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Identification of clinical features and biomarkers that may inform a personalized approach to rTMS for depression

Sarah L. Garnaat, Andrew M. Fukuda, Shiwen Yuan, Linda L. Carpenter*

Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, 345 Blackstone Blvd., Providence, RI 02906, USA
Butler Hospital, 345 Blackstone Blvd., Providence, RI 02906, USA

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS), an established treatment for treatment-resistant depression, may hold promise as a personalized medicine approach for the treatment of major depressive disorder (MDD). Clinical research has begun to identify patient-specific factors that could be used to guide rTMS treatment decisions or individualized treatment approaches. This literature review describes a range of patient factors which have been evaluated as potential biomarkers of rTMS treatment response, including patient- and illness-related characteristics, genetic factors, and biomarkers derived from neuroimaging and EEG. We highlight the need for validation data for imaging and electrophysiological biomarkers associated with rTMS as well as prospective evaluation of clinical predictors. Finally, we consider implications for future efforts to move toward a personalized medicine approach in the treatment of depression with rTMS.

1. Introduction

One promising area of research aimed at personalizing psychiatric interventions surrounds the delivery of repetitive transcranial magnetic stimulation (rTMS) therapy for depression. rTMS has increasingly been utilized as an intervention for treatment-resistant major depressive disorder (MDD) since the first device with this indication was cleared by the FDA in 2008. There are now seven FDA-cleared rTMS devices for depression, and rTMS is available to patients with depression in numerous clinics worldwide. Neuronal depolarization and induced currents in cortical tissues are produced through application of pulsed magnetic fields discharged from a treatment coil placed on the patient's head which delivers stimulation to a targeted brain region while the patient is awake and alert. Treatment protocols using rTMS have evolved over time, but standard protocols using a figure-8 shaped coil involve rTMS at high-frequency (10 Hz) primarily to the left dorsolateral prefrontal cortex (DLPFC), at low-frequency (1 Hz) to the right DLPFC, or bilaterally using both high- and low-frequency protocols sequentially. A distinct family of rTMS devices uses various "H-coils" that are larger and have complex windings to allow stimulation of a broader and possibly deeper area of cortical tissue; for depression these devices stimulate left > right DLPFC regions at 18 Hz (e.g., [1]). Acute treatment with rTMS for depression is typically comprised of a series of once-daily sessions over 4–6 weeks.

rTMS therapy for depression developed, in part, out of a need for alternative treatment approaches, particularly given the significant number of patients with depression do not respond adequately to (or cannot tolerate) standard antidepressant pharmacotherapy. A number of large randomized clinical trials (RCTs) have offered support for the efficacy of rTMS for treatment-resistant depression [1–3]. However, these studies, as well as naturalistic investigations, suggest that only about a quarter to half of patients experience a significant response to rTMS with standard "on-label" protocols, with naturalistic studies often showing higher response rates than RCTs. Such outcomes may be considered good for a population of depressed individuals who have already failed to benefit from multiple prior treatments, but there remains significant interest in understanding how to optimize the application of rTMS for each patient in order to get more patients into remission and to provide more efficient symptom relief.

Presumably, achieving a better match of rTMS treatment approaches with patient-specific symptoms and patterns of neural activity would produce the best outcomes on both individual and population levels. Selection of the specific patient characteristics or symptom features most strongly associated with response to a given rTMS protocol (based on available clinical outcome data from rTMS trials) represents the most readily available opportunity for personalizing this approach. Imaging and EEG data from rTMS depression trials have begun to suggest specific connectivity and oscillatory features that align with the

* Corresponding author at: c/o Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906, USA.
E-mail address: linda_carpenter_md@brown.edu (L.L. Carpenter).

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best outcomes to standard rTMS therapy for depression. Emerging data suggest that novel and potentially individually-customized delivery of rTMS might involve variations in the quality of the magnetic stimuli applied, variations in the targeted cortical region or circuit to be stimulated, variations in the "dose" of stimulation applied to achieve different effects on cortical activity, or concurrent administration of cognitive training, psychotherapy, or other directed neural activity in combination with stimulation to achieve additive or synergistic effects. Looking toward the personalization of rTMS therapy, we review select findings regarding clinical, genetic, neurobiological, and neuroimaging variables and their relation to rTMS treatment response, closing with a discussion of how these factors may inform a personalized medicine approach.

2. Demographic and clinical characteristics

Data informing identification of clinical and demographic factors related to rTMS clinical response have largely arisen from post-hoc analyses of efficacy trials of rTMS in which depression was treated with standard "on label" parameters, as well as meta-analyses focused on identification of predictors of treatment response. In the majority of cases, stimulation was delivered with a figure-8 shaped coil over the left dorsolateral prefrontal cortex (DLPFC) for unipolar major depressive episodes. Given the large variability in specific predictors examined across the literature, an exhaustive review is not presented here, but rather, we focus on some of the more commonly investigated clinical and demographic factors which may be most likely to inform a personalized medicine approach (see Table 1). These include patient factors such as age and illness characteristics such as symptom severity, duration of the current depressive episode, level of medication resistance, and specific symptom presentations.

Refractoriness of depressive episode appears to be one of the best supported predictors of rTMS response. A number of studies have suggested that a higher degree of medication resistance may be tied to worse rTMS outcomes in depression [4–6], including Lisanby et al. [7], who found that in patients with MDD receiving active rTMS (10 Hz to left DLPFC), those who had undergone multiple adequate antidepressant trials during the current episode without benefit fared worse than patients who had only one failed medication trial within the current episode. In contrast, Levkovitz et al. [1] did not find a difference in symptom improvement for patients with high- vs. low-resistance to medication; however, significantly more responders were classified as having the low medication resistance, suggesting that degree of medication resistance may indeed be of some predictive value. While the relationship between treatment resistance and rTMS outcome was not observed in a large naturalistically-treated sample (n = 307) [8] or in a meta-analysis of 29 randomized clinical trials (RCTs) (n = 1371) [9], the majority of findings from rTMS response predictor studies suggest that lower degree of pharmacoresistance is one of the more robust predictors of superior outcomes for rTMS therapy using standard stimulation parameters and targeting methods (e.g., [4–7]). Inconsistent findings may be due in part to inconsistent definitions of medication resistance, as some studies have classified failure of 2 medication trials as "medication resistant" (e.g., [8]) whereas in other studies this was considered "not resistant" (e.g., [1]). While definitive prospective studies are still needed, existing literature seems to support use of standard rTMS therapy relatively early in the course of treatment before a number of medication treatment failures have occurred.

Duration of depressive episode has also been frequently investigated as a predictor of treatment outcome in rTMS. A number of studies have explored whether shorter duration of current depressive episode may be associated with better rTMS outcome [4,7,10]. Overall, findings suggest that trying rTMS earlier in a depressive episode, rather than waiting longer, may be associated with better rTMS treatment outcome. However, limitations to these findings include small samples sizes, frequent dichotomization of time in episode (which may mask important relationships between episode duration and response), and large variability in approaches used to define duration variables for analyses. Additional work is needed to clarify whether and how chronicity of depressive episodes ultimately can contribute to individualized treatment decisions.

A range of symptoms and depressive subtypes have been investigated as candidate predictors of rTMS treatment outcomes, though a consistent signal has not emerged from this line of inquiry. In an analysis pooling data from six independent clinical trials of high-frequency rTMS to left DLPFC (n = 195) [5], none of the symptom-specific factors investigated (depression severity and individual Hamilton Depression Rating Scale item scores at baseline) was found to be a significant and unique predictor of response. Other work has found mixed results with regard to specific depressive symptoms. For example, some studies have found a relationship between both higher levels of sleep disturbance [4] and psychomotor retardation [6] with better outcomes with high-frequency rTMS to left DLPFC, while other studies find no such relationship [4,6]. Beyond investigations of specific symptoms, examination of baseline scores on standardized scales has largely failed to support a link between depression severity and treatment response [7,11]. This suggests that a personalized approach to rTMS would not necessarily exclude more severely ill patients, though additional studies are needed to more firmly establish the relationship of depressive symptom type and severity to rTMS response. At present, existing data do not appear to support illness-related characteristics as useful factors in directing rTMS treatment planning decisions, but efforts are underway to identify symptom endophenotypes relevant to rTMS therapy based on brain connectivity patterns, as described in detail below [12,13].

Patient age has been of much interest within the rTMS treatment literature and investigations into the relationship between age and rTMS efficacy have largely produced mixed results. A number of rTMS studies have found support for the notion that rTMS may be less effective for depression in older individuals (e.g., [5,14–16]), while others have not found age to be a significant predictor of rTMS outcomes (e.g., [6,7,17,18]). At least one group has found the relationship between age and rTMS outcome to be curvilinear [19]. Greater cortical atrophy has been linked to diminished response to rTMS [20] and strategies have been described to compensate for distance between scalp and cortex in older depressed patients (e.g., [21]). A recent RCT (n = 52) evaluated efficacy of 18 Hz rTMS administered with an H-coil device specifically among individuals with late-life depression (age 60 and older), using a sham-controlled design [22]. Outcomes were superior for active stimulation, with response rates consistent with those seen in studies with younger samples. In sum, available data do not currently suggest age of a depressed patient is a factor that should be used to guide rTMS treatment decisions, and more data are needed to determine whether it is necessary to adopt a customized approach which involves adjusting the stimulus intensity upward to compensate for greater scalp-to-cortex distance in older patients with frontal cortex atrophy.

3. Genetic predictors

A small number of studies have investigated possible genetic factors which may predict rTMS treatment outcome for depression. One (n = 19) found a seeming overrepresentation of patients who were Val/Val homozygotes on the brain-derived neurotrophic factor (BDNF) gene among responders to two weeks of low-frequency rTMS plus partial sleep deprivation, [23], though the Val/Val group treatment response did not statistically differ from other patients. Bocchio-Chiavetto et al. [24] (n = 36) also reported BDNF Val/Val homozygotes had better treatment response to either 1- or 17-Hz rTMS to left DLPFC. They also found LL homozygotes of the serotonin transporter-linked polymorphic region (5-HTTLPR) fared better. C/C genotype of the serotonin 1A receptor (5-HT1A) polymorphism has also been identified as potentially

Table 1
Studies examining demographic and clinical features as correlates and predictors of rTMS outcome.

Study	Study design	Sample (N)	rTMS parameters	Candidate predictor variables	Findings
Berlim, 2014 [9]	Systematic review and meta-analysis	RCTs (29, with data from n = 1371 subjects)	All studies included HF rTMS over left DLPFC Specific parameters varied by site.	Primary diagnosis (i.e., studies with unipolar vs. mixed uni- and bipolar samples); Use of rTMS as monotherapy vs. augmentation; degree of medication resistance (< vs. ≥2 failed antidepressant trials)	rTMS efficacy was not found to differ as a function of baseline medication resistance, rTMS monotherapy vs. augmentation, or primary diagnosis.
Brakemeier, 2007 [4]	Open trial	MDD (n = 62) or Bipolar II (n = 8)	Left DLPFC, 20 Hz, 100% MT; 10 sessions over 2 weeks	Depression severity (HAM-D, BDI); HAM-D factors: psychic depression, loss of motivated behavior, psychosis, anxiety, and sleep disturbances; CORE assessment of psychomotor disturbance; duration of current episode (< vs. ≥ 5 months), medication resistance (y/n), prior antidepressant treatments in the current episode (#)	At baseline, responders had shorter episode duration, fewer total antidepressant trials, lower agitation, greater psychomotor retardation, and lower anxiety (HAM-D), relative to non-responders. A smaller proportion of responders were classified as having medication resistance than non-responders. In a multivariable logistic regression, shorter duration of current depressive episode, fewer previous treatment trials, and greater sleep disturbance at baseline were significant predictors of responder status.
Brakemeier, 2008 [6]	Open trial (2 sites)	MDD (n = 75) or Bipolar II (n = 4)	Site 1: Left DLPFC, 10 Hz, 1500 pulses per session, 100% MT; Site 2: Left DLPFC, 20 Hz, 2000 pulses per session, 100% MT Average of 12.04 ± 2.42 sessions	Depression severity (HAM-D); HAM-D factors: psychic depression, loss of motivated behavior, psychosis, anxiety, and sleep disturbances; HAM-D subscales: psychomotor retardation and agitation; duration of current episode (< vs. ≥5 months), medication resistance (y/n), prior antidepressant treatments in the current episode (#)	At baseline, a greater proportion of responders had episode duration less than 5 months and fewer responders were classified as medication-resistant. Predictive models fit in Brakemeier et al., 2007 and Fregni et al., 2006 could not be replicated. An exploratory regression model found that lower medication resistance, depressed mood, guilt, and greater psychomotor retardation at baseline predicted greater symptom reduction.
Carpenter, 2012 [8]	Naturalistic study	MDD (n = 307)	rTMS delivered over left prefrontal cortex; Specific parameters varied by site.	Baseline depression severity, medication resistance (< vs. ≥2 failed antidepressant trials), presence of comorbid anxiety disorder (y/n), gender, age (≤ vs. > 55 years), prior psychiatric hospitalization for depression (y/n)	Lower baseline severity and younger age corresponded to greater treatment benefit. Greater medication resistance was not a predictor of treatment outcome.
Ciobanu, 2013 [17]	Naturalistic	MDD (n = 93)	Left prefrontal cortex, 10 Hz, 2000 pulses per session, 90% MT (n = 13) or right prefrontal cortex, 1 Hz, 1200 pulses per session, 90% MT (n = 80); 15 sessions over 3 weeks	Age (< vs. ≥65 years)	Older age was not associated with degree of change in depressive symptoms.
Conelea, 2017 [18]	Naturalistic	MDD (n = 231)	Left DLPFC, 5 or 10 Hz, 3000 pulses per session, 120% MT; Number of sessions varied	Age (< vs. ≥60 years)	Age group did not significantly predict depression severity at post-treatment, responder status, or remission status.
Figiel, 1998 [14]	Open trial	MDD (n = 53) or bipolar (n = 3)	Left prefrontal cortex, 10 Hz, 500 pulses per session, 110% MT; 5 sessions over 1 weeks	Age, gender, baseline depression severity, mental status	Responders were younger and had less severe depression at baseline, relative to non-responders.
Fregni, 2006 [5]	Data pooled from 1 open trial and 5 RCTs	MDD (n = 195)	Left DLPFC, high-frequency rTMS; 10 sessions over 2 weeks; Specific parameters differed by site	Age, gender, study site, baseline HAM-D (item and total scores), duration of depression, treatment refractoriness, medication use (y/n), change in HAM-D at post-treatment, rTMS frequency, number of pulses, and rTMS intensity	Younger age and lower treatment refractoriness were found to predict both greater change in depression severity and responder status.
Holtzheimer, 2004 [10]	Randomized, controlled trial, blinded, with optional open label crossover	MDD (n = 15)	Left DLPFC, 10 Hz, 1600 pulses per session, 100% MT; 10 sessions over 2 weeks	Duration of depressive episode (≤4 years vs. ≥ 10 years), number of previous antidepressant trials (< vs. ≥ 7)	Combining data from those randomized to active rTMS and those who crossed over to active rTMS following sham, it was found that participants with shorter episode duration had a greater reduction in symptom severity. There was no significant difference in % symptom change based on number of previous antidepressant trials.
Kaster, 2018 [22]	Randomized, controlled trial, double blinded		Deep rTMS over bilateral dorsolateral and ventrolateral prefrontal cortex, 18 Hz, 6012	N/A	Deep TMS was associated with significantly higher rates of remission in late life depression, relative to

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Table 1 (*continued*)

Study	Study design	Sample (N)	rTMS parameters	Candidate predictor variables	Findings
		Older adults (60–85 years) with MDD (n = 52)	pulses, 120% MT; 20 sessions over 4 weeks		sham. Remission rates observed appear similar to those reported in younger samples.
Levkovitz, 2015 [1]	Randomized, controlled, double-blinded	MDD diagnosis, N_{ITT} = 212, N_{PP} − 181	Prefrontal cortex, 18-Hz, 1980 pulses per session, 120% MT; 20 sessions over 4 weeks (followed by 12 weeks of biweekly session)	Medication resistance (failed 1 or 2 vs. 3+ medication trials in the current episode)	Average slopes of depression severity during the acute treatment phase (HAM-D, baseline to week 5,) were significantly different between active and sham groups for those with lower medication resistance. These slopes were not significantly different between active and sham groups with greater medication resistance. Similarly, rates of remission at week 5 in the low medication resistance group were significantly higher in the active (vs. sham) condition; there was not a significant difference in remission rates in the high medication resistance group.
Lisanby, 2009* [7]	Randomized, controlled trial, blinded	MDD (n = 301)	Left DLPFC, 10 Hz, 3000 pulses per session, 120% MT; 20 sessions over 4 weeks	Age, gender, current episode duration, comorbid anxiety disorder, course of illness, medication resistance, employment status, atypical depression, depression severity (MADRS), baseline MT	Within the active TMS arm, shorter duration of current episode and lower medication resistance predicted greater change in depression severity. In the open-label extension, absence of a comorbid anxiety disorder, lower medication resistance, and greater baseline symptom severity predicted better outcome in patients moving from sham to active rTMS.
Mosimann, 2004 [15]	Randomized, controlled trial, blinded	Older (age 40–90) patients with TRD (n = 24)	Left DLPFC, 20 Hz, 1600 pulses, 100% MT; 10 sessions over 2 weeks	Age, duration of current depressive episode	Change in depression severity did not correlate with age or current episode duration. No significant differences in antidepressant effects were found between the active and sham conditions.
Rostami, 2017 [16]	Naturalistic	Unipolar (n = 102) or bipolar (n = 146) depression	Participants received either: • Right DLPFC, 1 Hz, 2000 pulses per session, 120% MT (n = 161), • Left DLPFC, 10 Hz, 3750 pulses per session, 110% MT (n = 14), • Bilateral stimulation (n = 71); 20 sessions (3 sessions per week)	Age, gender, marital status, education level, and individual BDI-II items	No relation was observed between depression type (i.e., unipolar vs. bipolar) and response. Age was the only demographic variable found to significantly predict responder status. Significant clinical predictors of responder status included loss of interest, fatigue, past failure, agitation, pessimism, and irritability. Sadness, appetite problems, and indecisiveness were unique predictors of response in the bipolar subsample and worthlessness and sleep problems were unique predictors of response in unipolar depression.

BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; HF = high-frequency; MADRS = Montgomery-Asberg Depression Rating Scale; RCT = Randomized Controlled Trial; TMS = transcranial magnetic stimulation; TRD = treatment resistant depression; ITT = Intent to Treat; PP = Per Protocol

* Significance based on an a priori alpha level of 0.10.

predictive of response to high frequency rTMS in two studies (n = 99 [25] and n = 90 [26]).

4. Motor cortex excitability

The question of whether properties of motor cortex excitability may relate to rTMS response has also garnered some interest. While baseline motor threshold has not been found to be related to treatment response [7], recent work by Oliviera-Maia and colleagues [19] has suggested a potential relationship between modulation of motor cortex excitability prior to rTMS treatment and outcome with DLPFC stimulation. This finding (n = 51) must be considered preliminary due to the small sample size, as well as and the small number of motor evoked potentials used to assess excitability. Standard or "normal" reference values have not been established for this type of measure, but the study highlights an example of an easily measured and potentially useful marker of brain plasticity which could be evaluated in individual patients before or during a course of rTMS treatments.

5. Brain imaging correlates and predictors of outcome

The field's increasing appreciation of the basic neurophysiological effects of different rTMS parameters (such as pulse frequency), coupled with advancing methods for identifying specific imaging endophenotypes or circuit abnormalities at an individual patient-level, create tremendous potential for customizing rTMS therapy in the future. A necessary first step toward the development of this approach is observing how the depressed brain changes following treatment with rTMS and identifying specific changes which correspond to resolution of symptoms. An increasing number of clinical studies have recently incorporated brain imaging at baseline, with some also capturing data again at treatment endpoint, to better understand rTMS mechanisms of action and to identify resting state metabolic or connectivity predictors of response. Identification of such biomarkers relies on an ever-evolving understanding of the neurobiological underpinnings of MDD, along with efforts to understand how stimulation impacts the brain, as well as the changes in the brain that correspond with resolution of symptoms. Metabolic and functional imaging advances have provided a critical platform for exploration of biomarkers predictive of treatment response. A broad range of methods and study designs have used neuroimaging to investigate rTMS for depression (for example, see reviews by Silverstein et al. [27] and Philip et al. [27,28]); here we focus on main response predictor findings and how this work can be used to inform personalized rTMS approaches (see Table 2).

Activity in a number of brain regions implicated in depression has been reported to correspond to positive response to left-sided high-frequency rTMS. Early positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) studies found increased regional cerebral blood flow (rCBF; a proxy for regional neuronal activity) in prefrontal and limbic regions following a course of rTMS (e.g., [29,30]). Recent work has also highlighted potential importance of baseline and treatment-emergent activity in orbitofrontal cortex (OFC) and anterior cingulate (ACC; particularly, subgenual ACC; sgACC) activity. For example, Paillere Martinot et al. [31] found that at baseline, rTMS non-responders, (compared to responders,) had lower resting glucose metabolism on FDG-PET in left OFC and higher resting glucose in amygdala (n = 31). During a word generating task used to probe frontal circuitry, Hernandez-Ribas and colleagues [32] found smaller baseline functional magnetic resonance imaging (fMRI) deactivations in right perigenual ACC, left medial OFC, and left middle frontal gyrus correlated with reduced depression severity following a subsequent high-frequency rTMS intervention, as did greater activations in left putamen. Baeken et al. identified higher glucose metabolism in DLPFC, ACC [33] and sgACC [34] were related to better clinical response to both standard and accelerated high-frequency rTMS, respectively (with stimulation delivered to left DLPFC in all cases; n = 36 across both studies). Moreover, the latter of these studies showed that clinical response corresponded to reduced activity in sgACC following a course of rTMS therapy [34], a finding consistent with implications of a central role of sgACC in depression treatment response, more broadly.

Beyond regional activity markers, subgenual ACC resting state functional connectivity has also been investigated as a potential correlate and predictor of rTMS treatment response. Liston et al. [35] examined the relation of rTMS response to intra- and inter-network functioning (n = 17) and found that baseline hyperconnectivity of sgACC with both default mode and central executive networks at baseline independently predicted superior clinical outcomes. Moreover, rTMS treatment was associated with reductions in sgACC hyperconnectivity with default mode network. Fox and colleagues (n = 13) have suggested that stronger anti-correlations (negative connectivity) between DLPFC and sgACC at baseline may be related to better outcomes with high-frequency rTMS [36]. This notion has received some degree of preliminary support. For example, Baeken et al. (n = 20) [37] found that responders to accelerated high-frequency rTMS had a greater degree of anticorrelation between prefrontal areas (particularly Brodmann Area 10) and sgACC than did non-responders. Moreover, following the rTMS intervention, responders showed increases in functional connectivity between sgACC and prefrontal areas. This line of research has informed efforts to develop practical approaches to individualized rTMS targeting based on sgACC connectivity [38], (though methods for fMRI scanning and connectivity metrics are not widely standardized).

Even when rTMS is not delivered over a standard DLPFC target, sgACC connectivity has been implicated as a predictor of response, including in rTMS targeting dorsomedial prefrontal cortex (dmFPC). Salomons et al. [39] reported that in patients (n = 25) receiving 10 Hz rTMS over dmPFC, several baseline predictors related to positive outcome, including greater connectivity of dmPFC to sgACC, greater connectivity of sgACC to DLPFC, as well as lesser cortico-thalamic, cortico-striatal, and cortico-limbic connectivity. In addition, treatment response was associated with decreased connectivity between sgACC and caudate, as well as increased connectivity between dmPFC and thalamus. This work offers preliminary support for the notion that sgACC connectivity may be a corollary of successful resolution of depressive symptoms following rTMS that is not specific to stimulation site.

While both high-frequency rTMS to the left hemisphere and slow-frequency rTMS to the right hemisphere have shown efficacy for depression, these approaches may be associated with some distinct, as well as some overlapping potential biomarkers. Low frequency stimulation to the right side has been found to elicit reduced rCBF in the right prefrontal cortex, as well as left mediotemporal cortex, basal ganglia, and amygdala (n = 10) [30]. Superior outcomes with 1-Hz rTMS have been tied to greater rCBF at baseline in left prefrontal regions, OFC, sgACC, insula and limbic regions (n = 14) [40]. In a separate study, Kito et al., [41] found that response to 1-Hz rTMS was associated more broadly with pre-treatment rCBF in dorsal medial prefrontal areas, including ACC and OFC, but not in dorsolateral areas (n = 26). Following treatment with right-sided slow frequency rTMS, group-level decreases in rCBF have been observed in prefrontal regions, OFC, insula, and sgACC [40,42] as well as in left parietal cortex [40], globus pallidus, thalamus, and midbrain [42]. Improvement in depressive symptoms was similarly found to be related to decreased rCBF in right prefrontal cortex, OFC, right sgACC, as well as right putamen and insula [42]. Thus, regional activity and changes in sgACC, as well as in OFC and limbic regions, show some consistency in correlating with response to high- and low-frequency rTMS.

Equally valuable for personalizing rTMS therapy may be findings that predict *nonresponse* to standard rTMS. Baseline hyperconnectivity between the posterior cingulate and insula was found by Taylor and colleagues to predict nonresponse to standard 10-Hz rTMS in (n = 40) patients with MDD [43]. An additional study found that inertness in sgACC connectivity throughout treatment was a signature among non-

Table 2
Studies examining neuroimaging findings as correlates and predictors of rTMS outcome.

Study	Study design	Sample (N)	Imaging methods	Timing of scan	rTMS parameters	Findings
Baeken et al., 2009 [33]	Open-label	Melancholic MDD (n = 21)	PET, glucose metabolism (CMRglc)	Baseline, post-treatment	Left DLPFC, 10 Hz, 1560 pulses per session, 110% MT; 10 sessions in total	Successful rTMS treatment was not related to changes in CMRglc in DLPFC or ACC. However, responders did show increases in CMRglc in Brodmann areas 32 (bilaterally) and 24 (right) from baseline to post-treatment. Non-responders did not show similar increases. Greater baseline left side activity in DLPFC and ACC predicted better response. Relative to non-responders, responders had a higher level of baseline left-to-right lateralization in ACC.
Baeken et al., 2014 [37]	Randomized, sham-controlled, crossover	MDD (n = 20)	RSFC	Baseline, post-treatment	Left DLPFC, 20 Hz, 1560 pulses per session, 110% MT; 20 sessions over 4 days per condition	Negative connectivity between sgACC and left superior frontal gyrus was reduced in responders, following rTMS; sgACC connectivity did not significantly change in non-responders. Stronger baseline (negative) connectivity between sgACC and left superior medial PFC corresponded to better clinical outcome.
Baeken et al., 2015 [34]	Sham-controlled, crossover	Melancholic MDD (n = 15)	PET, glucose metabolism (CMRglc)	Baseline, 1 week, post-treatment	Left DLPFC, 20 Hz, 110% MT, 1560 pulses per session; 20 sessions over 4 days	At baseline, responders were found to have higher baseline sgACC CMRglc than non-responders. A significant decrease in sgACC CMRglc over the full two weeks was found for responders, but not for non-responders. Overall, degree of symptom improvement corresponded to decreased activity in sgACC.
Hernandez-Ribas et al., 2013 [32]	Randomized, sham-controlled trial	MDD (n = 21)	fMRI	Baseline only	Left DLPFC, 15 Hz, 1500 pulses per session, 100% MT; 15 sessions over 3 weeks	Greater symptom reduction over the course of rTMS corresponded to smaller task-related deactivations in ACC, left medial OFC, and right middle frontal gyrus at baseline, as well as larger activation in left ventral-caudal putamen.
Kito et al., 2008 [40]	Open-label	MDD (n = 14)	SPECT, rCBF	Baseline, post-treatment	Right DLPFC, 1 Hz, 300 pulses per session, 100% MT; 12 sessions over 3 weeks	Following rTMS, decreases in rCBF were noted in bilateral prefrontal, OFC, anterior insula, left ACC, right sgACC and left parietal cortex. No increases in rCBF were detected following rTMS. At baseline, responders had greater rCBF in prefrontal and limbic/paralimbic regions, including left prefrontal cortex, OFC, sgACC, anterior insula, parahippocampus and amygdala, and inferior parietal regions, relative to non-responders.
Kito et al., 2011 [42]	Open-label	MDD (n = 26)	SPECT, rCBF	Baseline, post-treatment	Right DLPFC, 1 Hz, 300 pulses per session, 100% MT; 12 sessions over 3 weeks	Following rTMS, decreased rCBF was found in PFC, OFC, sgACC, basal ganglia, thalamus, insula, and midbrain. Improvement in depression was correlated with reduced rCBF in right premotor and prefrontal cortex, OFC bilaterally, sgACC, right putamen, and right anterior insula. No increases in rCBF were detected after rTMS and no increases in rCBF correlated with degree of treatment response.
Kito et al., 2012 [41]	Open-label	MDD (n = 26)	SPECT, rCBF	Baseline only	Right DLPFC, 1 Hz, 300 pulses per session, 100% MT; 12 sessions over 3 weeks	Higher VMPFC rCBF before rTMS treatment predicted better treatment outcome.

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Table 2 (*continued*)

Study	Study design	Sample (N)	Imaging methods	Timing of scan	rTMS parameters	Findings
Liston et al., 2014 [35]	Open-label	MDD (n = 14); Bipolar Depression (n = 3)	RSFC	Baseline, post-treatment	Left DLPFC, 10 Hz, 3000 pulses per session, 80–120% MT; 25 sessions over 5 weeks	Prior to treatment, depressed patients showed hyperconnectivty within DMN and hypoconnectivity within CEN, relative to healthy controls. Following rTMS, no changes in connectivity were observed in CEN and hyperconnectivity in DMN was reduced. Following rTMS, depressed patients showed decreased hyperconnectivity of sgACC within DMN, as well as greater reductions in DLPFC-to-DMN (vmPFC, PCC) connectivity. Baseline connectivity of DLPFC with CEN or DMN did not predict treatment response. Greater baseline connectivity between sgACC and nodes of both DMN and ECN connectivity corresponded to better treatment outcomes.
Martinot et al., 2011 [31]	Analyzed data from active condition of a double-blind randomized, controlled trial	MDD (n = 31); HC (n = 39)	PET, resting-state cerebral glucose uptake index (gluMI)	Baseline only	Left DLPFC, 10 Hz, 1600 pulses per session, 90% MT, for a total of 10 sessions	In non-responders vs. responders, baseline gluMI was lower in left lateral OFC (though this was partially explained by reduced gray matter) and higher in left amygdala and UF. In responders, OFC and amygdala gluMI were positively correlated, where these were negatively correlated in non-responders.
Salomons et al., 2014 [39]	Open-label	MDD (n = 21); Bipolar (n = 4)	RSFC	Baseline, post-treatment	DMPFC, 10 Hz, 3000 pulses per session, 120% MT; 20 total sessions	Higher baseline connectivity between inferior DMPFC and sgACC/VMPFC was associated with better treatment response as was lower baseline connectivity between inferior DMPFC and right putamen, right thalamus, and right hippocampus/amygdala. Higher baseline connectivity between sgACC and DLPFC was also related to better clinical outcomes, as was lower baseline connectivity between sgACC and insula, putamen, and parahippocampus/amygdala. Better treatment responses were associated with reduced DMPFC connectivity with insula and parahippocampus/amygdala over the course of rTMS, and decreased connectivity of sgACC with both ventral striatum and a portion of DMPFC.
Speer et al., 2000 [30]	Double-blind, sham-controlled, crossover	Unipolar depression (n = 8); Bipolar depression (n = 2)	PET, rCBF	Baseline; 72 h after 10 daily treatments with 20 Hz rTMS and 10 daily treatments with 1 Hz rTMS given in a randomized order	Left DLPFC, 1 Hz or 20 Hz, 1600 pulses per session, 100% MT, 10 daily sessions of each frequency then crossover (order randomized).	Following 20 Hz rTMS, increased rCBF in prefrontal, limbic, and paralimbic regions was noted. In contrast, 1 Hz resulted in decreased blood flow in smaller areas, including right prefrontal cortex and left medial temporal cortex, amygdala, and basal ganglia. Individuals whose mood improved with one frequency of rTMS generally worsened with the other. No correlation was found between clinical improvement and change in rCBF for either rTMS protocol.

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Table 2 (*continued*)

Study	Study design	Sample (N)	Imaging methods	Timing of scan	rTMS parameters	Findings
Taylor et al., 2018 [43]	Sham-controlled, double-blinded, randomized trial	MDD (n = 32)	RSFC	Baseline, post-treatment	Left DLPFC, 10 Hz, 3000 pulses per session, 120% MT; total 20 sessions over 4 weeks	For significant responders, including those responding to both sham and active rTMS, sgACC connectivity to DMN, FPN, and AN was decreased over the treatment period. sgACC connectivity to inferior parietal lobule and left OFC were also decreased in responders. There was no significant effect of active rTMS vs sham on connectivity. Including participants who responded to open-label rTMS following the blinded trial, lower baseline connectivity of PCC with anterior insula and right inferior frontal gyrus was found for responders vs. non-responders.
Teneback et al., 1999 [29]	RCT, double-blind (5 Hz, 20H, or sham)	MDD (n = 22)	Resting SPECT	Baseline, post-treatment	Left DLPFC, 5 Hz or 20 Hz, 100% MT, total of 10 sessions	At baseline, responders showed greater activity in inferior frontal regions compared to nonresponders and this difference increased at post-treatment. Changes in rCBF in the limbic system corresponded to improved mood over the course of the rTMS treatment.

AN = affective network; CEN = central executive network; DLPFC = dorsolateral prefrontal cortex; DMN = Default mode network; DMPFC = dorsomedial prefrontal cortex; FPN = frontoparietal network; MAOI = monoamine oxidase inhibitors; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; rCBF = regional cerebral blood flow; RSFC = resting-state functional connectivity; sgACC = Subgenual anterior cingulate cortex; SPECT = single photon emission computed tomography; TMS = transcranial magnetic stimulation; UF = uncinate fasciculus; VMPFC = ventromedial prefrontal cortex.

responders to high-frequency rTMS treatment [37]. Such information might preclude the investment of time and resources into futile treatment attempts for patients unlikely to benefit from a given intervention approach.

Multiple limiting factors confound accurate interpretation of findings across these studies, particularly in terms of treatment parameters, imaging modalities, small sample sizes, and variation in analytical approaches. Replication and prospective examination of findings in future studies will be critical. At present, direct clinical implementation of these predictive biomarkers is not feasible or practical; nevertheless, with accumulating evidence, brain regions like sgACC are beginning to stand out critical hubs of depression pathology that appear relevant to rTMS treatment mechanisms. Recently, a novel concurrent TMS-fMRI method was developed by Vink et al. [44] for recording direct effects of TMS on the brain. TMS pulses delivered to the DLPFC were shown to propagate to the sgACC. Though replication and extension of this work is clearly needed, propagation activity was proposed as another potential biomarker for rTMS efficacy.

6. EEG correlates and predictors of outcome

Electroencephalogram (EEG) represents another promising tool for informing a personalized medicine approach to rTMS treatment due to its non-invasive nature, relative ease of clinical application, and lower cost compared to other neuroimaging methods (see Table 3). EEG captures differences in oscillatory brain signals between different regions of the brain across time via superficial electrodes on the scalp. Quantitative EEG analyses utilizes mathematical transformations of EEG signals to objectively analyze EEG data in numerical format (as opposed to qualitative characterization of EEG waveforms).

Much of the EEG biomarker identification work has focused on differentiating responders from non-responders to rTMS treatment. One of the earlier studies attempting to differentiate responders from non-responders using resting state EEG (rsEEG) retrospectively identified several pretreatment variables in depressed rTMS patients (n = 90) which distinguished these groups [45]. Specifically, responders were distinguished from nonresponders by the following EEG metrics: higher (anterior) peak individual alpha frequency (IAF) values, lower power in the fronto-central theta frequency band, smaller P300 amplitudes at Pz during task, and increased prefrontal delta and beta cordance values. As these preliminary data were promising, a replication of the original study was undertaken to confirm the findings. Interestingly, in the replication study (n = 106), no significant differences were found between responders and non-responders in IAF, frontal theta, nor P300 amplitude, even after controlling for gender or age [46]. The stability of IAF over time and its relationship to rTMS outcome was also investigated by Petrosino and colleagues [47] in a sample of patients with PTSD and MDD (n = 35); IAF did not change significantly over the course of treatment, and pre-treatment IAF was not found to correlate with rTMS clinical outcome. Recently, a retrospective analysis of IAF values in relationship to the pulse frequency used for rTMS treatment sessions was undertaken with data from 2 naturalistically treated clinic samples [48]; results suggested there may be a subset of patients for whom the link between IAF and outcome is salient.

While IAF has not consistently emerged as a reliable indicator of rTMS outcome, rTMS pulse delivery customized to the unique IAF of individual patients with MDD has shown promising therapeutic results in several pilot studies [49,50]. This approach is theoretically based on the thalamocortical dysrhythmia model of depression [51], and hypothesizes that part of the therapeutic mechanism of action for rTMS rests on its ability to recalibrate the pathological oscillatory pattern to normal non-pathologic physiologic state [52]. If subsequent prospective, controlled studies provide support for this approach, IAF may eventually be developed as a marker for customizing rTMS parameters to optimize outcomes.

Beyond investigations of IAF, work is still underway to investigate

cordance, theta power and theta connectivity EEG markers of rTMS response. Cordance is a product of several algorithms involving absolute and relative theta powers and has been shown to correlate well with cerebral perfusion and metabolism via paired fMRI and EEG studies [53]. Though cordance was found to differ significantly between responders and non-responders in the original study by Arns et al. [45] it was not examined in the group's subsequent validation/replication study [46]. Other work has found that early cordance changes (e.g., after one week of daily rTMS sessions) may be a successful predictor of treatment response to rTMS administered to prefrontal regions [54,55]. In addition, work investigating the relation of resting state [56], EEG to treatment-outcome in treatment-resistant depression patients (n = 50) and healthy control participants (n = 21; assessed at a single timepoint, only) has demonstrated higher resting state theta connectivity in responders compared to non-responders at baseline and week 1 of rTMS treatment. These findings provide a preliminary suggestion that theta-derived metrics may represent a promising predictor of treatment response.

Several novel analytic approaches to EEG data have been put forth as potentially promising strategies for identifying predictive biomarkers of rTMS treatment response. Permutation entropy is a non-linear measure which aims to quantify the complexity, or the irregularity, of a given system and has been hypothesized to have higher predictive power for rTMS treatment response than other linear methods (such as frequency-based analysis,) due to the complex non-linear characteristics of cerebral functions and neural processes [57]. Shalbaf et al. [57] found that, within 7 days of initiating a course of rTMS (n = 62), treatment responders had a significantly higher entropy value compared to non-responders, particularly in prefrontal regions. Results also showed superior treatment response prediction by blinded raters using the permutation entropy metric, compared to traditional frequency band measures.

Cumulative brain engagement index (cBEI) is a novel EEG marker derived from attention-associated event related potentials using template matching. A study by Isserles and colleagues [58] utilizing an existing dataset (n = 180 patients who generated 2700 EEG sampling sessions) found significant group difference in two channel-derived cBEI after the first few rTMS treatments between depressed patients who eventually responded and those who did not. The authors postulate, based on these findings, that withdrawing those patients with cBEI below a certain threshold at the earlier sessions could have eliminated most of the remaining ineffective treatments. It should be noted that this preliminary study included a large sample rejection rate due to excessive noise and replication of findings will be crucial. However, given the large number of data points recorded by EEG, this approach and other data driven methods have proven to be powerful tools for response prediction (e.g., [48,59]).

Overall, while there are a number of promising EEG metrics associated with positive rTMS treatment outcomes in depressed patients, currently there is insufficient data for deployment of any of them in a standard clinical setting. Indeed, results of a recent meta-analysis underscore the fact that there is presently insufficient evidence to recommend use of EEG for guiding rTMS or other psychiatric treatment decisions at the present time [60]. As noted by the authors, several factors characterizing the currently published body of EEG biomarker studies may contribute, including under-publication of negative results, lack of out of sample validation, and insufficient direct replication of previous findings. Continued efforts to identify and validate predictive and treatment-emergent EEG-based biomarkers of rTMS outcome are needed to evaluate whether such approaches may ultimately hold promise for future clinical application.

7. Conclusions & opportunities for a personalized-medicine approach to rTMS therapy

By its nature, rTMS therapy for depression has significant potential to be individually customized. Adjustments could be made to treatment protocol parameters, including pulse frequency, magnetic field intensity, length of consecutive pulse "trains", total number of pulses per session, total number of sessions, etc. rTMS could be combined with other concurrent brain activation or deactivation techniques. New methods could be developed and implemented focused on precision targeting of specific brain regions or circuits beyond the DLPFC. Directing the stimulation to functionally-defined target(s) on an individual-patient level based on brain imaging or neurophysiological data represents another opportunity for a personalized medicine approach to rTMS. Despite the potential for personalization, a significant gap still exists between the identification of patient-specific factors associated with outcome and the ability to create an individualized treatment approach.

Researchers' attempts to identify meaningful predictors and correlates of rTMS antidepressant effects have varied widely in scope and method. Arguably, the greatest amount of exploratory work for this purpose has been possible with clinical trial data, where patient clinical and demographic characteristics are routinely ascertained at baseline. Indeed, identification of such easily identifiable factors would have great practical utility and allow easy identification of patients who may represent "optimal" responders. However, readily discernable clinical and disease characteristics have generally not emerged as helpful predictors of rTMS outcomes thus far. Across studies, only level of medication resistance has emerged as a semi-consistently supported correlate of rTMS outcomes. Genetics studies to date have not generated replicable, robust signals. In the longer-term, it is possible that more sophisticated measures of brain plasticity, akin to motor cortex excitability, will be developed and recognized as viable markers for guiding some treatment decisions.

Efforts to identify meaningful predictors of treatment response have faced a number of challenges and limitations. One such limitation is inconsistency in the way in which variables or metrics are defined or computed across investigations. This is particularly apparent within the work to identify clinical predictors of treatment outcome, where some studies dichotomize continuous variables, (e.g., age, episode length) while these same variables are treated as continuous in other studies. Such discrepancies are not unique to research surrounding rTMS or depression, though such differences in methodology may obscure important relationships between candidate predictors and outcome variables. Another limitation relates to heterogeneity of samples across studies and inherent heterogeneity within the diagnostic category of major depressive disorder. Not only do rTMS trials frequently differ in inclusion and exclusion criteria, treatment parameters, and TMS devices used, but the heterogeneity of depressive symptom subtypes and neuropsychiatric comorbidities is tremendous, particularly in naturalistically treated samples. It is possible that predictors of rTMS outcome will vary by diagnosis or symptom subphenotypes, as suggested by Rostami et al. [16], and thus may not be detected in highly heterogeneous samples. An additional limitation of this work is the relative dearth of prospective studies that have been conducted aiming to test candidate predictors of rTMS response. Not unexpectedly, the majority of studies examining potential predictors of rTMS response have been performed retrospectively as secondary or exploratory investigations.

One particular challenge in furthering a personalized medicine approach to rTMS depression treatment (and to personalized medicine approaches more broadly) is that traditional statistical methods used to identify predictors of treatment outcome have relied heavily on obtaining large samples of patients (of which a small percent are treatment responders) in order to test numerous potential predictors at the group level. Studies such as these require large amounts of time and significant resources to conduct, yet still allow for testing of only a very limited number of potential predictors within each study. Moreover, the results of these studies do not necessarily provide information that can be used to inform treatment decisions on an individual patient level.

Consideration of alternative methodologies, including data driven

Table 3
Studies examining EEG metrics as correlates and predictors of rTMS outcomes.

Study	Study Design	Sample (N)	EEG Metrics	EEG Timing	rTMS Parameters	Findings
Arns et al., 2012 [45]	Open label, multi-site	MDD (n = 86) or Dysthymia (n = 4)	Individual alpha peak frequency, Theta power, Cordance, P300	Prior to initiation of rTMS	Left DLPFC 10 Hz, 110% MT, 1500 pulses per session –OR– Right DLPFC 1 Hz, 110% MT, 1200 pulses per session (if presence of focal left beta spindles during EEG); Average 20.7 sessions	Relative to responders, at baseline non-responders had: 1) ↑Frontal-central theta power 2) Slower anterior individual alpha peak frequency 3) Larger P300 amplitude 4) ↓Pre-frontal delta and beta cordance
Bailey et al., 2018 [62]	Open label outpatient treatment	MDD (n = 39); Controls (n = 20; received only baseline EEG and no rTMS)	Theta power, alpha power, gamma power, connectivity, theta-gamma coupling	EEG during working memory task at baseline and after 1 week of treatment	Left DLPFC, 10 Hz, 2000 pulses per session, 110% MT, 5–8 weeks of treatment; (some non-responders at week 3 were assigned to receive right DLPFC 1 Hz or bilateral stimulation protocols for the remainder of sessions)	Greater working memory-related fronto-midline theta power and theta connectivity in responders at baseline and week 1 compared to non-responders. Increased gamma connectivity from baseline to week 1 in responders.
Bailey et al., 2019 [56]	Open label outpatient treatment	MDD (n = 42); Controls (n = 21; received only baseline EEG and no rTMS)	Alpha power, theta power, theta cordance, individualized alpha peak frequency, alpha connectivity, theta connectivity	Baseline and after 1 week of treatment	Left DLPFC, 10 Hz, 2000 pulses per session, 110%MT, 5–8 weeks of treatment; (some non-responders at week 3 were assigned to receive right DLPFC 1 Hz or bilateral stimulation protocols for the remainder of sessions)	Larger theta connectivity at baseline and at 1 week in responders compared to non-responders. No other baseline EEG measures differed between responders and non-responders.
Bares et al., 2015 [54]	Randomized, blinded, sham controlled	MDD (n = 60; inpatients)	Prefrontal theta cordance	Baseline and after 1 week of treatment	Right DLPFC, 1-Hz, 600 pulses per session, 100% MT, for 20 consecutive working days	Decrease of cordance after 1 week of treatment predicted response. Compared to baseline, theta cordance at week 1 was significantly decreased in responders, but not in nonresponders to rTMS.
Cook et al., 2018 [64]	Randomized, double-blinded, sham controlled	MDD (n = 16)	Absolute and relative power at delta, theta, alpha, beta; Current source density, magnitude squared coherence	Prior to sTMS treatment	Same as Leuchter et al., 2015, below.	Active and sham groups did not differ in absolute or relative power, and there were no within-group changes over time. Within the active group, increases in alpha current source density were positively correlated with self-reported depressive symptoms for midline and anterior voxels. For multiple channel pairings, higher alpha and beta coherence values at baseline were associated with greater improvement in self-reported depressive symptoms.
Corlier et al., 2019 *paper in press* [48]	Open label outpatient treatment	MDD (n = 147)	Individual alpha frequency, Absolute difference between IAF and 10 Hz (i.e., |IAF – 10 Hz|)	Pre-treatment	Initial: 10 Hz left DLPFC ≥ 80% MT If not tolerating or subtherapeutic, changed to either: ● Simultaneous bilateral stimulation w/ 1 Hz on right DLPFC ● Continued unilateral left DLPFC at 5 Hz	There was no correlation between either IAF or |IAF-10 Hz| values and clinical outcome in the overall sample. Significant correlations were found for both IAF and |IAF-10 Hz| and the 10 Hz group's clinical outcome. No such relationship was found in the simultaneous bilateral or 5 Hz sub-groups. Clinical outcomes of top IAF quartile of the 10 Hz group were significantly better as compared to the bottom quartile.
Hunter et al., 2018 [55]	Open label outpatient treatment	MDD (n = 18; outpatient)	Change in theta cordance	Baseline and after 1 week of treatment	Left DLPFC, 10 Hz, 3000 pulses per session, 120% MT for 5 days per week over 6 weeks.	Change in central regional cordance after 1 week was associated with improvement after 6 weeks of treatment.

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Table 3 (*continued*)

Study	Study Design	Sample (N)	EEG Metrics	EEG Timing	rTMS Parameters	Findings
Jin et al., 2014 [49]	Randomized, sham controlled, double-blinded trial; 3 arms: active synchronized TMS with fixed frequency set at individualized alpha frequency, active synchronized TMS with random frequency from 8 to 13 Hz, and sham TMS.	MDD (n = 52)	Individual alpha frequency	Prior to rTMS to determine individual alpha frequency	Experimental synchronized TMS device: cylindrical magnets positioned sagitally along midline with axis of rotation perpendicular to midline. Compared to standard rTMS devices, magnetic waveforms are sinusoidal with energy of magnetic field < 1% of standard	Statistically significant clinical improvement was seen in the active group compared to sham, but not between the random frequency and fixed individualized alpha frequency groups.
Krepel et al., 2018 [46]	Open label, multi-site	MDD or Dysthymia (n = 106 Total)	Individual alpha peak frequency, Theta power, P300	Prior to initiation of rTMS	Left DLPFC 10 Hz –OR– Right DLPFC 1 Hz	No difference between responders and nonresponders for individual alpha peak frequency, theta power, or P300 prior to initiation of rTMS.
Leuchter et al., 2015 [50]	Randomized, double-blinded, sham controlled trial (synchronized rTMS with fixed frequency set at individualized alpha frequency vs. sham)	MDD (n = 202)	Individual alpha frequency	Prior to rTMS to determine individual Alpha Frequency	Same experimental synchronized TMS device as above (Jin et al., 2014)	No statistical significance with ITT analysis. Significantly lower HAM-D score in the active treatment group with PP analysis (n = 120, 59 active and 61 sham)
Noda et al., 2017 [65]	Open label	MDD (n = 31)	Gamma power, theta-gamma coupling	Baseline and post-treatment	Left DLPFC, 20 Hz, 1000 pulses/session, 10 sessions over 2 weeks	Resting gamma power increased over the course of rTMS treatment in prefrontal regions; this increase in left prefrontal regions correlated with improvement in depression severity. Modulation index of theta-gamma coupling increased over treatment in left central regions; this change correlated with improvement on an executive functioning task.
Petrosino et al., 2018 [47]	Open label	MDD + PTSD (n = 21)	Intrinsic alpha frequency	Baseline and post-treatment	Left DLPFC, 5 Hz, 120% MT, 3000–4000 pulses/session, up to 40 sessions	No IAF changes were found between baseline and follow-up. There was not a significant relation between baseline IAF and clinical outcome.
Philip et al., 2019[63]	Randomized, double-blinded, sham controlled trial	MDD (n = 120)	Individual alpha peak frequency	Prior to initiation of rTMS to determine sinusoidal wave periodicity for subsequent treatments	Same as Leuchter et al., 2015, above.	Baseline IAF did not predict change in self-reported depression in the blinded phase. In a stepwise regression of the full sample in the open label phase of the study, greater severity of depressive symptoms and higher IAF quartile at baseline predicted greater clinical improvement, with a higher number of failed medication trials predicting worse outcome.
Shalbaf et al., 2018 [57]	Data from 2 single-blind randomized, controlled trials	MDD (n = 51) and Healthy Comparison (n = 25)	Permutation entropy intrinsic mode function index, relative power of delta, theta, alpha, beta, gamma band	Pre-treatment	120% MT, either high frequency TMS (n = 25) or theta burst TMS (n = 26) over left DLPFC	Responders had higher permutation entropy intrinsic mode function index relative to non-responders, particularly at left frontal locations. Permutation entropy intrinsic mode function index was a superior predictor of treatment response than relative power of frequency bands

IAF = individual alpha frequency; ITT = intent to treat, PP = per protocol, MDD = major depressive disorder, DLPFC = dorsolateral prefrontal cortex.

approaches, may be one promising path forward. For example, latent class analyses or latent trajectory analyses such as latent growth mixture models or latent class growth models may be useful in identifying subclasses of patients or treatment response trajectories for further investigation. An example of this type of approach was recently published by Kaster and colleagues [61], which used group-based trajectory modeling to identify four classes of patients showing distinct patterns of response to either traditional high-frequency or intermittent theta-burst rTMS. By conducting further exploratory analyses, they also identified candidate characteristics which may relate to response trajectory membership, including depression severity, age, and use of benzodiazapines. These exploratory findings can be used to inform prospective studies to confirm the predictive value of these patients-specific factors.

Data-driven methods are also being applied within the field of neuroimaging, where researchers have been seeking a pathway to better categorize clinically depressed patients in a way that meaningfully accounts for significant heterogeneity in the clinical manifestations of the disorder and in rTMS treatment outcomes. Recently, Dysdale et al. [12] demonstrated a model separating MDD patient into 4 discrete biotypes according to their frontostriatal and limbic connectivity. With this method, a subgroup of patients (n = 124) were identified who showed superior response to DMPFC rTMS treatment, and were characterized by reduced connectivity in frontoamygdala networks as well as in anterior cingulate and orbitofrontal areas. Finally, beyond latent class and clustering approaches, machine learning approaches, which are already being applied in EEG (e.g., [48,59]) may also prove useful for identifying potential predictors from a large number of candidate variables to be further evaluated as predictors of treatment outcome in prospective designs.

Only a small number of likely predictors of treatment outcome have been identified for rTMS depression treatment, and more research will be required to translate any of the above described findings into guidance for delivery of therapy. Moreover, as new stimulation modalities are developed, such as theta-burst rTMS and accelerated rTMS schedules, it will be important to consider whether novel treatment approaches or parameters are differentially effective for various subsets of patients, with particular attention to patients who are the most chronically ill and resistant to medications and psychotherapies. The formation of large-scale collaborative research consortiums and data repositories, structured to promote sharing of data and harmonization of measurement methods across research centers, holds significant promise for increasing the sample sizes and reducing methodological and technical differences that currently hinder the identification of meaningful rTMS biomarkers.

Declaration of Competing Interest

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