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Accelerated TMS for Depression: A Systematic Review and Meta-Analysis

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Abstract

Repetitive transcranial magnetic stimulation (TMS) is now widely available for the clinical treatment of depression, but the associated financial and time burdens are problematic for patients. Accelerated TMS (aTMS) protocols address these burdens and attempt to increase the efficiency of standard TMS. This systematic review and meta-analysis aimed to examine accelerated TMS studies for depressive disorders in accordance with PRISMA guidelines. Inclusion criteria consisted of studies with full text publications available in English describing more than one session of TMS (repetitive or theta burst stimulation) per day. Studies describing accelerated TMS protocols for conditions other than depression or alternative neuromodulation methods, preclinical studies, and neurophysiology studies regarding transcranial stimulation were excluded. Eighteen articles describing eleven distinct studies (seven publications described overlapping samples) met eligibility criteria. A Hedges' *g* effect size and confidence intervals were calculated. The summary analysis of three suitable randomized control trials revealed a cumulative effect size of 0.39 (95% CI 0.005–0.779). A separate analysis including open-label trials and active arms of suitable RCTs revealed a *g* of 1.27 (95% CI 0.902–1.637). Overall, the meta-analysis suggested that aTMS improves depressive symptom severity. In general, study methodologies were acceptable, but future efforts could enhance sham techniques and blinding.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:

1. Search Strategy
2. Included Studies and Characteristics
3. Risk of Bias Assessment
4. Meta-Analysis
5. PRISMA Checklist

Registrations: https://www.crd.york.ac.uk/PROSPERO registration number is: CRD42018092258

Keywords

Accelerated TMS; Depression; Major Depressive Disorder; MDD; TMS; Treatment resistant depression; TRD

1. Introduction

Major depressive disorder (MDD) is a common and chronic condition, affecting more than 300 million people. It is a leading cause of disability worldwide and a major contributor to the overall global burden of disease (World Health Organization, 2018). MDD is also highly prevalent; in the U.S., approximately 10.4% of adults have suffered from MDD in the past 12 months, and 20.6% experience MDD in a lifetime (Hasin et al., 2018). In addition to poor quality of life, MDD is associated with increased mortality rates, with one of the most important causes being suicide (Mathew, 2008). Mortality due to suicide in depression is a major public health concern. Every year, more than 800,000 people die from suicide worldwide; this roughly corresponds to one death every 40 seconds (World Health Organization, 2014). Recent literature highlighted that U.S. suicide rates have increased by 30% since 1999 (Stone et al., 2018). Thus, the development of effective, accessible interventions for MDD is a high priority for improving public health.

First-line, evidence-based treatment options for MDD include psychopharmacology and psychotherapeutic approaches such as cognitive behavioral therapy. However, often depressive symptoms are refractory to these treatment options. Approximately 20–30% of patients continue to experience pervasive depressive symptoms despite adequate trials of medication and psychotherapy (Rush et al., 2006). Prior antidepressant resistance also decreases the likelihood of responding to subsequent interventions (Rush et al., 2006). Because of the high prevalence of treatment resistance and the challenges with conventional therapeutic options for MDD, effective second-line treatments are of paramount importance. Neuromodulation modalities such as electroconvulsive therapy and transcranial magnetic stimulation (TMS) are options for treatment-resistant depression.

Repetitive transcranial magnetic stimulation (rTMS) is an evidence-based treatment for MDD (Lefaucheur et al., 2014; McClintock et al., 2018). Typically, rTMS protocols for MDD deliver 10 Hz stimulation to the left dorsolateral prefrontal cortex (L-DLPFC) over 4–6 weeks in once-daily stimulation sessions. Patients typically receive four or more weeks of treatment for symptomatic improvement, and dosing is not personalized. Generally, for left, prefrontal, high-frequency (HF) rTMS, the response rates are 20–30% (Avery et al., 2008; George et al., 2010; O'Reardon et al., 2007). A meta-analysis also suggested that standard rTMS protocols involving HF-rTMS demonstrated numbers needed to treat of 8 and 6 to achieve clinical remission and clinical response, respectively (Berlim et al., 2014).

Novel dosing approaches have the prospect of optimizing the response and remission rates of TMS (De Raedt et al., 2015; Gross et al., 2007). Standard rTMS is also seldom useful in acutely suicidal patients because of the delayed time-to-response. The daily administration schedule over several weeks is another barrier limiting its feasibility for patients who work

full time or have transportation challenges. Hence, consolidating the treatment to a few days could increase the utility of TMS in both inpatient and intensive outpatient program settings.

Accelerated TMS (aTMS) protocols with both rTMS and theta burst stimulation (TBS) are increasingly under study to address the practical limitations of conventional daily rTMS for MDD. TBS is a newer form of rTMS which mimics endogenous hippocampal theta patterns (Huang et al., 2005), and may have comparable efficacy to standard rTMS in treating depression (Blumberger et al., 2018). The rationale for an accelerated approach is based on two major principles: first, the presumption that equal or greater effects are induced by the repeated application of stimulation within a short time interval; and second, that the effects induced within densely scheduled sessions have durable efficacy (Fitzgerald, 2013). In addition, accelerated response to treatment (within days) is a theoretical advantage of aTMS protocols. Previous neurophysiologic evidence suggests that a greater effect of rTMS on cortical excitability is achieved if a second rTMS session is provided within 24 hours of the first session (Maeda et al., 2000). Other research proposed a dose (number of stimuli) – response relationship for rTMS (George, 2010).

Although there is much interest in aTMS protocols for depression, little is known about the efficacy and tolerability. In view of this important knowledge gap, we aimed to systematically review existing studies of aTMS for depression. Systematic data on study designs, treatment protocols, efficacy, and tolerability would have utility for both clinical and research communities. We anticipated that existing aTMS studies would have variable treatment parameters, treatment schedules, study quality, and outcome data. A meta-analysis was performed to determine the cumulative effect size for the treatment of depression with L-DLPFC aTMS.

2. Methods

A systematic review of the literature on aTMS protocols in patients with depressive disorders was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). This systematic review was registered with PROSPERO (ID number: CRD42018092258).

2.1. Search strategy and selection criteria

Studies were identified by searching electronic databases and checking reference lists of articles. Experienced medical reference librarians developed and ran searches in the EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Ovid MEDLINE(R) Epub Ahead of Print In-Process & Other Non-Indexed Citations, Ovid MEDLINE 1946 to December 29, 2017, PsycINFO, SCOPUS, and Web of Science databases. The search strategies were peer-reviewed by another experienced librarian. No exclusion criteria, or limits to language or publication date, were applied to the initial search. The initial search was completed on December 29, 2017. The full search strategies are described in detail in the supplementary materials.

Studies that described more than one session of rTMS or TBS per day were included. Studies were not limited based on the age of participants. All trials were included for

qualitative analysis, and only sham-controlled, randomized control trials were further elaborated for primary quantitative analysis. A second, exploratory quantitative analysis included active arms of randomized trials as well as open-label studies. Studies describing accelerated TMS protocols for conditions other than depression or alternative neuromodulation methods (such as transcranial direct current stimulation, electroconvulsive therapy, deep brain stimulation, etc.), preclinical studies, and basic neurophysiology studies regarding transcranial stimulation were excluded. Articles were included only if the full text was available in English. Abstracts, case reports, reviews, and editorials were excluded.

2.2. Outcomes

The primary outcome of interest of this review and meta-analysis was the change in depression scale means between study baseline and end of treatment. Additional outcomes reported in trials were adverse effects, study withdrawal, response rates, changes in suicidal ideation, effects on neurocognitive function, changes in functional magnetic resonance imaging (MRI) scans (functional connectivity or hemodynamic activation), and metabolic changes in brain regions.

2.3. Data abstraction and analysis

Two independent reviewers (A.I.S., A.L.N.) assessed study eligibility by screening the titles and abstracts. Conflicts regarding study inclusion/exclusion were discussed among the two reviewers and a third author (P.E.C.) and were resolved by consensus. The authors reviewed full articles for studies that did not clearly specify the number of daily stimulation sessions. Full texts of potentially relevant studies were reviewed in detail by A.I.S and P.E.C. The initial agreement between reviewers for eligibility was good (kappa = 0.71). A data extraction spreadsheet was created based on the Cochrane Handbook for Systematic Reviews of Interventions and modified to fit the parameters of interest (Higgins and Green, 2011). A.I.S. extracted the following data from studies meeting inclusion criteria, and P.E.C. verified the extracted data. Disagreements were resolved by discussion between the two review authors (A.I.S. and P.E.C.). Extracted data included authors, publication year, country of study, study design, patient demographics, diagnostic assessment instruments, detailed stimulation parameters (frequency in Hz, stimulation intensity, total stimuli, pulses per session, sessions per day, intersession interval in minutes, trains per session, inter-train interval in seconds), and sham control procedures.

The primary outcome variable for all studies was defined as the change in depression severity scores between study baseline and end of treatment. For cross-over trials, only data from the initial randomization were used. Data that could not be directly retrieved from the original publications were requested from the authors. For the majority of included studies, depression severity was measured on the Hamilton Depression Rating Scale (HDRS), and thus change in HDRS scores comprised the primary outcome for these studies. If ratings for more than one scale were reported, change in HDRS scores were used as the outcome. For studies that did not use the HDRS, the change in another depressive symptoms scale (e.g., Quick Inventory of Depressive Symptomatology, Montgomery–Asberg Depression Scale) was used as the primary outcome measure.

Hedges' *g*, standardized mean difference (*d*) multiplied by a correction factor (J), was computed as an index of effect size for continuous outcome data because in this approach, the standard deviations are used to standardize the mean differences to a single scale (see Section 9.2.3.2, (Higgins and Green, 2011), as well as in the computation of study weights. Thus, it was possible to compare outcomes of change scores on different depression scales or different versions of the HDRS. For studies that did not give the mean difference with standard deviation between post-treatments and baseline scores, an estimate of standard deviation was calculated using pre- and post-treatment values and an estimate of the pre–post correlation coefficient for the HDRS. Detailed computations are provided in Supplementary Materials Section 4.

A Funnel plot was visually inspected to assess potential publication bias. Heterogeneity between studies was assessed with the total Q statistic, which estimates whether the variance of the effect sizes is greater than expected due to sampling error. A p value smaller than 0.01 provides indication of significant heterogeneity (Cochran, 1954). The I^2 statistic was performed for each analysis to indicate what percentage of the observed variance in effect sizes reflects real differences. I^2 values of 25%, 50%, and 75% represent little, moderate, and high heterogeneity, respectively (Higgins et al., 2003). In order to assess robustness of the results, sensitivity analysis was run with a variety of correlation estimates (ranging between 0.5 and 0.8) as suggested by Cochrane Handbook (see section 16.4.6.3, (Higgins and Green, 2011).

Analyses were conducted using Comprehensive Meta-Analysis (Borenstein et al., 2013), and IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for data processing.

To determine the risk of bias in eligible randomized controlled trials, authors (A.I.S. and P.E.C.) reviewed the adequacy of randomization, allocation concealment, blinding, and whether incomplete reporting of outcome data occurred. The Cochrane risk of bias tool was followed as a guideline (Higgins et al., 2011). A risk of bias figure was generated with RevMan software (2014).

3. Results

3.1. Overview

A total of 18 publications from 11 unique studies (6 randomized controlled trials and 5 open-label trials) met inclusion criteria (Fig. 1). Stimulation parameters and sample characteristics are summarized in Table 1 and Table 2, respectively. Ten publications meeting inclusion criteria were derived from shared samples; 4 from a larger rTMS study (Baeken et al., 2013; Baeken et al., 2014; Baeken et al., 2015; Baeken et al., 2017b), 4 from a larger intermittent TBS (iTBS) study (Baeken et al., 2017a; Desmyter et al., 2016; Duprat et al., 2016; Duprat et al., 2017), and 2 from an open-label rTMS study (McGirr et al., 2015; Tovar-Perdomo et al., 2017). Randomized controlled trials (RCTs) included a total of 301 unique patients. Amongst these, 197 were allocated to aTMS protocols. The five open-label studies involved a total of 65 unique patients. The results of our risk of bias assessment are presented in supplementary materials.

Five of the 6 RCTs and all 5 open-label trials reported changes in depression symptoms severity, and 2 RCTs reported changes in ratings of suicidal ideation.

3.2. Meta-analysis of aTMS vs sham on depressive symptom severity in RCTs

Data from included trials were analyzed if the aTMS and sham were applied to the L-DLPFC and if the primary outcome was depression severity. Three out of 6 randomized trials did not report the required data. These RCTs were excluded from the primary analysis due to using cTBS, having two active arms comparing aTMS over classical rTMS, and investigating anti-suicidal effects with suicidal patients, respectively (Chistyakov et al., 2015; Fitzgerald et al., 2018; George et al., 2014).

Of the remaining 3 studies, two provided the primary data. The calculated estimate of correlation between baseline and post-intervention HDRS scores was 0.64. In the studies that were analyzed, 105 participants received aTMS. Table 1 and Table 2 include details of population profiles and stimulation parameters of these studies.

In the 3 RCTs analyzed, a cumulative effect size of 0.39 (95% CI 0.005–0.779) was found. The average change in mean HDRS from before aTMS to after aTMS was 6.28 (±0.78 SE) for the active group and 3.63 (90% CI ±0.74 SE) for the sham group (Fig. 2). The group change for active aTMS was significantly greater than the group receiving sham ($p = 0.041$). The sensitivity analysis revealed that lower values will result in confidence intervals to involve zero.

The test for heterogeneity was not significant ($I^2 = 0.0\%$; $Q_2 = 0.043$, $p = 0.98$) supporting the rationale for computing a fixed effect model. As the trials of interest had substantial clinical and methodological diversity, a random effect model was also computed. The ensuing results with fixed and random effects were same (Higgins and Green, 2011; section 9.5.4).

3.3. Meta-analysis of aTMS effect on depressive symptom severity in all studies

An exploratory analysis was conducted with data from both the active arms of randomized trials and open-label studies to determine whether the intervention favored improvement or worsening of depressive symptom severity over the course of treatment. One open-label trial was excluded because the intervention was applied to the right DLPFC (Tor et al., 2016); the remaining 4 open-label studies were included. A continuous outcome analysis was conducted for paired groups with pre- and post-intervention values. One manuscript reported primary data of participants (Williams et al., 2018). An imputed estimate of correlation for HDRS scores was required for one study (Holtzheimer III et al., 2010). One study reported the mean difference with standard deviation (Dardenne et al., 2018). Authors kindly provided the required values with correlation for QIDS-C for one study (McGirr et al., 2015). Mean percentage reductions of depression rating scale scores in open-label trials ranged between 25% and 76%.

For the combined random effects analysis of active arms of the 4 RCTs and 4 open-label trials, the cumulative effect size was 1.27 (95% CI 0.902–1.637) (Fig. 3). The test for heterogeneity was significant as expected ($I^2 = 71.5\%$; $Q_2 = 24.59$, $p = 0.001$). Sensitivity

analyses were run using different values (ranging between 0.5–0.8) for the estimate of correlation. These values for a correlation coefficient were imputed from individual studies in the meta-analysis. Significance of the results did not change with differing correlation estimates.

A composite funnel plot was generated and is included in the supplementary materials (Supplementary Fig. 2). Caution is warranted in interpretation of the plot given the small number studies and heterogeneity of study designs. Tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Higgins and Green, 2011; see section 10.4.3.1).

3.4. Adverse events

No study included mortality or cost as an outcome. All studies that reported clinical efficacy data provided information on adverse events (AEs); however, only 5 studies provided quantitative data on AE frequency or incidence (Baeken et al., 2013; Dardenne et al., 2018; Fitzgerald et al., 2018; George et al., 2014; Loo et al., 2007). There were a total of 224 patients in these trials, and 122 adverse events were recorded. Amongst these, headache was the most frequent (52/224), followed by local discomfort (29/224), nausea (4/224) and dizziness (4/224). McGirr et al. (2015) revealed results of self-reported FIBSER (Frequency, Intensity, and Burden of Side Effects Ratings) ratings. Seven out of 27 patients reported side effects more than half of the time; 6 had moderate to severe side effects, while 5 experienced functional impairment (McGirr et al., 2015).

3.5. Tolerability

From the 366 unique patients in all trials (RCTs and open-label), 42 did not complete the stimulation protocols. Nine trials specified the number of drop outs due to AEs (Baeken et al., 2013; Dardenne et al., 2018; Duprat et al., 2016; Fitzgerald et al., 2018; George et al., 2014; Holtzheimer III et al., 2010; McGirr et al., 2015; Tor et al., 2016; Williams et al., 2018). Eight participants in 4 trials withdrew due to AEs (Duprat et al., 2016; Fitzgerald et al., 2018; George et al., 2014; Holtzheimer III et al., 2010).

3.6. Other Outcome Measures

3.6.1. Antidepressant response rates in RCTs—Accelerated TMS over left DLPFC was not associated with a statistically significantly higher rate of response compared to sham. The odds ratio of response was OR = 3.12 compared to sham (k = 3, 95% CI 0.98–9.97, p = 0.054) (Fig. 4).

3.6.2. aTMS vs standard rTMS—Fitzgerald and colleagues (2018) compared standard rTMS to an aTMS protocol. The mean reductions in depression severity in the standard and accelerated groups were 31% and 23%, respectively, at week 4. Remission rates favored aTMS, but this was not statistically significant. The standardized mean difference for aTMS over standard rTMS was 0.368 (95% CI −0.0006–0.7367) (Supplementary Fig. 3).

3.6.3. Anti-suicidal efficacy—Two studies examined suicidal ideation outcomes. George et al. (2014) reported a 26% and 28% mean change in the Beck Scale of Suicidal Ideation (SSI) in the sham and accelerated groups, respectively. Standardized mean difference (*d*) was 0.047 (95% CI −0.636–0.731) (Supplementary Fig. 4). Desmyter et al. (2016) demonstrated a significant decrease in SSI scores ($p < 0.05$) between baseline and at the end of the first treatment week, third treatment week, and 2 weeks after last session, which occurred in both active and sham stimulation groups.

3.6.4. Neurocognitive functioning—Four open-label trials and two RCTs examined neurocognitive functioning (Fitzgerald et al., 2018; Holtzheimer III et al., 2010; Loo et al., 2007; Tor et al., 2016; Tovar-Perdomo et al., 2017; Williams et al., 2018). None of the open-label trials showed a decline in cognitive functioning, including measures of attention, memory, executive function, decision making, or impulse control. One study showed significant improvement in the total score of a neurocognitive battery (RBANS, Repeatable Battery for the Assessment of Neuropsychological Status) at week 6 follow-up assessment (Holtzheimer III et al., 2010). There were no statistically significant differences in cognitive variables between standard and aTMS protocols at the end of treatments in one RCT (Fitzgerald et al., 2018). One RCT demonstrated significant improvement in the Trail Making Test A in the sham group and worsening in the active group (Loo et al., 2007).

3.6.5. Neuroimaging outcomes—Imaging outcomes were the primary measures in six reports. Modalities used were functional MRI (Baeken et al., 2014; Baeken et al., 2017a; Duprat et al., 2017; Williams et al., 2018), ^{18}FDG PET (Baeken et al., 2015), and ^{1}H MR spectroscopy (Baeken et al., 2017b). Changes in functional connectivity, metabolism in regions of interest, and neurochemical levels were examined in these reports. Results are summarized in Table 3.

4. Discussion

Open-label and randomized studies have examined aTMS for the treatment of depression. Initial findings suggest that accelerated approaches may have utility for addressing the practical limitations of standard TMS and optimizing the dosing of TMS. These existing studies serve a critical role in demonstrating the safety, feasibility, and tolerability of aTMS. However, the number of studies to date is small, and thus the results of this systematic review and meta-analysis must be interpreted with caution. The range of parameters in these protocols also complicates the comparison of studies. Further investigation may provide opportunities for precision medicine approaches to TMS with dosing interventions tailored to neurophysiology, clinical characteristics, and patient preferences. However, at present, definitive approaches to aTMS are lacking, and the existing literature has substantial limitations.

In eleven unique studies, aTMS sessions were administered at a frequency ranging between 2 and 10 sessions per day. Intersession interval varied from 12 minutes to 2 hours. The total stimuli delivered ranged between 15,000 and 90,000. This diversity of stimulation parameters should encourage further work, as most of the participants in the studies included in this review generally tolerated the treatments well. Overall, these aTMS trials were safe in

terms of adverse events. Suicidal ideation decreased over the course of treatment (Desmyter et al., 2016; George et al., 2014).

This meta-analysis provides preliminary support for aTMS reducing depressive symptoms and having a role in the treatment of depression. The cumulative effect size was significant, yet not particularly robust, most likely due to the relatively small sample sizes and low number of studies. Notably, there were no statistically significant differences in response rates between TMS and sham (OR 1.00 CI 95% CI 0.02 – 55.27) in a recent network meta-analysis (Brunoni et al., 2017).

Although aTMS may be an effective treatment for depression, a variety of parameters have been used with each protocol. The optimal TMS dosing strategy for aTMS is unknown. Additional research is required to assess whether the total stimuli, number of sessions per day, intersession intervals, or any other stimulation parameter is the most influential in generating clinical benefit. One example of a once-daily high dose rTMS trial was conducted by Hadley et al. (2011). In this open-label study, researchers provided a 2-week HF-rTMS protocol involving 6800 pulses/day in once-daily sessions (compared to approximately 3000 pulses/day in conventional HF-rTMS protocols) to 19 patients with treatment-resistant MDD. 33% of patients met criteria for clinical remission at the conclusion of the study (Hadley et al., 2011). Since the protocol consisted of once-daily sessions, this study was not included in this systematic review. However, the total stimuli delivered (68,000) in this study are within the range of studies included in this review.

Further detailed mechanistic work will be required to optimize aTMS for maximum safely, effectiveness and applicability. Trials incorporating neuroimaging procedures will yield insights on how manipulating these parameters affect neurophysiology and eventually clinical outcomes, as well as potentially identifying new stimulation targets. Several of the aTMS studies included in the current review have incorporated imaging outcomes.

Three (2 iTBS, 1 rTMS) out of 6 studies with neuroimaging outcomes reported functional connectivity (FC) patterns (Baeken et al., 2017a; Baeken et al., 2014; Williams et al., 2018). The accelerated protocol investigating rTMS showed that baseline anti-correlation in resting state FC in subgenual anterior cingulate cortex (sgACC) and parts of perigenual anterior cingulate (pgACC)/superior medial frontal gyrus was reversed in responders after aTMS treatment but not in non-responders, supporting previous work (Baeken et al., 2014; Hamilton et al., 2011). The stronger anti-correlation between the sgACC and parts of left prefrontal cortex at baseline could be a potential predictor in clinical outcomes of aTMS. Interestingly, the aforementioned area of prefrontal cortex did not include the DLPFC, which was the stimulation target, but rather parts of the left superior medial frontal gyrus located anterior to the DLPFC. This suggests that neural network effects extend beyond the cortical stimulation target and raises the possibility of new targets for treatment of depression. Functional connectivity of the L-DLPFC with different cortical locations was also investigated in iTBS trials. Williams et al. (2018) demonstrated an increased anti-correlation between functional subregions of the L-DLPFC and subcallosal cingulate (SCC) after 4 days of iTBS stimulation in 6 patients in an open-label design. Baeken et al. (2017a) found that sgACC-medial orbitofrontal cortex (mOFC) FC distinguished responders and non-

responders, increased in responders with treatment, and was associated with decreases in hopelessness. It remains to be determined whether classic or accelerated HF-rTMS and/or iTBS protocols applied to the left DLPFC produce similar or divergent neurophysiological effects in MDD patients (Baeken et al., 2017a; Baeken et al., 2015; Prasser et al., 2015; Salomons et al., 2013).

Results from PET imaging showed that aTMS responders displayed higher sgACC cerebral metabolic rate of glucose (CMRglc) at baseline compared to non-responders (Baeken et al., 2015). While responders showed a significant CMRglc decrease after the treatments, non-responders did not, and the percent of clinical improvement was positively correlated with the attenuation of sgACC CMRglc. This suggests that baseline metabolic activity may predict clinical outcomes of aTMS and may serve as an index of response. The observed sgACC CMRglc decreases with clinical response to aTMS were similar to previous standard rTMS trials (Baeken et al., 2015; Langguth et al., 2007; Kito et al., 2008; Takahashi et al., 2013) and other neuromodulatory interventions such as deep brain stimulation (DBS) and electroconvulsive therapy (ECT) (Mayberg, 2009). Notably, the aTMS effects related to sgACC CMRglc were evident after 4 days of stimulation as opposed to longer periods seen in prior brain stimulation treatment protocols.

Findings from the one spectroscopy analysis showed that treatment-resistant depression (TRD) patients had decreased glutamate+glutamine (Glx) and a trend to lower γ-aminobutyric acid (GABA) levels in the L-DLPFC compared to healthy controls (Baeken et al., 2017b). Prior research has identified reductions in glutamatergic metabolites in DLPFC and ACC in depressed individuals (Auer et al., 2000; Hasler et al., 2007; Rosenberg et al., 2005). GABA deficits in the ACC have been found previously in MDD patients (Gabbay et al., 2017). Clinical improvement has been associated with GABA concentration increases in the DLPFC, which was previously also shown in standard rTMS trials with healthy individuals and MDD patients (Vidal-Piñeiro et al., 2015). Baseline tNAA/tCr ratios, a measure of neural integrity, were not indicative of clinical response, nor were these concentrations affected by aTMS, in contrast to the findings of Zheng et al. (2015) with standard rTMS.

One week of accelerated iTBS over the left DLPFC in TRD patients differently modulates the reward system depending on anhedonia severity as shown via functional magnetic resonance imaging (Duprat et al., 2017). After active stimulation, low anhedonic patients had lower activity in the putamen, whereas high anhedonic patients had higher activity in bilateral putamen and caudate. There were no major baseline differences in right vs left hemisphere activity in both groups. However, less bilateral striatal activity was associated with higher anhedonia levels, in line with previous research (Epstein et al., 2006).

Common limitations to all of the studies included in this review were small sample size and limited statistical power. Another common concern was maintaining the integrity of blinding due to sham techniques. Also, there is the risk of carryover effect in crossover studies if real stimuli were delivered in the first phase, while on the other hand, delayed effects cannot be measured if real TMS was received in the second phase without a longer follow-up period. Baeken and colleagues (2013) also acknowledged the added risk of compromised blinding

due to single center environment where all raters were familiar with TMS protocols. Four RCTs (Chistyakov et al., 2015; Fitzgerald et al., 2018; George et al., 2014; Loo et al., 2007) allowed participants to continue their medication regimens during aTMS; this limits interpretation of efficacy data for applications of aTMS beyond the adjunctive treatment of medicated patients. Only one study (Fitzgerald et al., 2018) compared accelerated protocol to a standard daily rTMS protocol. However, patients were not blinded due to obvious challenges in masking single versus multiple sessions per day, and sham control was not incorporated in this study design. However, this study provides preliminary evidence comparing aTMS with standard techniques, and further studies with direct head-to-head comparison will be necessary to establish the therapeutic equivalence, or potentially superiority, of aTMS versus standard rTMS protocols.

While George et al. (2014) allowed continuing medication regimens, which may have affected the results, Desmyter et al. (2016) included only antidepressant-free participants, which in turn limits the interpretation and generalizability of results in real-life emergency room suicidal patients, who frequently must be maintained on pharmacologic treatments. In general, participants appeared to continue antidepressant medication regimens in all open-label studies (Dardenne et al., 2018; Holtzheimer III et al., 2010; McGirr et al., 2015; Tor et al., 2016; Tovar-Perdomo et al., 2017; Williams et al., 2018).

An additional limitation of the aTMS literature to date is the lack of follow-up assessment beyond the end of treatment (see Table 2). In the study with the longest follow-up period of six months (George et al., 2014), high dropout rate was a limiting factor in the interpretation of the longitudinal data. Among open-label studies, Holtzheimer III et al. (2010) assessed patients after end of treatment (at 6 weeks from baseline and a two-day aTMS protocol), and only 9 patients out of 14 completed follow-up assessments. Preliminary evidence from these studies indicates that improvement in symptoms continued to take place in follow-up assessments several weeks after the conclusion of accelerated rTMS (Holtzheimer III et al., 2010) and iTBS (Duprat et al., 2016), suggesting that clinical improvement may have delayed onset even after accelerated stimulation protocols. The lack of adequate follow-up assessments in the majority of aTMS studies to date has limited these studies' ability to detect possible therapeutic efficacy occurring beyond the end of treatment. Future studies of aTMS should consider regular follow-up assessments in the weeks after stimulation is completed. Additionally, there currently is little data on the factors impacting time-to-response, and future studies with robust longitudinal assessments will enable researchers to unravel the mechanisms that ultimately will lead to more rapidly-acting interventions.

Common limitations of open-label trials can be summarized as not having sham procedures, inability to assess placebo effect, frequently small sample sizes, and short or no follow-up assessments. To our knowledge, only one systematic review and meta-analysis to date has compared different types of TMS to sham (Brunoni et al., 2017). In their study, Brunoni and colleagues reported no significant difference of aTMS over sham. However, only one aTMS protocol (Baeken et al., 2013) was included in this analysis, and as more evidence on this topic accumulates, a new meta-analysis with a larger number of studies and patients will be required.

5. Conclusions

TMS is now widely available for the clinical treatment of depression. However, standard rTMS treatment protocols have limitations in efficacy and present pragmatic barriers for many patients. Novel and optimized dosing schedules may address these limitations and provide opportunities for precision medicine approaches for TMS delivery. Protocols with aTMS are one example, and existing preliminary work suggests that these compact treatment schedules are safe, tolerable, and feasible. Larger, systematic trials with enhanced blinding and sham delivery are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

DDC receives research grant support from the Mayo Foundation Departmental Small Grant Program. JLVV receives equipment in-kind support from Assurex Health, Inc. for an investigator-initiated study and is a site investigator for a multicenter study funded by Neuronetics, Inc. SK receives research support from the Mayo Clinic Department of Psychiatry and Psychology and equipment in-kind support from Assurex Health, Inc. and Neuronetics, Inc. He is a site investigator for a multicenter trial funded by NeoSync, Inc. and has received speaker support from Psychopharmacology Institute. CPL receives research grant support from the Mayo Foundation Departmental Small Grant Program and is a site investigator on multicenter studies funded by Neuronetics, Inc. and NeoSync, Inc. PEC has received research grant support from Pfizer, Inc., has received equipment support from Neuronetics, Inc.; and receives supplies and genotyping services from Assurex Health, Inc. for an investigator-initiated study. He is the primary investigator for a multicenter study funded by Neuronetics, Inc. and a site primary investigator for a study funded by NeoSync, Inc. AIS and ALN have no financial conflicts of interest.

Abbreviations

ACC	anterior cingulate cortex
AE	adverse event
aTMS	accelerated transcranial magnetic stimulation
CMRglc	cerebral metabolic rate of glucose or regional glucose metabolism
cTBS	continuous theta burst stimulation
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
ECT	electroconvulsive therapy
FC	functional connectivity

GABA	γ-aminobutyric acid
Glx	glutamate+glutamine
HDRS	Hamilton Depression Rating Scale
HF	high frequency
iTBS	intermittent heta burst stimulation
L-DLPFC	left dorsolateral prefrontal cortex
MDD	major depressive disorder
mOFC	medial orbitofrontal cortex
MRI	magnetic resonance imaging
NAA	*N*-acetylaspartate
PET	positron emission tomography
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
rTMS	repetitive transcranial magnetic stimulation
SCC	subcallosal cingulate
sgACC	subgenual anterior cingulate cortex
SSI	Beck's Scale for Suicide Ideation
TBS	theta burst stimulation
TENS	transcutaneous electrical nerve stimulation
TMS	transcranial magnetic stimulation
TRD	treatment-resistant depression

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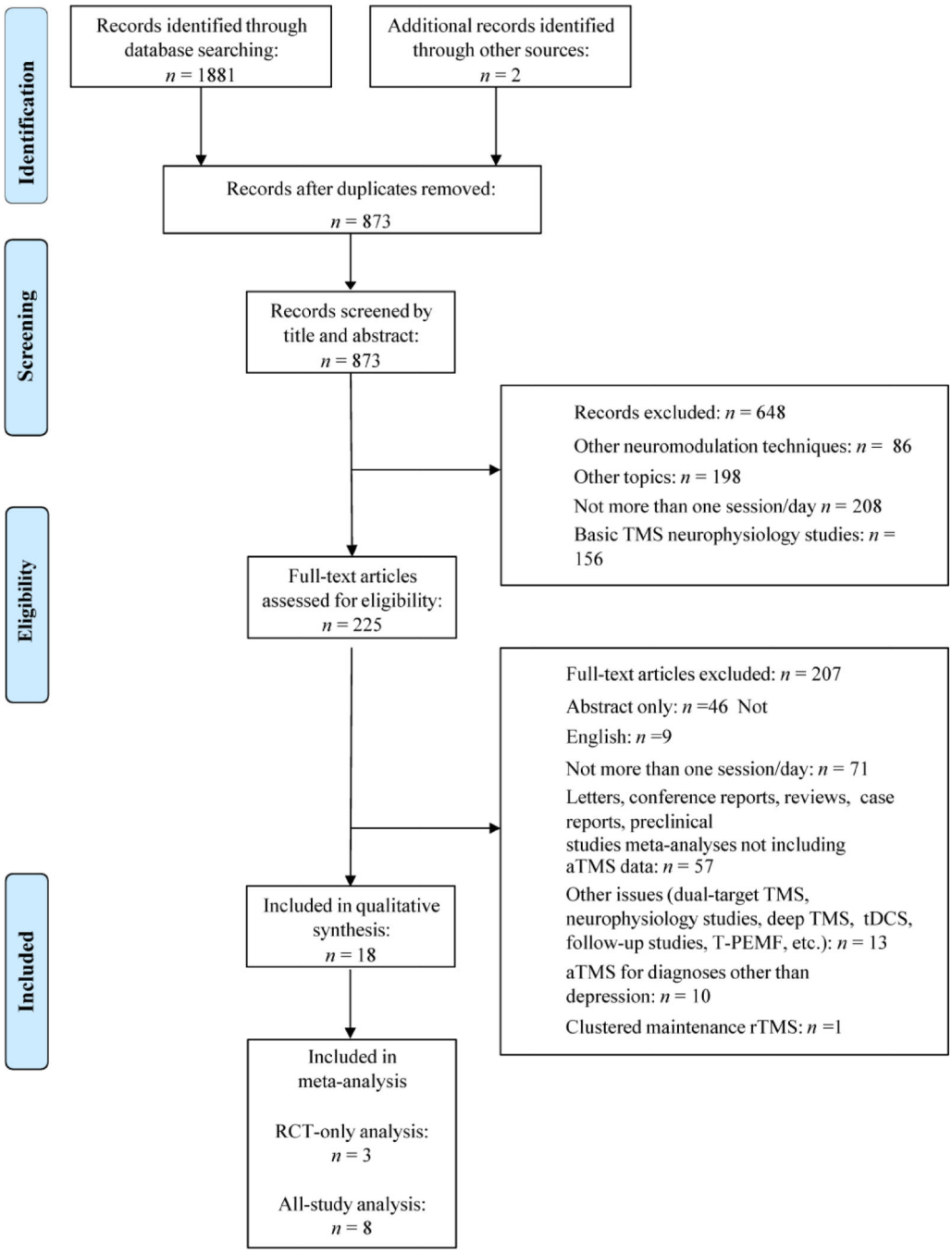

Fig. 1. PRISMA flow diagram.

Note: TMS= transcranial magnetic stimulation; aTMS = accelerated transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; T-PEMF = transcranial pulsating electromagnetic fields.

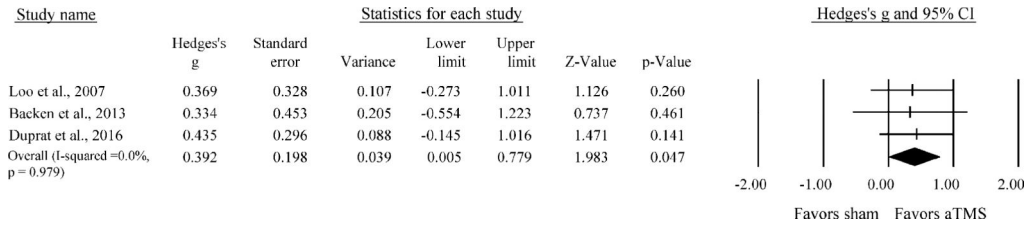

Fig. 2.
Forest plot of RCT-only meta-analysis

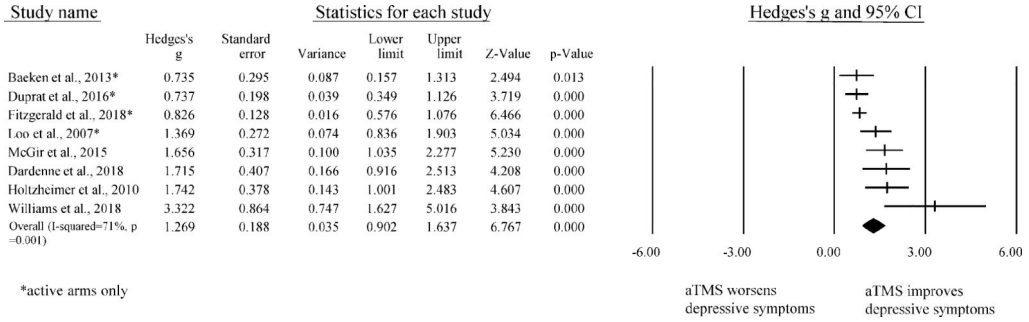

Fig. 3.
Forest plot of all study meta-analysis

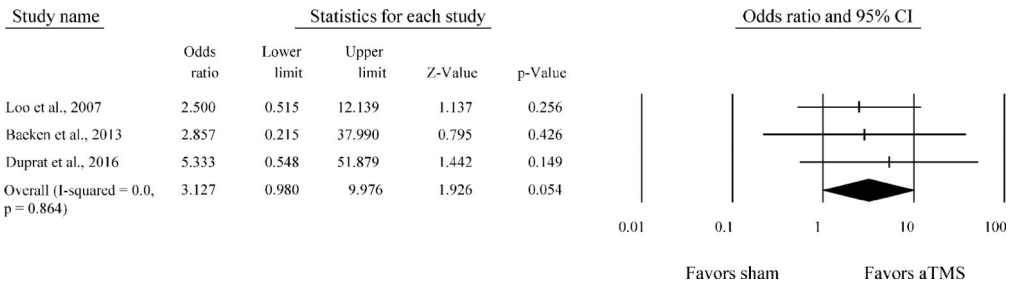

Fig. 4.
Forest plot of RCT response rates

Table 1

Summary of stimulation parameters and findings.

Author (year)	Type Site	Frequency Intensity	Total stimuli Total days Total	Stimuli/session Sessions/day Intersession	Trains/session Train length Intertrain	Outcome scale	Outcome	*d*
Loo et al. (2007)	rTMS L-DLPFC	10 Hz 110%	30000 10 20	1500 2 120 min	30 5 s 25 s	MADRS 17-HDRS	Active treatment resulted in statistically greater improvement at the end of two weeks. At the end of the blinded phase 23% of patients responded and 13% remitted.	0.38
Baeken et al. (2013)	rTMS L-DLPFC	20 Hz 110%	31200 4 20	1560 5 12 min	40 1.9 s 12 s	17-HDRS	No statistically significant difference between active and sham stimulation.	0.35
Duprat et al. (2016)[a]	iTBS L-DLPFC	See below [c] 110%	32400 4	1620 5 15 min	54 2 s 8 s	17-HDRS	No statistically significant difference between sham and active stimulation. Post-treatment response rate was 28%, remission rate was 15%. Two weeks after last session response rate was 38%, remission rate was 30%.	0.44
Desmyter et al. (2016)[a]	iTBS L-DLPFC	See below [c] 110%	32400 4 20	1620 5 15 min	54 2 s 8 s	SSI	A decrease in SSI without statistically significant difference between the active and sham treatment at week 4.	n/a
Chistyakov et al. (2015)	cTBS RDLPFC	See below [b] 100%	36000 10 10 72000 20 20	[i] 3600 1 - 3600 1 -	4 2 s 15 min 4 2 s 15 min	21-HDRS	There was no statistically significant difference in clinical improvement between active and sham group at the end of blinded phase.	0.44[d]
Fitzgerald et al. (2018)	rTMS L-DLPFC	10 Hz 120% 10 Hz 120%	63000 6 18 63000 20 20	3500 3 15 or 30 min 3150 1 -	83 4.2 s 15 s 75 4.2 25s	MADRS 17-HDRS	There was no statistically significant difference in response rates between accelerated and standard group. At week 4, response rates were 23.7 and 33.3% in accelerated and standard group. Remission rates were 15.3 and 12.3%. No overall difference in degree or pattern of response between groups was observed.	0.84[e] 0.37[f]
George et al. (2014)	rTMS L-DLPFC	10 Hz 120%	54000 3 9	6000 3 60 min	n/s 5 s 10 s	SSI	No statistically significant difference between real and sham stimulation.	0.05
Dardenne et al. (2018)	rTMS L-DLPFC	20 Hz 110%	31200 5 20	1560 4 n/s	39 2 s 12 s	17-HDRS	Mean reduction of scores were 47% after the last session. 40% of patients responded and 20% remitted.	1.87
Holtzheimer et al. (2010)	rTMS L-DLPFC	10 Hz 100%	15000 2 15	[ii] 1000 5/10 50 min	20 5 s 25 s	24-HDRS	Mean reduction of scores were 47% at day three. 42% of patients responded and 28% of patients remitted.	1.87
McGirr et al. (2015)	rTMS L-DLPFC	10 Hz 120%	60000 10 20	3000 2 60 min	75 n/s 26 s	QIDS-C-16	55% of patients were responders and 37% were in remission within the third week from baseline.	1.7
Tor et al. (2016)	rTMS R-DLPFC	1 Hz 120%	16200 10 18	[iii] 900 1/5/5/1 ×7 30 min	n/s n/s n/s	MADRS	No subject achieved response during the study. Mean reduction of scores 25% at the end of day ten.	n/a
Williams et al. (2018)	iTBS L-DLPFC	50 Hz 90%	90000 5 50	1800 10 50 min	n/s 2 s 8 s	MADRS 17-HDRS	Mean reduction of scores were 76% after the last session. 83% of patients responded and 66% remitted.	3.9

Note: rTMS = repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation; cTBS = continuous theta burst stimulation; L-DLPFC = left dorsolateral prefrontal cortex; R-DLPFC = right dorsolateral prefrontal cortex; HDRS = Hamilton Depression Rating Scale; SSI = Beck Scale for Suicide Ideation; MADRS = Montgomery–Åsberg Depression Scale; QIDS-C = Quick Inventory of Depressive Symptomatology; n/s = not stated; n/a = not available; the standardized mean differences (*d*) were calculated and then multiplied by a correction factor (J) to compute *g*.

[i] Participants received four trains of cTBS in one session with an inter-train interval of 15 minutes.

[ii] Participants received five sessions on day 1 and ten stimulations on day 2.

[iii] Participants received five sessions on day 2 and 3, and then continued to receive daily sessions for 7 days.

[a] Overlapping sample from Ghent University Hospital, Belgium, NCT01832805.

[b] Triple-pulse 50 Hz bursts given at a rate of 5 Hz; 200 ms between each burst in uninterrupted trains.

[c] 54 triplet bursts with train duration of 2 seconds, inter-train interval of 8 seconds; applied in a 50 Hz frequency, bursts repeated every 200 ms i.e. 1 iTBS session consisted of 54 trains of 10 bursts of 3 stimuli, 2 s of stimulation alternated by 8 s of rest period.

[d] Reported in the manuscript.

[e] Accelerated arm within group effect size was calculated.

[f] Across groups effect size was calculated.

Table 2.

Demographics and study design.

Author (year)	Population, Sample Size	Mean age (SD)	Study Design	Diagnosis Criteria/Method	Treatment Resistance	Medication Status	Washout Period	Mean Duration of Current Episode	Follow up	Country
Loo et al. (2007)	MDE, *n*=38	Sham 45.7 (15) Active 49.8 (2.5)	RCT - Parallel	DSM-IV	Stage I or lower	Psychotropic allowed	-	Sham (*n*=19) 10.4 months Active (*n*=19) 12.3 months	1 month	Australia
Baeken et al. (2013)	Unipolar TRD, *n*=21	49.33 (12.50)	RCT - Cross over	MINI (DSM-IV)	Stage III, *n*=14 Stage IV, *n*=1 Stage V, *n*=5	Benzodiaz epine only	+	7.83 years	-	Belgium
Duprat et al. (2016)[a]	Unipolar TRD, *n*=47	41.72 (11.80)	RCT - Cross over	MINI (DSM-IV)	Stage I, *n*=9 Stage II, *n*=24 Stage III, *n*=14	Benzodiaz epine only	+	3.87 years	2 weeks	Belgium
Desmyter et al. (2016)[a]	Unipolar TRD, *n*=32	41.9 (11.77)	RCT - Cross over	MINI (DSM-IV)	Stage I or higher	Benzodiaz epine only	+	n/s	2 weeks	Belgium
Chistyakov et al. (2015)	Unipolar, *n*=19 Bipolar, *n*=10	51.8 (14.2)	RCT - Cross over	DSM-IV criteria, consensus of two psychiatrists	n/s	Psychotro pic allowed	-	12.6 months	-	Israel
Fitzgerald et al. (2018)	Accelerated Unipolar, *n*=49 Bipolar, *n*=8 Standard Unipolar, *n*=47 Bipolar, *n*=8	Accelerated 48.2 (14.4) Standard 49.9 (13.3)	RCT - Parallel	MINI (DSM-IV)	Stage II	Psychotro pic allowed	-	Accelerated (*n*=58) 10 years Standard (*n*=60) 8.2 years	4 or 5 weeks	Canada
George et al. (2014)	MDE, *n*=41 with mTBI, *n*=1 PTSD, *n*=17 PTSD+ mTBI, *n*=23	42.5 (15.7)	RCT - Parallel	DSM-IV	n/s	Psychotro pic - allowed	-	n/s	6 months	USA
Dardenne et al. (2018)	MDD, *n*=10	73.9 (5.7)	Open-label	MINI (DSM-IV)	n/s	Psychotro pic - allowed	-	n/s	-	Belgium
Holtzheimer et al. (2010)	MDE *n*=13 Bipolar *n*=1	49 (15.5)[a]	Open-label	SCID (DSM-IV)	n/s	Psychotro pic - allowed	-	29 months[iii]	6 weeks	USA
McGirr et al. (2015)	MDE, *n*=27 PTSD, *n*=10 OCD, *n*=6	47.68 (11.42)	Open-label	MINI (DSM-IV)	n/s	Psychotro pic - allowed	-	46.43 months	-	Canada
Tor et al. (2016)	MDD, *n*=3 Bipolar, *n*=4	36 (range 23–53)	Open-label	MINI (DSM-IV)	n/s	Psychotro pic - allowed	-	17 months	-	Singapore
Williams et al. (2018)	MDD, *n*=4 Bipolar, *n*=1 OCD, *n*=1	56 (12.1)	Open-label	SCID (DSM-5)	Stage V	Psychotro pic - allowed	-	14.8 years	4 weeks	USA

Note: *n* = sample size; TRD = treatment-resistant depression; SD = standard deviation; RCT = randomized controlled trial; MINI = Mini-International Neuropsychiatric Interview; DSM = Diagnostic and Statistical Manual of Mental Disorders; n/s = not stated; MDE = major depressive episode; mTBI = mild traumatic brain injury; PTSD = post-traumatic stress disorder; MDD = major depressive disorder; SCID = Structured Clinical Interview for DSM Diagnoses.

The study by Loo et al. (2007) consisted of 10 days (2 weeks) of twice daily real or sham stimulation. A second phase of this study offered 4 weeks of open label once daily rTMS. Fitzgerald et al. (2018) compared a 3 week long accelerated protocol with a 4-week-long standard rTMS protocol. The protocol by Tor et al. (2016) consisted of 10 days of stimulation in which the subjects received 5 sessions per day only on the second and third days. In the trial by Holtzheimer et al. (2010), participants received 5 sessions on the first day and 10 sessions on the second.

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Table 3

Summary of imaging studies.

Study	Imaging Modality	*n*	Outcomes	Stimulation Parameters[i]
Baeken et al. 2015[a]	^{18}FDG PET	15[d]	Clinical responders compared to non-responders displayed higher sgACC CMRglc at baseline.In responders, the sgACC CMRglc significantly decreased between T0 and T2.Percentage of clinical improvement positively correlated with the attenuation of sgACC CMRglc.	rTMS (20 Hz), left DLPFC, 110%, 1560 stimuli/session, 5 sessions/day, 32–36 (15–20) min, 4 days, 20 total sessions, 31200 total stimuli.
Baeken et al. 2014[a]	fMRI	20[e]	HF-rTMS responders showed significantly greater resting-state functional connectivity anti-correlation between sgACC and parts of the left superior medial prefrontal cortex.After successful treatment an inverted relative strength of the anti-correlations was observed in the perigenual prefrontal cortex.No effects on sgACC rsFC were observed in non-responders.	rTMS (20 Hz), left DLPFC, 110%, 1560 stimuli/session, 5 sessions/day, 32–36 (15–20) min, 4 days, 20 total sessions, 31200 total stimuli.
Baeken et al. 2017[a]	^{1}H MR spectroscopy	18	Compared to healthy individuals, TRD patients displayed significantly lower baseline glutamatergic (sum of the absolute concentrations of glutamate and glutamine) concentrations in the left DLPFC.aTMS did not significantly alter neurochemical concentrations in the ACC, left DLPFC or right DLPFC.Clinical improvement was associated in increased GABA in the left DLPFC.	rTMS (20 Hz), left DLPFC, 110%, 1560 stimuli/session, 5 sessions/day, 32–36 (15–20) min, 4 days, 20 total sessions, 31200 total stimuli.
Duprat et al. 2017[a]	fMRI	50[f]	At baseline, low anhedonic patients displayed higher neural activity in caudate and putamen. After the first week of aiTBS, a decreased neural activity within reward system was found in contrast to the increased activity observed high anhedonic patients.After active stimulation, low anhedonic patients had lower activity in the putamen, whereas high anhedonic patients had higher activity in bilateral putamen and caudate.No differences in reward related regions after first week of sham.	iTBS; left DLPFC, 110%, 1620 stimuli/session, 5 sessions/day, 5 (15) min, 4 days, 20 total sessions, 32400 total stimuli.
Baeken et al. 2017[a]	fMRI	50[g]	A positive sgACC FC correlation with the medial orbitofrontal cortex could distinguish aiTBS responders from nonresponders at baseline.Beneficial aiTBS treatment strengthened sgACC-medial orbitofrontal cortex FC patterns.Increased FC pattern was associated with a decrease in feelings of hopelessness.	iTBS; left DLPFC, 110%, 1620 stimuli/session, 5 sessions/day, 5 (15) min, 4 days, 20 total sessions, 32400 total stimuli.
Williams et al. 2018	fMRI	6	5 of 6 participants demonstrated and increased magnitude in anti-correlation between the functional subregions of the L-DLPFC and SCC.Individual participants FC maps displayed increased anti-correlations after iTBS in many SCC voxels.	iTBS; left DLPFC, 90%, 1800 stimuli/session, 10 sessions/day, 10 (50) min, 5 days, 50 total sessions, 90000 total stimuli.

Note: *n* = sample size; rTMS = repetitive transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation; sgACC = subgenual anterior cingulate cortex; CMRglc = regional glucose metabolism; fMRI = functional MRI; H^1MR spectroscopy = proton magnetic resonance spectroscopy; rsFC = resting state functional connectivity; TRD = treatment-resistant depression; aTMS = accelerated TMS; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; SCC = subcallosal cingulate.

[i] Type of TMS (frequency in Hz), stimulation site, stimulation intensity as % of motor threshold, stimuli per session, number of sessions/day, session length (intersession interval) in min, total days of stimulation, total number of sessions, total number of stimuli.

[a] Overlapping sample from Ghent University Hospital, Belgium.

[b] Overlapping sample from Ghent University Hospital, Belgium, NCT01832805.

[c] 3-pulse 50-Hz bursts at 5 Hz for 2-s trains with trains every 10 s i.e. 54 triplet bursts with train duration of 2 s and 8 s cycling period (inter-train interval).

[d] 14 patients were analyzed.

[e] 12 patients received the scan.

[f] 37 patients had complete scans.

[g] 44patients had complete scans.