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RESEARCH ARTICLE

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Predictors of response to synchronized transcranial magnetic stimulation for major depressive disorder

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Background: Synchronized transcranial magnetic stimulation (sTMS) is a new modality to reduce symptoms of major depressive disorder (MDD). sTMS uses rotating neodymium magnets to deliver low-field stimulation matched to the individual alpha frequency (IAF). A previous multisite study showed that sTMS significantly reduced MDD symptoms in the per-protocol sample. To this end, we evaluated clinical features associated with optimal sTMS outcomes.

Methods: Using the per-protocol sample (n = 120) from the parent sham-controlled trial, we performed univariate and stepwise linear regression to identify predictors of response after 6 weeks of sTMS. A subsample (n = 83) that entered a 4-week open/active continuation phase also was examined. Candidate variables included age, sex, comorbid anxiety, number of failed antidepressants in the current depressive episode, MDD severity (17-item Hamilton Depression Rating Scale; HAMD17), anxiety symptom severity (HAMD17 anxiety/somatization factor), and IAF.

Results: We found that greater baseline depressive ($p < 0.001$) and anxiety ($p < 0.001$) symptom severity were associated with better response to active sTMS, whereas fewer failed antidepressant trials predicted superior response to sham ($p < 0.001$). MDD severity and antidepressant resistance predicted outcomes in open/active phase sTMS; lower IAF predicted poorer response in participants who received 10 weeks of active sTMS ($p = 0.001$).

Conclusions: Participants with greater severity of depression and higher anxiety had superior responses to active sTMS, whereas treatment naïve individuals exhibited a greater response to sham. These results lend support to the primary efficacy findings, and support further investigation of sTMS as a therapeutic noninvasive brain stimulation modality.

KEYWORDS
anxiety, brain stimulation, individualized alpha frequency, major depressive disorder, predictors of response, synchronized transcranial magnetic stimulation

1 | INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS, or simply "TMS") delivered to the left prefrontal cortex at supra-threshold intensity is safe and effective for treating pharmacoresistant major depressive disorder (MDD), and research into novel types of noninvasive therapeutic brain stimulation is a rapidly growing area. While the putative therapeutic mechanism of antidepressant action of TMS remains unclear, one proposed mechanism involves manipulation of oscillatory neural signaling (Fuggetta & Noh, 2013; Johnson, Hamidi, & Postle, 2010; Leuchter, Hunter, Krantz, & Cook, 2015b). Entrainment of endogenous activity in the alpha frequency range, using high-field (~1.5T) magnetic pulses, may function to reset thalamocortical oscillators that are abnormal in depressed individuals, thereby restoring brain signaling necessary for regulation of cognitive and emotion functions (Fuggetta & Noh, 2013; Johnson et al., 2010; Leuchter et al., 2015b). It follows that low-field transcranial stimulation with wave periodicity synchronized to match the individual's alpha brain rhythms (i.e., synchronized TMS; sTMS), might be an effective method for targeting and entraining key neural oscillators to bring about the changes necessary to improve symptoms of depression. Such an approach would represent a novel modality for therapeutic brain stimulation, and one that is safe and feasible for home administration.

A programmatic series of experiments and pilot studies established the principles and rationale for sTMS. Initial studies demonstrated that low-intensity stimulation was effective at entraining ongoing neuronal activity (Anastassiou, Perin, Markram, & Koch, 2011; Fröhlich & McCormick, 2010; Ozen et al., 2010; Reato, Rahman, Bikson, & Parra,

2010), and it was hypothesized imparting low-intensity sinusoidal stimulation to the cortex with a series of rotating neodymium magnets could be used modulate brain activity in humans (Leuchter et al., 2015b). It was further hypothesized that stimulation synchronized to each subject's individual alpha frequency (IAF) as measured by electroencephalography (EEG) would provide therapeutic benefit at much lower magnetic field strength than traditional TMS by taking advantage of the brain's natural resonant frequency (Fröhlich, 2015; Leuchter et al., 2015b). The potential for this approach to relieve depressive symptoms was demonstrated in a pilot sTMS study ($N = 52$) (Jin & Phillips, 2014), and more recently tested in a large-multisite sham-controlled study of sTMS for MDD (Leuchter et al., 2015a).

In the randomized-controlled trial ($N = 202$), stimulation was found to be safe and well tolerated, with no differences in adverse events between active and sham groups and no significant adverse events attributable to sTMS. Antidepressant outcomes did not statistically differ between active and sham sTMS conditions using the intent-to-treat (ITT) population. However, a considerable portion of the study participants ($n = 67$) did not receive at least 80% of their prescribed sTMS sessions within the allotted 60-day treatment window, and technical problems precluded treatment at the correct IAF in some participants ($n = 15$). In the subsample that received sTMS as intended (i.e., the per-protocol population, PP, $n = 120$), active sTMS was superior to sham stimulation for reducing depression severity, where PP sample reductions in Hamilton Depression Rating Scale 17-item (HAMD17; (Hamilton, 1960)) scores at the 6-week endpoint were 9.00 for the active group and 6.65 for sham ($p = 0.033$).

In light of the promising efficacy signal emerging from PP sample analysis in that clinical trial and to better understand the potential therapeutic and mechanistic effects of sTMS, we performed additional secondary analyses to determine whether specific clinical factors assessed at baseline could predict subsequent clinical response to sTMS. Based on previously observed effects in other TMS treatment trials (Lisanby et al., 2009; O'Reardon et al., 2007), we hypothesized that greater antidepressant resistance and comorbid anxiety symptoms would be associated with inferior clinical outcomes to active stimulation.

2 | MATERIAL AND METHODS

2.1 | Study overview

A randomized-controlled study of sTMS in unipolar depression was conducted at 17 US-based sites with active enrollment between June 2011 and July 2013 (NCT01370733; Leuchter, 2015a, sponsored by NeoSync, Inc.). The study design included 30 double-blind sham-controlled sTMS sessions delivered to medication-free depressed adults with a schedule of five per week over 6–8 weeks. Subjects who did not achieve clinical remission at the end of the blinded phase were eligible to enter a 4-week active/open-label continuation phase, with up to 20 additional sTMS sessions delivered by a third device that was identical in appearance but sounded distinct from the active and sham devices used in the blinded trial.

2.2 | Participants

See Leuchter et al. (2015a) for full details of the inclusion and exclusion criteria. In brief, a total of 202 medication-free participants (ages 22–65) with primary MDD and at least moderate severity depression (minimum HAMD17 score of 17) were included. Inclusion and exclusion criteria were generally consistent with other multisite studies of TMS for MDD (e.g., George et al., 2010; O'Reardon et al., 2007; Philip et al., 2016). If a participant's IAF could not be detected with single-channel EEG at baseline, they were excluded from subsequent participation. Antidepressant treatment resistance in the current episode was measured using the Antidepressant Treatment History Form (ATHF; Sackeim, 2001). A specific level of pharmacoresistance was not required to enter the study, and participants were permitted limited use of certain anxiolytics/hypnotics during the study (e.g., equivalent of 0.5 mg lorazepam twice per week).

Of the total ($N = 202$) participants, 120 (54.9%; 59 active, 61 sham) received sTMS per protocol. Only the PP sample (i.e., participants that completed >80% treatment visits in the blinded phase and were treated at the correct IAF) was used in this secondary round of analyses to identify clinical factors predictive of positive response.

2.3 | sTMS device

Prior to the first treatment, each participant's peak IAF was obtained using a short, single-channel EEG recording (FPz and Oz locations using the International 10–20 EEG Electrode system). This IAF was used to establish the sTMS sinusoidal wave periodicity used for all subsequent treatments. Throughout the study, additional single-channel EEG recordings were used, after the conclusion of the trial, to evaluate the accuracy of initial IAF determination. Because peak IAF has a very high intra-individual stability (Kondacs & Szabó, 1999), the IAF recorded and implemented at baseline was retrospectively considered to be incorrect if subsequent EEG recordings generated a mean IAF value that differed by at least 1 Hz from the pretreatment IAF.

The sTMS device housed three diametrically magnetized cylindrical neodymium magnets, which were placed near the scalp in sagittal alignment between the subject's forehead and crown of the head. The magnets were rotated by motors in the device to produce sinusoidal waveform magnetic fields with IAF periodicity for 30 min per treatment session. Subjects were maintained supine in an eyes-closed, awake state, and observed to ensure they remained awake throughout the treatment sessions. Sham procedures were identical, except that a nonmagnetic rotating metal shaft replaced the magnets.

The Neosync sTMS device was reviewed by the FDA and classified as a nonsignificant risk device prior to this clinical trial. Safety was confirmed by the very low prevalence of adverse events during the randomized clinical trial, with no significant difference between active and sham groups in the incidence, severity or clinical significance of adverse events. Accordingly, there were no significant differences in treatment discontinuation rates because of adverse events, and no differences in suicidal ideation between groups. There was one suicide attempt during the study, which occurred in a sham-treated subject. No significant adverse events were attributable to sTMS (active or sham).

TABLE 1 Participant Demographic and Clinical Characteristics

Baseline Characteristic	Active ($n = 59$)	Sham ($n = 61$)	p-Value
Age in years, mean (SD[a])	46.7 (11.2)	45.7 (12.6)	0.65
Female, *N* (%)	32 (54.2%)	38 (62.3%)	0.37
Race, *N* (%)			
Caucasian	47 (79.7%)	50 (82.0%)	0.71
All other	12 (20.3%)	11 (18.0%)	–
Length current episode in months, mean (SD)	11.2 (7.0)	10.9 (6.7)	0.83
Depression episode type, *N* (%)			
Single episode	3 (5.1%)	3 (4.9%)	0.97
Recurrent episode	56 (94.9%)	58 (95.1%)	–
Comorbid anxiety diagnosis, *N* (%)	9 (15.3%)	1 (1.6%)	0.008
Antidepressant exposure in current episode, *N* (%) [b]			
Inadequate dose or duration of ≥1 medication	3 (5.1%)	7 (11.5%)	0.32
Intolerant of ≥1 medication	4 (6.8%)	1 (1.7%)	0.20
Treatment naïve (no medication exposure, current episode)	21 (35.6%)	24 (39.3%)	0.71
Nonresponse to 1 adequate medication trial (ATHF[c] = 1)	20 (33.9%)	15 (24.2%)	0.24
Nonresponse to 2 or more medication trials (ATHF = 2–6)	11 (18.6%)	13 (21.3%)	0.72
Baseline depression severity, mean (SD)			
HAMD17[d] total	21.8 (3.8)	21.2 (2.9)	0.37
HAMD anxiety/somatization factor score	7.0 (2.2)	6.9 (1.8)	0.76
Individual alpha frequency (Hz; mean±SD)	9.9 (1.0)	9.9 (0.9)	0.84

[a]SD, standard deviation.
[b]Denominator for sham is $n = 60$ since one patient was missing status of previous medication exposure.
[c]ATHF, antidepressant history form.
[d]HAMD17, 17-item Hamilton rating scale of depression.

2.4 | Candidate variables

Candidate variables for this predictor analysis included those previously indicated as related to antidepressant/TMS outcomes or of interest to the field. Categorical variables included randomized treatment group (active/sham), sex, age, permitted anxiety disorder (yes/no), recurrent depressive episode (first/recurrent), permitted anxiety medication use (yes/no), and antidepressant resistance (ATHF score ≥ 1; yes/no). Continuous variables included IAF (range 8–13 Hz), IAF quartile (evaluated to detect potential nonlinear effects), number of double-blind sTMS treatments, baseline depression severity (i.e., HAMD17 total score), baseline anxiety symptom severity (i.e., HAMD17 anxiety/somatization factor score (Farabaugh et al., 2010)), number of failed antidepressant trials in the current episode (i.e., ATHF score), and lifetime antidepressant exposure (i.e., number of lifetime antidepressant trials).

2.5 | Statistical analysis

Descriptive statistics, Fisher's Exact test, chi-square, and *t*-tests were used to compare treatment groups at baseline (pre-randomized treatment in the double-blind phase). Exploratory multivariate linear regression analyses were conducted to detect baseline predictors of clinical efficacy in the PP sample, where the clinical efficacy endpoint was the 6-week change in HAMD17 score from baseline during the blinded treatment phase of the randomized trial (Leuchter et al., 2015a). The significance of the relationship of each independent variable with the outcome was assessed using simple linear regression within each treatment group and for both treatment groups combined. Stepwise linear regression then followed, using a 0.05 level of significance for entry and for staying in the model. These stepwise regression analyses were also conducted for each treatment group separately and for both treatment groups combined. These analyses were repeated for the 4-week open/active phase ($n = 92$; $n = 83$ with data up through week 10) which (a) included $n = 42$ subjects who received 6 weeks blinded active sTMS and continued with 4 more weeks of active/open sTMS together and (b) $n = 41$ subjects who received 6 weeks of sham before starting a course of up to 20 active sessions. The open-label analyses efficacy outcome was change in HAMD17 from baseline to the end of 10-week open-label phase.

All *p*-values presented are two-sided, and significance defined at $p = 0.05$. Analyses were conducted using SAS (v9.4, Cary NC).

3 | RESULTS

3.1 | Characteristics of the study population

Participant demographic and clinical characteristics are described in Table 1. At baseline, more participants in the active than sham group had a comorbid anxiety disorder, although numbers for both groups were very low (active group, $n = 9$ (15.3%) vs. sham $n = 1$ (1.6%) in sham; $p = 0.008$). All other baseline variables did not differ between the two groups. Approximately, the same percentage of participants in each group were resistant to at least one adequate antidepressant medication in the current episode (ATHF score ≥ 1; 52.5% and 45.9% in the active and sham groups, respectively; $p = 0.47$), and approximately one third of participants were antidepressant naïve (ATHF = 0) in the current episode (35.6% and 40.0% of active and sham groups, respectively; $p = 0.62$). Groups also did not differ on mean IAF, which was within the expected range.

3.2 | Double-blind phase: Univariate analyses

Results from simple linear regression assessing relationship of 6-week HAMD17 change in the double-blind phase with each categorical and continuous variable are described in Table 2. The categorical variable of ATHF ≥ 1 was the only variable significantly related to 6-week HAMD17 change, where ATHF ≥1 status predicted worse outcome in the sham group only ($\beta = 4.38$; $p = 0.003$). No other categorical variable emerged as a statistically significant predictor of clinical improvement within each treatment group or for both treatment groups combined.

TABLE 2 Predictors of Acute Synchronized Transcranial Magnetic Stimulation (sTMS) Treatment Outcome (Change in 17-item Hamilton Rating Scale of Depression (HAMD17) from Baseline to Blinded Endpoint): Univariate Analyses of Candidate Clinical Variables in Both Treatments Combined

Variable Name (Definition)	*p*-Value[a]	Direction of Effect on Outcome [b]
Categorical		
Treatment group (active vs. sham)	0.03	Active had larger mean decrease from baseline than sham
Sex (male vs. female)	0.93	–[b]
Comorbid anxiety disorder (yes vs. no)	0.10	–
Depressive episode type (first vs. recurrent)	0.92	–
Anxiety medication use (yes vs. no)	0.51	–
Treatment resistance (ATHF[c] ≥ 1) (yes vs. no)	0.01	Less resistance predicted superior outcomes (sham arm only, $p = 0.003$; $p = 0.29$ for active)
Continuous		
Age (at baseline)	0.69	–
Baseline IAF[d] (range 8.0–13.0 Hz)	0.61	–
Baseline IAF quartile	0.51	–
Number of double-blind treatments (active or sham sTMS sessions received across 6 weeks; range of 28–30)	0.56	–
Depression severity (baseline HAMD17 total score)	<0.001	More severe depression predicted superior outcome (active arm only, $p < 0.001$; $p = 0.74$ for sham)
Anxiety symptom severity (baseline HAMD17 anxiety/somatization factor score; range 1–13)	<0.001	More severe anxiety predicted superior outcome (active arm only, $p < 0.001$; $p = 0.33$ for sham)
Number of failed AD[e] trials in current episode (ATHF[a] score)	0.003	Fewer trials predicted superior outcome (sham arm only, $p < 0.001$; $p = 0.18$for active)
Lifetime AD exposure (number of lifetime AD trials)	0.43	–

[a]*p*-Value assesses significance of predictor variable effect on symptom improvement (as defined by change in HAMD17 over 6 weeks in the blinded phase) for both treatments combined.
[b]"–" Indicates no statistically significant benefit in both treatment groups combined or within each treatment group separately.
[c]ATHF, antidepressant history form.
[d]IAF, individualized alpha frequency.
[e]AD, antidepressant.

Several continuous variables emerged as significant clinical predictors. Within the active group only, higher baseline depression severity ($\beta = -0.78$; $p < 0.001$) and more severe anxiety symptoms ($\beta = -1.27$; $p < 0.001$) predicted greater reduction in HAMD17 at week 6. Because greater HAMD17 anxiety factor values could be collinear with total HAMD17 (all items) score, we explored the predictive value of a baseline HAMD17 depression severity score that did not include the anxiety factor items. When excluding anxiety items, greater baseline depression severity still predicted clinical improvement among participants who received active sTMS ($p = 0.007$). In the sham group only, lower levels of unsuccessful antidepressant trials predicted greater improvement ($p < 0.001$).

3.3 | Double-blind phase: Stepwise linear regression

Significant predictor variables from the stepwise regression model in the double-blind phase are shown in Table 3. The final model for both treatments combined was significant ($p < 0.001$) and explained 21.0% of the variance. Significant predictors for the pooled sample included treatment condition ($\beta = -2.46$, $p = 0.021$), baseline anxiety severity ($\beta = -1.06$, $p < 0.001$), and ATHF ≥ 1 status ($\beta = 3.68$, $p < 0.001$). Therefore, active sTMS and higher anxiety at baseline both predicted superior outcomes, while being resistant to medication was associated with inferior outcomes.

Among participants treated with sham stimulation, only higher ATHF score was related to change in HAMD17, i.e., more failed trials predicted worse outcome ($\beta = 2.63$, $p < 0.001$). Within the group that received active sTMS, only greater baseline HAMD17 severity was a significant predictor of improvement at week 6 ($\beta = -0.78$, $p < 0.001$).

3.4 | Open/active continuation phase: Univariate analysis

Eighty-three participants entered the open/active phase of the study after completing the double-blind trial, comprised by 41 of 61 (67%) originally in the sham group and 42 of 59 (71%) from the active sTMS group. In the pooled analysis for this phase, female gender was associated with a statistical trend toward greater HAMD17 reduction at week 10 ($\beta = -2.72$; $p = 0.082$). Higher baseline depressive symptom severity ($\beta = -0.91$; $p < 0.001$) again predicted superior clinical improvement, as did greater baseline anxiety severity ($\beta = -1.02$; $p = 0.008$).

In the group who continued from blinded active sTMS to the open/active phase (i.e., extending their acute course to 10 total weeks of sTMS), greater severity of both depression and anxiety symptoms predicted superior improvement ($\beta = -1.09$; $p < 0.001$; and $\beta = -1.24$; $p = 017$, respectively). There were no statistically significant predictors of response that emerged when examining the sham-to-active (crossover) group.

3.5 | Open/active phase: Stepwise linear regression

Stepwise regression of the pooled sample entering the open/active phase ($n = 83$) identified significant predictors of week 10 changes

TABLE 3 Significant Predictors of Acute Synchronized Transcranial Magnetic Stimulation (sTMS) Treatment Outcomes (Change in 17-item Hamilton Rating Scale of Depression (HAMD17) from Baseline to Blinded Endpoint) Retained in Stepwise Regression Model

Sample	Variable Name (Definition)	Parameter Estimate	Standard Error	*p*-Value
PP[a] ($n = 120$)				
	Treatment group (sham vs. active)	−2.46	1.05	0.021
	Anxiety symptom severity (baseline HAMD17 anxiety/somatization factor score)	−1.06	0.26	<0.001
	Treatment resistance (ATHF[c] ≥ 1)	3.68	1.05	<0.001
Sham	Number of failed AD[b] trials in current episode (ATHF[c] score)	2.63	0.72	<0.001
Active	Depression severity (baseline HAMD17 total score)	−0.78	0.20	<0.001

[a]PP, per-protocol population.
[b]AD, antidepressant.
[c]ATHF, antidepressant history form.

from baseline in HAMD17 score. A significant model ($p = 0.001$) explaining 24.2% of the variance identified higher baseline HAMD17 score ($\beta = -0.91, p < 0.001$) and higher baseline IAF quartile ($\beta = -1.39$, $p = 0.031$) as predictors of clinical improvement, whereas greater number of prior failed antidepressant trials ($\beta = 1.67, p = 0.011$) predicted poorer response. After adjusting for other significant predictors in the model, mean HAMD17 reductions at week 10 for the participants in each IAF quartile were −6.84 (first/lowest; 8.10–9.08 Hz), −9.92 (second; 9.12–9.86 Hz), −10.24 (third; 9.89–10.44 Hz) and −11.40 (fourth/highest; 10.46–12.71 Hz). There was a significant difference between the highest and lowest quartiles with respect to clinical outcome ($p = 0.025$); otherwise, there were no statistically significant differences in mean HAMD17 change among the IAF quartiles.

When the active-to-active and sham-to-active subsets were analyzed separately, no variables predicted response in the sham-to-active group. However, in the active-to-active group, higher baseline depression severity score ($\beta = -1.14, p < 0.001$) and higher IAF quartile ($\beta = -2.50$, $p = 0.001$) predicted clinical improvement, whereas greater ATHF score predicted poorer response ($\beta = 1.87$, $p = 0.008$). After adjusting for the other significant predictors, mean HAMD17 reductions at week 10 for participants in each quartile were −5.16 (first/lowest; 8.10–9.08 Hz), −10.80 (second; 9.33–9.86 Hz), −11.44 (third; 9.93–10.23 Hz) and −13.13 (fourth/highest; 10.47–12.71 Hz). All contrasts versus the lowest quartile were significant ($p \leq 0.026$), and there were no statistically significant differences in HAMD17 change between the second, third, and fourth quartiles.

4 | DISCUSSION

In this analysis of response to sTMS, we found that greater depressive and anxiety symptoms at baseline, and lower levels of antidepressant resistance, predicted superior antidepressant response in the blinded trial. When treatment groups were examined separately, less-medication nonresponse was a predictor of better outcome only among those who received sham sTMS. For the group who received active stimulation in the blinded trial, more severe depression and anxiety symptoms at baseline predicted better outcome. During open/active phase sTMS, treatment resistance was associated with poorer response, and IAF quartile emerged as a predictor of response after 10 weeks of active sTMS.

These predictors differ somewhat from those identified for standard 10 Hz TMS (Lisanby et al., 2009). In that study, lower levels of antidepressant treatment resistance (active arm only), shorter duration of current MDD episode, and absence of anxiety disorder emerged as significant predictors of positive response. Here, we observed that lower levels of medication resistance predicted superior response to sham, consistent with the literature on sham response in the antidepressant neuromodulation literature (e.g., reviewed in Brunoni, Lopes, Kaptchuk, & Fregni, 2009). During the active and continuation phase, we observed increased antidepressant resistance predicted poorer response, which is consistent with prior observations (Lisanby et al., 2009). Furthermore, anxiety symptoms emerged as a predictor of positive response in this study, a finding that is broadly supportive of prospectively testing sTMS in other disorders where anxiety is prominent or comorbid (Carpenter et al., 2018; Diefenbach et al., 2016; Philip et al., 2016).

Several predictors of response did not emerge from our analysis. Prior TMS studies indicated that older age was associated with poorer response (Figiel et al., 1998; Manes et al., 2001; Mosimann et al., 2002, 2004; Su, Huang, & Wei, 2005; but also see Conelea et al., 2017). This age result was not replicated in the Lisanby et al. (2009) analyses of predictors of rTMS response, nor found here. One explanation of prior negative findings included the use of rTMS delivered at 120% of motor threshold (O'Reardon et al., 2007), thought to be sufficient to address age-related cortical atrophy (Nahas et al., 2004). While we excluded participants over 65, this explanation is not sufficient for the current study because sTMS does not calibrate the stimulation intensity based on a motor-evoked response. We interpret this to indicate that either the current device delivered sufficiently large magnetic fields to counteract potential age-related issues, or age may not be a negative prognostic indicator of sTMS' efficacy.

We found several aspects of IAF-predicted response. We previously compared clinical outcomes in participants treated at the correct IAF versus those treated at the incorrect frequency and found significantly poorer outcomes associated with mismatched sTMS (incorrect IAF: -0.36 ± 7.03 vs. correct IAF: -9.00 ± 6.54; $p < 0.001$; $n = 15$) (Leuchter et al., 2015a). In this analysis, IAF quartile emerged as a predictor of

response for participants who received an extended sTMS series (i.e., those who started with active sTMS and continued to receive sTMS during the open/active study phase), where those with the lowest IAF quartile (8.10–9.08 Hz) exhibited the least clinical improvement. Lower IAF values could represent lifetime traits for these subjects, but also could represent the effects of neurodegeneration (e.g., Bonanni et al. (2008)) some other form of subthreshold brain pathology. Additionally, because lower frequency stimulation corresponds with slower rotation of the sTMS magnets (i.e., according to Faraday's law for sinusoidal varying magnetic fields), it these participants may have received an attenuated induced electrical field, although the physiological impact of this effect is, at best, speculative. Furthermore, it is notable that this finding was the strongest for participants who received the largest "dose" (i.e., greatest number of active sTMS sessions). While we interpret this EEG result with caution, it indicates that further research is required to examine whether baseline IAF can predict sTMS response, particularly if sTMS is delivered over longer periods of time.

Limitations of this study are those inherent to a follow-up, exploratory evaluation of a multisite clinical efficacy study. In that study, there was a modest range of demographic features and level of antidepressant resistance that may have limited our ability to detect other clinically significant predictors of response. It is possible that observed symptom reductions represented regression to the mean, such that participants with higher symptom severity could exhibit greater improvement over time. Yet, we observed that greater depressive and anxiety symptom severity at baseline predicted superior response only in participants who received active stimulation, which indicates our results are related to sTMS, rather than a nonspecific phenomenon. To confirm observed results were not due to collinearity between HAMD anxiety and HAMD total scores, post-hoc tests evaluated the effect of anxiety subscores derived from other rating scales used in the efficacy study and found comparable results. For example, we found that baseline HAMD anxiety score significantly predicted depressive symptom reduction at endpoint measured on the Montgomery Asberg Rating Scale (Montgomery & Åsberg, 1979), and baseline anxiety score measured using a subscale of the Inventory of Depressive Symptomatology (Rush et al., 2003) significantly predicted reduction in HAMD total score (all $p < 0.05$). Additionally, in this analysis we chose to focus on the PP sample to characterize the most appropriate predictors of response when using the device as intended, and recognize this approach had an inherent impact on our results; randomization also produced a numerically small but statistically significant difference in anxiety diagnoses, but not on anxiety symptoms, which could have influenced outcomes. Finally, the parent study utilized a single approach to sTMS delivery at the IAF, and it remains unknown whether modifications or other techniques (e.g., different target frequency, magnet placement, etc.) can be used to improve clinical efficacy.

5 | CONCLUSIONS

In summary, greater depressive symptom severity and comorbid anxiety predicted clinical improvement with sTMS, whereas sham response was associated with less treatment resistance. While the efficacy of sTMS in more severely ill MDD patients with comorbid anxiety patients should be prospectively examined, these results indicate that sTMS has a different efficacy profile from standard rTMS and may represent an important new treatment option when considering the care of patients with treatment-resistant MDD.

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