketamine for treatment-resistant depression patients who have failed to respond to transcranial magnetic stimulation: A case series. *Journal of Affective Disorders*, 333, 18-20.
- Peters, M. D. J., Godfrey, C., McInerney, P., Khalil, H., Larsen, P., Marnie, C., Pollock, D., Tricco, A. C., & Munn, Z. (2022). Best practice guidance and reporting items for the development of scoping review protocols. *JBIM Evid Synth*, 20(4), 953-968. <https://doi.org/10.11124/JBIES-21-00242>
- Philip, N. S., Barredo, J., Aiken, E., & Carpenter, L. L. (2018). Neuroimaging Mechanisms of Therapeutic Transcranial Magnetic Stimulation for Major Depressive Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*, 3(3), 211-222. <https://doi.org/10.1016/j.bpsc.2017.10.007>
- Phouthavong, L., & Thorkelson, G. (2021). Neurofeedback Modulation of Frontal Midline Theta Activity at the Rostral Anterior Cingulate Cortex (rACC) to Promote Improved Response Rates in High-Frequency Repetitive Transcranial Magnetic Stimulation

- (rTMS): A Case Series. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 14(6), 1698-1699.
- Piccoli, E., Cerioli, M., Castiglioni, M., Larini, L., Scarpa, C., & Dell'Osso, B. (2022). Recent innovations in non-invasive brain stimulation (NIBS) for the treatment of unipolar and bipolar depression: a narrative review. *Int Rev Psychiatry*, 34(7-8), 715-726. <https://doi.org/10.1080/09540261.2022.2132137>
- Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*, 36(1), 183-206. <https://doi.org/10.1038/npp.2010.166>
- Pizzagalli, D. A., Oakes, T. R., & Davidson, R. J. (2003). Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. *Psychophysiology*, 40(6), 939-949. <https://doi.org/10.1111/1469-8986.00112>
- Pizzagalli, D. A., & Roberts, A. C. (2022). Prefrontal cortex and depression. *Neuropsychopharmacology*, 47(1), 225-246.
- Pizzagalli, D. A., Webb, C. A., Dillon, D. G., Tenke, C. E., Kayser, J., Goer, F., Fava, M., McGrath, P., Weissman, M., & Parsey, R. (2018). Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: a randomized clinical trial. *JAMA Psychiatry*, 75(6), 547-554.
- Poydasheva, A., Sinitsyn, D., Bakulin, I., Suponeva, N., Maslennikov, N., Tsukarzi, E., Mosolov, S., & Piradov, M. (2019). Target determination for transcranial magnetic stimulation in patients with a pharmacotherapy-resistant depressive episode based on the individual parameters of resting-state functional magnetic resonance imaging (a pilot blind controlled trial). *Neurology, Neuropsychiatry, Psychosomatics*, 11(4), 44-50.
- Pozdniakov, I., Vorobiova, A. N., Galli, G., Rossi, S., & Feurra, M. (2021). Online and offline effects of transcranial alternating current stimulation of the primary motor cortex. *Scientific Reports*, 11(1), 3854.
- Prentice, A., Kolken, Y., Tuttle, C., van Neijenhof, J., Pitch, R., van Oostrom, I., Kruiver, V., Downar, J., Sack, A. T., & Arns, M. (2023). 1Hz right orbitofrontal TMS benefits depressed patients unresponsive to dorsolateral prefrontal cortex TMS. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 16(6), 1572-1575.
- Price, G. W., Lee, J. W., Garvey, C.-A. L., & Gibson, N. (2010). The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: a controlled comparison with standard techniques. *Brain stimulation*, 3(3), 140-152.
- Proskovec, A. L., Wiesman, A. I., Heinrichs-Graham, E., & Wilson, T. W. (2018). Beta Oscillatory Dynamics in the Prefrontal and Superior Temporal Cortices Predict Spatial Working Memory Performance. *Sci Rep*, 8(1), 8488. <https://doi.org/10.1038/s41598-018-26863-x>
- Raes, F., Hermans, D., & Williams, J. M. (2006). Negative bias in the perception of others' facial emotional expressions in major depression: the role of depressive rumination. *J Nerv Ment Dis*, 194(10), 796-799. <https://doi.org/10.1097/01.nmd.0000240187.80270.bb>
- Rajan, A., Siegel, S. N., Liu, Y., Bengson, J., Mangun, G. R., & Ding, M. (2018). Theta Oscillations Index Frontal Decision-Making and Mediate Reciprocal Frontal–Parietal Interactions in Willed Attention. *Cerebral Cortex*, 29(7), 2832-2843. <https://doi.org/10.1093/cercor/bhy149>

- Rajkowska, G., & Goldman-Rakic, P. S. (1995). Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach Coordinate System. *Cereb Cortex*, 5(4), 323-337. <https://doi.org/10.1093/cercor/5.4.323>
- Rakesh, G., Cordero, P., Khanal, R., Himelhoch, S. S., & Rush, C. R. (2024). Optimally combining transcranial magnetic stimulation with antidepressants in major depressive disorder: A systematic review and Meta-analysis. *J Affect Disord*, 358, 432-439. <https://doi.org/10.1016/j.jad.2024.05.037>
- Riedinger, M., van Son, G., van der Wee, N., Giltay, E., & de Leeuw, M. (2025). Effectiveness of bright light therapy in patients suffering from unipolar or bipolar depression; A naturalistic study. *The European Journal of Psychiatry*, 39(3), 100294.
- Ross, R. E., VanDerwerker, C. J., George, M. S., & Gregory, C. M. (2023). Feasibility of performing a multi-arm clinical trial examining the novel combination of repetitive transcranial magnetic stimulation and aerobic exercise for post-stroke depression. *Topics in stroke rehabilitation*, 30(7), 649-662.
- Rybak, M., Bruno, R., Turnier-Shea, Y., & Pridmore, S. (2005). An attempt to increase the rate and magnitude of the antidepressant effect of transcranial magnetic stimulation (TMS). A pilot study. *German Journal of Psychiatry*, 8(4), 59-65.
- Sabesan, P., Lankappa, S., Khalifa, N., Krishnan, V., Gandhi, R., & Palaniyappan, L. (2015). Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls. *World J Psychiatry*, 5(2), 170-181. <https://doi.org/10.5498/wjp.v5.i2.170>
- Sack, A. T., Paneva, J., K  the, T., Dijkstra, E., Zwienenberg, L., Arns, M., & Schuhmann, T. (2024). Target engagement and brain state dependence of transcranial magnetic stimulation: implications for clinical practice. *Biological psychiatry*, 95(6), 536-544.
- Salehinejad, M. A., Ghanavati, E., Rashid, M. H. A., & Nitsche, M. A. (2021). Hot and cold executive functions in the brain: A prefrontal-cingular network. *Brain Neurosci Adv*, 5, 23982128211007769. <https://doi.org/10.1177/23982128211007769>
- Sathappan, A. V., Lubner, B. M., & Lisanby, S. H. (2019). The Dynamic Duo: Combining noninvasive brain stimulation with cognitive interventions. *Prog Neuropsychopharmacol Biol Psychiatry*, 89, 347-360. <https://doi.org/10.1016/j.pnpbp.2018.10.006>
- Schade, S., & Paulus, W. (2016). D-Cycloserine in Neuropsychiatric Diseases: A Systematic Review. *Int J Neuropsychopharmacol*, 19(4). <https://doi.org/10.1093/ijnp/pyv102>
- Schiena, G., Maggioni, E., Pozzoli, S., & Brambilla, P. (2020). Transcranial magnetic stimulation in major depressive disorder: Response modulation and state dependency. *Journal of Affective Disorders*, 266, 793-801. <https://doi.org/https://doi.org/10.1016/j.jad.2020.02.006>
- Schiena, G., Maggioni, E., Pozzoli, S., & Brambilla, P. (2020). Transcranial magnetic stimulation in major depressive disorder: Response modulation and state dependency. *J Affect Disord*, 266, 793-801. <https://doi.org/10.1016/j.jad.2020.02.006>
- Sch  le, C., Zwanzger, P., Baghai, T., Mikhael, P., Thoma, H., M  ller, H.-J., Rupprecht, R., & Padberg, F. (2003). Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: an open follow-up study. *Journal of psychiatric research*, 37(2), 145-153.
- Schweitzer, I., Tuckwell, V., & Johnson, G. (1997). A review of the use of augmentation therapy for the treatment of resistant depression: implications for the clinician. *Aust N Z J Psychiatry*, 31(3), 340-352. <https://doi.org/10.3109/00048679709073843>
- Seemann, O., Hechinger, S., & Kr  mer, B. (2023). Combination of TPS and TMS in a patient with post-COVID-19 depression. *stem cells*, 9, 10.

- Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv Res*, 17(1), 88. <https://doi.org/10.1186/s12913-017-2031-8>
- Serafini, G., Pompili, M., Innamorati, M., Dwivedi, Y., Brahmachari, G., & Girardi, P. (2013). Pharmacological properties of glutamatergic drugs targeting NMDA receptors and their application in major depression. *Current pharmaceutical design*, 19(10), 1898-1922.
- Shanok, N. A., Muzac, S., Brown, L., Barrera, M., & Rodriguez, R. (2024). Synergistic use of deep TMS therapy with IV ketamine infusions for major depressive disorder: a pilot study. *Psychopharmacology (Berl)*, 241(7), 1427-1433. <https://doi.org/10.1007/s00213-024-06573-1>
- Sheffler, Z. M., Patel, P., & Abdijadid, S. (2023). Antidepressants. In *StatPearls [Internet]*. StatPearls Publishing.
- Shen, J., Zhao, S., Yao, Y., Wang, Y., & Feng, L. (2017). A novel depression detection method based on pervasive EEG and EEG splitting criterion. 2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM),
- Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topogr*, 21(1), 1-10. <https://doi.org/10.1007/s10548-008-0067-0>
- Sohn, M. N., Brown, J. C., Sharma, P., Ziemann, U., & McGirr, A. (2024). Pharmacological adjuncts and transcranial magnetic stimulation-induced synaptic plasticity: a systematic review. *J Psychiatry Neurosci*, 49(1), E59-E76. <https://doi.org/10.1503/jpn.230090>
- Somani, A., & Kar, S. K. (2019). Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. *General Psychiatry*, 32(4).
- Sperl, M. F. J., Panitz, C., Rosso, I. M., Dillon, D. G., Kumar, P., Hermann, A., Whitton, A. E., Hermann, C., Pizzagalli, D. A., & Mueller, E. M. (2019). Fear Extinction Recall Modulates Human Frontomedial Theta and Amygdala Activity. *Cereb Cortex*, 29(2), 701-715. <https://doi.org/10.1093/cercor/bhx353>
- Spitz, N. A., Ten Eyck, P., Nizar, K., Boes, A. D., & Trapp, N. T. (2022). Similar Outcomes in Treating Major Depressive Disorder With 10 Hz Repetitive Transcranial Magnetic Stimulation (rTMS) Versus Intermittent Theta Burst Stimulation (iTBS): A Naturalistic Observational Study. *J Psychiatr Pract*, 28(2), 98-107. <https://doi.org/10.1097/prs.0000000000000611>
- Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*, 166(10), 1092-1097. <https://doi.org/10.1001/archinte.166.10.1092>
- Sporn, S., Hein, T., & Herrojo Ruiz, M. (2020). Alterations in the amplitude and burst rate of beta oscillations impair reward-dependent motor learning in anxiety. *Elife*, 9. <https://doi.org/10.7554/eLife.50654>
- Stevens, F. L., Hurley, R. A., & Taber, K. H. (2011). Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci*, 23(2), 121-125. <https://doi.org/10.1176/jnp.23.2.jnp121>
- Stillianesis, G., Cavaleri, R., Tang, C. Y., & Summers, S. J. (2022). Exploring Patient Perceptions of Noninvasive Brain Stimulation: A Systematic Review. *Neuromodulation*, 25(4), 487-493. <https://doi.org/10.1111/ner.13461>
- Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biol Mood Anxiety Disord*, 1(1), 10. <https://doi.org/10.1186/2045-5380-1-10>
- Stultz, D. J., Osburn, S., Burns, T., Pawlowska-Wajswol, S., & Walton, R. (2020). Transcranial Magnetic Stimulation (TMS) Safety with Respect to Seizures: A

- Literature Review. *Neuropsychiatr Dis Treat*, 16, 2989-3000.
<https://doi.org/10.2147/NDT.S276635>
- Suddell, S., Müller-Glodge, M., Lumsden, J., Looi, C. Y., Granger, K., Barnett, J. H., Robinson, O. J., Munafò, M. R., & Penton-Voak, I. S. (2023). Emotional bias training as a treatment for anxiety and depression: evidence from experimental medicine studies in healthy and medicated samples. *Psychological medicine*, 53(3), 696-705.
- Tadayonnejad, R., Citrenbaum, C., Ngo, T. D. P., Corlier, J., Wilke, S. A., Slan, A., Distler, M. G., Hoftman, G., Adelekun, A. E., & Leuchter, M. K. (2023). Right lateral orbitofrontal cortex inhibitory transcranial magnetic stimulation for treatment of refractory mood and depression. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 16(5), 1374-1376.
- Taib, S., Arbus, C., Sauvaget, A., Sporer, M., Schmitt, L., & Yroni, A. (2018). How does repetitive transcranial magnetic stimulation influence the brain in depressive disorders?: a review of neuroimaging magnetic resonance imaging studies. *The Journal of ECT*, 34(2), 79-86.
- Takano, K., & Tanno, Y. (2009). Self-rumination, self-reflection, and depression: self-rumination counteracts the adaptive effect of self-reflection. *Behav Res Ther*, 47(3), 260-264. <https://doi.org/10.1016/j.brat.2008.12.008>
- Tendler, A., Gersner, R., Roth, Y., & Zangen, A. (2018). Alternate day dTMS combined with SSRIs for chronic treatment resistant depression: a prospective multicenter study. *Journal of Affective Disorders*, 240, 130-136.
- Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, 2(2), 1-11.
- Terao, I., & Kodama, W. (2025). Effectiveness of personalized repetitive transcranial magnetic stimulation for major depressive disorder: A systematic review and meta-analysis of randomized active-controlled trials. *J Affect Disord*, 381, 275-280.
<https://doi.org/10.1016/j.jad.2025.04.028>
- Thut, G., Miniussi, C., & Gross, J. (2012). The functional importance of rhythmic activity in the brain. *Current Biology*, 22(16), R658-R663.
- Thut, G., Schyns, P. G., & Gross, J. (2011). Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front Psychol*, 2, 170. <https://doi.org/10.3389/fpsyg.2011.00170>
- Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., & Windischberger, C. (2017). Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increase in functional connectivity. *Neuroimage*, 162, 289-296.
<https://doi.org/10.1016/j.neuroimage.2017.09.022>
- To, W. T., De Ridder, D., Hart Jr, J., & Vanneste, S. (2018). Changing brain networks through non-invasive neuromodulation. *Frontiers in human neuroscience*, 12, 128.
- Torrico, T. J., & Abdijadid, S. (2019). Neuroanatomy, limbic system.
- Trapp, N. T., Purgianto, A., Taylor, J. J., Singh, M. K., Oberman, L. M., Mickey, B. J., Youssef, N. A., Solzbacher, D., Zebly, B., Cabrera, L. Y., Conroy, S., Cristancho, M., Richards, J. R., Flood, M. J., Barbour, T., Blumberger, D. M., Taylor, S. F., Feifel, D., Reti, I. M., . . . Husain, M. M. (2024). Consensus review and considerations on TMS to treat depression: A comprehensive Update Endorsed by the National Network of depression Centers, the clinical TMS Society, and the International Federation of clinical Neurophysiology. *Clinical Neurophysiology*.
<https://doi.org/https://doi.org/10.1016/j.clinph.2024.12.015>
- Trevizol, A. P., Goldberger, K. W., Mulsant, B. H., Rajji, T. K., Downar, J., Daskalakis, Z. J., & Blumberger, D. M. (2019). Unilateral and bilateral repetitive transcranial magnetic

- stimulation for treatment-resistant late-life depression. *Int J Geriatr Psychiatry*, 34(6), 822-827. <https://doi.org/10.1002/gps.5091>
- Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., . . . Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*, 169(7), 467-473. <https://doi.org/10.7326/M18-0850>
- Tsai, Y.-C., Li, C.-T., & Juan, C.-H. (2023). A review of critical brain oscillations in depression and the efficacy of transcranial magnetic stimulation treatment. *Frontiers in Psychiatry*, 14, 1073984.
- Tsai, Y. C., Li, C. T., & Juan, C. H. (2023). A review of critical brain oscillations in depression and the efficacy of transcranial magnetic stimulation treatment. *Front Psychiatry*, 14, 1073984. <https://doi.org/10.3389/fpsy.2023.1073984>
- Tsai, Y. C., Li, C. T., Liang, W. K., Muggleton, N. G., Tsai, C. C., Huang, N. E., & Juan, C. H. (2022). Critical role of rhythms in prefrontal transcranial magnetic stimulation for depression: A randomized sham-controlled study. *Human Brain Mapping*, 43(5), 1535-1547.
- Tundo, A., Betro, S., Iommi, M., & de Filippis, R. (2022). Efficacy and safety of 24-week pramipexole augmentation in patients with treatment resistant depression. A retrospective cohort study. *Prog Neuropsychopharmacol Biol Psychiatry*, 112, 110425. <https://doi.org/10.1016/j.pnpbp.2021.110425>
- Valiengo, L., Maia, A., Cotovio, G., Gordon, P. C., Brunoni, A. R., Forlenza, O. V., & Oliveira-Maia, A. J. (2022). Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder in Older Adults: Systematic Review and Meta-analysis. *J Gerontol A Biol Sci Med Sci*, 77(4), 851-860. <https://doi.org/10.1093/gerona/glab235>
- Valter, Y., Rapallo, F., Burlando, B., Crossen, M., Baeken, C., Datta, A., & Deblieck, C. (2024). Efficacy of non-invasive brain stimulation and neuronavigation for major depressive disorder: a systematic review and meta-analysis. *Expert Rev Med Devices*, 21(7), 643-658. <https://doi.org/10.1080/17434440.2024.2370820>
- Vedeniapin, A., Cheng, L., & George, M. S. (2010). Feasibility of simultaneous cognitive behavioral therapy (CBT) and left prefrontal rTMS for treatment resistant depression. *Brain stimulation*, 3(4), 207.
- Veniero, D., Vossen, A., Gross, J., & Thut, G. (2015). Lasting EEG/MEG Aftereffects of Rhythmic Transcranial Brain Stimulation: Level of Control Over Oscillatory Network Activity. *Front Cell Neurosci*, 9, 477. <https://doi.org/10.3389/fncel.2015.00477>
- Vida, R. G., Saghy, E., Bella, R., Kovacs, S., Erdosi, D., Jozwiak-Hagymasy, J., Zemlenyi, A., Tenyi, T., Osvath, P., & Voros, V. (2023). Efficacy of repetitive transcranial magnetic stimulation (rTMS) adjunctive therapy for major depressive disorder (MDD) after two antidepressant treatment failures: meta-analysis of randomized sham-controlled trials. *BMC Psychiatry*, 23(1), 545. <https://doi.org/10.1186/s12888-023-05033-y>
- Vidya, K. L., Srivastava, S., Singh, B., & Kar, S. K. (2024). Investigating the impact of adjunctive priming repetitive transcranial magnetic stimulation in late-life depression: a pilot single-blind randomized control study. *CNS Spectr*, 29(1), 76-82. <https://doi.org/10.1017/S1092852923002407>
- Vink, J. J. T., Mandija, S., Petrov, P. I., van den Berg, C. A. T., Sommer, I. E. C., & Neggers, S. F. W. (2018). A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. *Hum Brain Mapp*, 39(11), 4580-4592. <https://doi.org/10.1002/hbm.24307>

- Voigt, J., Carpenter, L., & Leuchter, A. (2019). A systematic literature review of the clinical efficacy of repetitive transcranial magnetic stimulation (rTMS) in non-treatment resistant patients with major depressive disorder. *BMC Psychiatry*, 19(1), 13. <https://doi.org/10.1186/s12888-018-1989-z>
- Voineskos, D., Daskalakis, Z. J., & Blumberger, D. M. (2020). Management of Treatment-Resistant Depression: Challenges and Strategies. *Neuropsychiatr Dis Treat*, 16, 221-234. <https://doi.org/10.2147/NDT.S198774>
- Vossen, A., Gross, J., & Thut, G. (2015). Alpha power increase after transcranial alternating current stimulation at alpha frequency (α -tACS) reflects plastic changes rather than entrainment. *Brain stimulation*, 8(3), 499-508.
- Wang, S., Zhang, Z., Yao, L., Ding, N., Jiang, L., & Wu, Y. (2020). Bright light therapy in the treatment of patients with bipolar disorder: A systematic review and meta-analysis. *PLoS One*, 15(5), e0232798. <https://doi.org/10.1371/journal.pone.0232798>
- Wang, X., Wang, Z., Liu, J., Chen, J., Liu, X., Nie, G., Byun, J. S., Liang, Y., Park, J., Huang, R., Liu, M., Liu, B., & Kong, J. (2016). Repeated acupuncture treatments modulate amygdala resting state functional connectivity of depressive patients. *Neuroimage Clin*, 12, 746-752. <https://doi.org/10.1016/j.nicl.2016.07.011>
- Ward, L. M. (2003). Synchronous neural oscillations and cognitive processes. *Trends Cogn Sci*, 7(12), 553-559. <https://doi.org/10.1016/j.tics.2003.10.012>
- Wells, T. T., Clerkin, E. M., Ellis, A. J., & Beevers, C. G. (2014). Effect of antidepressant medication use on emotional information processing in major depression. *Am J Psychiatry*, 171(2), 195-200. <https://doi.org/10.1176/appi.ajp.2013.12091243>
- Wen, K. S., & Zheng, W. (2023). Optimization Strategies of Transcranial Magnetic Stimulation in Major Depressive Disorder. *Alpha Psychiatry*, 24(6), 270-272. <https://doi.org/10.5152/alphapsychiatry.2023.231401>
- WHO. (2017). Depression and other common mental disorders: global health estimates.
- Wischnewski, M., Engelhardt, M., Salehinejad, M., Schutter, D., Kuo, M.-F., & Nitsche, M. (2019). NMDA receptor-mediated motor cortex plasticity after 20 Hz transcranial alternating current stimulation. *Cerebral Cortex*, 29(7), 2924-2931.
- Wu, X., Zhou, L., Qian, C., Gan, L., & Zhang, D. (2015). Attentional modulations of the early and later stages of the neural processing of visual completion. *Sci Rep*, 5, 8346. <https://doi.org/10.1038/srep08346>
- Xiao, K., Li, X., Hu, W., & Li, X. (2024). Acupuncture combined with repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: a systematic evaluation and meta-analysis based on a randomised controlled trial. *Front Neurol*, 15, 1360437. <https://doi.org/10.3389/fneur.2024.1360437>
- Xu, N., He, Y., Wei, Y. N., Bai, L., & Wang, L. (2025). Possible antidepressant mechanism of acupuncture: targeting neuroplasticity. *Front Neurosci*, 19, 1512073. <https://doi.org/10.3389/fnins.2025.1512073>
- Yan, L.-d., Zhou, P., Lai, M.-Q., Wu, M., Zhang, Y., Tang, R.-D., Sun, R., Luo, Y., Li, M., & Sun, J.-L. (2023). Effect of acupuncture combined with low frequency rTMS on comorbid mild-to-moderate depressive disorder and insomnia: a randomized controlled trial. In.
- Yang, D., Kang, M. K., Huang, G., Eggebrecht, A. T., & Hong, K. S. (2024). Repetitive Transcranial Alternating Current Stimulation to Improve Working Memory: An EEG-fNIRS Study. *IEEE Trans Neural Syst Rehabil Eng*, 32, 1257-1266. <https://doi.org/10.1109/tnsre.2024.3377138>
- Yang, N. N., Lin, L. L., Li, Y. J., Li, H. P., Cao, Y., Tan, C. X., Hao, X. W., Ma, S. M., Wang, L., & Liu, C. Z. (2022). Potential Mechanisms and Clinical Effectiveness of

- Acupuncture in Depression. *Curr Neuropsychopharmacol*, 20(4), 738-750.
<https://doi.org/10.2174/1570159X19666210609162809>
- Yang, Y., Chen, Y. K., & Xie, M. Z. (2024). Exploring the transformative impact of traditional Chinese medicine on depression: Insights from animal models. *World J Psychiatry*, 14(5), 607-623. <https://doi.org/10.5498/wjp.v14.i5.607>
- Yin, Z.-L., Ge, S., Huang, L.-H., Cao, X.-X., & Wu, J.-H. (2022). Acupuncture combined with repetitive transcranial magnetic stimulation for post-stroke depression: a randomized controlled trial. *Zhongguo zhen jiu= Chinese acupuncture & moxibustion*, 42(11), 1216-1220.
- Yip, A. G., George, M. S., Tendler, A., Roth, Y., Zangen, A., & Carpenter, L. L. (2017). 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. *Brain stimulation*, 10(4), 847-849.
- Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS One*, 5(11), e13766.
- Zaidi, A., Shami, R., Sewell, I. J., Cao, X., Giacobbe, P., Rabin, J. S., Goubran, M., Hamani, C., Swardfager, W., Davidson, B., Lipsman, N., & Nestor, S. M. (2024). Antidepressant class and concurrent rTMS outcomes in major depressive disorder: a systematic review and meta-analysis. *EClinicalMedicine*, 75, 102760.
<https://doi.org/10.1016/j.eclinm.2024.102760>
- Zanos, P., & Gould, T. (2018). Mechanisms of ketamine action as an antidepressant. *Molecular psychiatry*, 23(4), 801-811.
- Zhang, J. J., Bai, Z., & Fong, K. N. K. (2024). Methodological considerations of priming repetitive transcranial magnetic stimulation protocols in clinical populations. *Gen Psychiatry*, 37(1), e101237. <https://doi.org/10.1136/gpsych-2023-101237>
- Zhang, L., Yu, F., Hu, Q., Qiao, Y., Xuan, R., Ji, G., Zhu, C., Cai, C., & Wang, K. (2020). Effects of SSRI Antidepressants on Attentional Bias toward Emotional Scenes in First-Episode Depressive Patients: Evidence from an Eye-Tracking Study. *Psychiatry Investig*, 17(9), 871-879. <https://doi.org/10.30773/pi.2019.0345>
- Zhang, M., Wang, R., Luo, X., Zhang, S., Zhong, X., Ning, Y., & Zhang, B. (2021). Repetitive transcranial magnetic stimulation target location methods for depression. *Frontiers in Neuroscience*, 15, 695423.
- Zhang, T., Huang, Y., Jin, Y., Ma, X., & Liu, Z. (2021). Treatment for Major Depressive Disorder by Repetitive Transcranial Magnetic Stimulation in Different Parameters: A Randomized Double-Blinded Controlled Trial. *Front Psychiatry*, 12, 623765.
<https://doi.org/10.3389/fpsyt.2021.623765>
- Zhang, T., Zhang, J., Huang, J., Zheng, Z., & Wang, P. (2021). Neural Activation via Acupuncture in Patients With Major Depressive Disorder: A Functional Near-Infrared Spectroscopy Study. *Front Psychiatry*, 12, 669533.
<https://doi.org/10.3389/fpsyt.2021.669533>
- Zhang, Z., Zhang, H., Xie, C. M., Zhang, M., Shi, Y., Song, R., Lu, X., Zhang, H., Li, K., Wang, B., Yang, Y., Li, X., Zhu, J., Zhao, Y., Yuan, T. F., & Northoff, G. (2021). Task-related functional magnetic resonance imaging-based neuronavigation for the treatment of depression by individualized repetitive transcranial magnetic stimulation of the visual cortex. *Sci China Life Sci*, 64(1), 96-106. <https://doi.org/10.1007/s11427-020-1730-5>
- Zhou, D., Li, X., Wei, S., Yu, C., Wang, D., Li, Y., Li, J., Liu, J., Li, S., Zhuang, W., Li, Y., Luo, R., Liu, Z., Liu, J., Xu, Y., Fan, J., Zhu, G., Xu, W., Tang, Y., . . . Zhang, X. Y. (2024). Transcranial Direct Current Stimulation Combined With Repetitive Transcranial Magnetic Stimulation for Depression: A Randomized Clinical Trial.

JAMA Netw Open, 7(11), e2444306.

<https://doi.org/10.1001/jamanetworkopen.2024.44306>