Brain Stimulation 16 (2023) 1753–1763

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

EEG synchronized left prefrontal transcranial magnetic stimulation (TMS) for treatment resistant depression is feasible and produces an entrainment dependent clinical response: A randomized controlled double blind clinical trial

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ARTICLE INFO

Keywords:
EEG
TMS
EEG synchronization
Entrainment
Depression

ABSTRACT

Background: Synchronizing a TMS pulse with a person's underlying EEG rhythm can modify the brain's response. It is unclear if synchronizing rTMS trains might boost the antidepressant effect of TMS. In this first-in-human trial, we demonstrated that a single TMS pulse over the prefrontal cortex produces larger effects in the anterior cingulate depending on when it is fired relative to the individual's EEG alpha phase.

Objective/hypotheses: We had three hypotheses. 1) It is feasible to synchronize repetitive TMS (rTMS) delivery to a person's preferred prefrontal alpha phase in each train of every session during a 30-visit TMS depression treatment course. 2) EEG-synchronized rTMS would produce progressive entrainment greater than unsynchronized (UNSYNC) rTMS. And 3) SYNC TMS would have better antidepressant effects than UNSYNC (remission, final Hamilton Depression Rating <10).

Methods: We enrolled (n = 34) and treated (n = 28) adults with treatment resistant depression (TRD) and randomized them to receive six weeks (30 treatments) of left prefrontal rTMS at their individual alpha frequency (IAF) (range 6–13 Hz). Prior to starting the clinical trial, all patients had an interleaved fMRI-EEG-TMS (fET) scan to determine which phase of their alpha rhythm would produce the largest BOLD response in their dorsal anterior cingulate. Our clinical EEG-rTMS system then delivered the first TMS pulse in each train time-locked to this patient-specific 'preferred phase' of each patient's left prefrontal alpha oscillation. We randomized patients (1:1) to SYNC or UNSYNC, and all were treated at their IAF. Only the SYNC patients had the first pulse of each train for all sessions synchronized to their individualized preferred alpha phase (75 trains/session ×30 sessions, 2250 synchronizations per patient over six weeks). The UNSYNC group used a random firing with respect to the alpha wave. All other TMS parameters were balanced between the two groups.

The system interfaced with a MagStim Horizon air-cooled Fig. 8 TMS coil. All patients were treated at their IAF, coil in the F3 position, 120 % MT, frequency 6–13 Hz, 40 pulses per train, average 15-s inter-train interval, 3000 pulses per session. All patients, raters, and treaters were blinded.

Results: In the intent to treat (ITT) sample, both groups had significant clinical improvement from baseline with no significant between-group differences, with the USYNC group having mathematically more remitters but fewer responders. (ITT -15 SYNC; 13 UNSYNC, response 5 (33 %), 1 (7 %), remission 2 (13 %), 6 (46 %). The same was true with the completer sample - 12 SYNC; 12 UNSYNC, response 4, 4 (both 30 %), remission 2 (17 %), 3 (25 %)). The clinical EEG phase synchronization system performed well with no failures. The average treatment session was approximately 90 min, with 30 min for placing the EEG cap and the actual TMS treatment for

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https://doi.org/10.1016/j.brs.2023.11.010
Received 25 January 2023; Received in revised form 19 October 2023; Accepted 19 November 2023
Available online 2 December 2023

45 min (which included gathering 10 min of resting EEG). Four subjects (1 SYNC) withdrew before six weeks of treatment. All 24 completer patients were treated for six weeks despite the trial occurring during the COVID pandemic. SYNC patients exhibited increased post-stimulation EEG entrainment over the six weeks. A detailed secondary analysis of entrainment data in the SYNC group showed that responders and non-responders in this group could be cleanly separated based on the total number of sessions with entrainment and the session-to-session precision of the entrained phase. For the SYNC group only, depression improvement was greater when more sessions were entrained at similar phases.

Conclusions: Synchronizing prefrontal TMS with a patient's prefrontal alpha frequency in a blinded clinical trial is possible and produces progressive EEG entrainment in synchronized patients only. There was no difference in overall clinical response in this small clinical trial. A secondary analysis showed that the consistency of the entrained phase across sessions was significantly associated with response outcome only in the SYNC group. These effects may not simply be due to how the stimulation is delivered but also whether the patient's brain can reliably entrain to a precise phase. EEG-synchronized clinical delivery of TMS is feasible and requires further study to determine the best method for determining the phase for synchronization.

1. Background

Daily prefrontal TMS for depression was FDA-approved in 2008 and is now widely used [1–4]. One of the earliest hypotheses held that rTMS might be an effective antidepressant because the proximal stimulation over DLPFC could cause changes in a circuit involving distal brain regions, including the anterior cingulate cortex (ACC) and the subgenual ACC (sgACC), where these distal regions are believed to be linked to the disease state [5–11].

As initially developed, TMS treatment delivered pulses to the prefrontal cortex at a standard frequency (e.g., 10Hz) and did not measure EEG or try to synchronize with underlying brain rhythms. In cardiology, to stimulate the heart effectively, one must know the heartbeat's rhythm and phase to perform cardioversion. For most of the 30-year history of developing TMS as a research tool and clinical treatment, the field largely ignored the brain's natural oscillations that cycle between excitability and inhibitory states [12]. Recently, neuroscientists have discovered that coordinating brain stimulation with underlying brain rhythms can have additive or canceling effects [13]. For example, using TMS over the motor cortex and measuring motor evoked potentials (MEP), Zrenner and colleagues showed that the phase of the ongoing sensorimotor mu-rhythm modulates corticospinal excitability, with the highest excitability at the rising phase [14]. Since then, others have shown phase dependence of TMS effects in the visual cortex and other regions [15–19].

We wondered whether the neural or behavioral effects of prefrontal rTMS might depend on the prefrontal alpha rhythm. Theoretically, the effect of a single TMS pulse, or a train of pulses (rTMS), might be diminished if it was delivered when the brain was temporarily less excitable.

To review, frequency is the total number of rotation cycles occurring per second and is expressed in cycles per second or hertz (Hz). In this manuscript, the term 'phase matching' refers to timing the TMS pulse delivery with the endogenous oscillatory activity in the alpha frequency band. [We deliver TMS in the standard biphasic magnetic pulse but as this is exceedingly brief relative to the EEG phase, we do not try and coordinate the biphasic TMS phases with the EEG. We simply treat the TMS pulse as a single unit to time with the patient's EEG phase. (see Fig. 6 sinewave).

To address this question, we designed and constructed a combined fMRI/EEG/TMS (fET) system. With this system, we found that prefrontal TMS pulses have different effects in the cingulate gyrus as a function of the EEG alpha phase [20]. In both healthy controls and depressed patients, TMS-evoked functional connectivity between DLPFC and subgenual ACC (sgACC) depended on the prefrontal EEG alpha phase. Pulses delivered during a rising phase produced larger blood flow changes at a *trans*-synaptic site deep in the brain (the ACC) than did pulses delivered during a falling phase. Using the fET system, we identified the specific phase of an individual's prefrontal EEG alpha rhythm that maximally increased BOLD activity in the dorsal ACC (dACC) when TMS was applied at that phase.

Using this knowledge and method, we then carried out a six-week course of the therapeutic rTMS sessions. In this single enrolling site clinical trial, we developed a novel closed-loop system that delivers personalized EEG-triggered rTMS to patients undergoing treatment for major depressive disorder. The control condition used this same system but delivered the first pulse of each train randomly with respect to the EEG phase–i.e., a random phase for the start of each rTMS train, with the train still at the individual's IAF. Without unblinding the clinical results, we recently reported in a subsample of this trial that when rTMS is applied over the dorsal lateral prefrontal cortex (DLPFC) and synchronized to the patient's prefrontal alpha rhythm, patients develop strong phase entrainment over a period of weeks, both over the stimulation site as well as in a subset of areas distal to the stimulation site [21]. In addition, at the end of the course of treatment, this group's entrainment phase shifted closer to the phase that optimally engages the distal target, namely the ACC. These entrainment effects were not observed in the group that was given rTMS without initial EEG synchronization of each TMS train. The entrainment effects built over the course of days/weeks, suggesting that these effects engage neuroplastic changes, which may have clinical consequences in depression or other diseases.

Here, we report the unblinded and full clinical antidepressant results of this trial and describe how the EEG entrainment changes we observed relate to clinical outcome, particularly within the SYNC group.

2. Methods

2.1. General study design

This study took place at the Medical University of South Carolina (MUSC) Institute of Psychiatry between November 2018 and January 2022. It was funded by the NIMH in an R21/R33 format (ClinicalTrials.gov listing NCT032421808). Prior to any study procedures, all patients signed a written consent form approved by the MUSC IRB.

Advertising was done through mailings to key clinical providers in the Charleston area and flyers and email postings. Patients with treatment resistant unipolar major depression with a baseline Hamilton Rating Scale for Depression (HRSD) score (24-item) >20 were enrolled. Inclusion/Exclusion Criteria: Patients had to have a diagnosis on the SCID-P to derive DSM-IV criteria of a diagnosis of unipolar major depressive disorder without psychosis. They had to have a Hamilton Depression Rating Scale 24 item score of ≥20 and be between 21 and 70 years old. They could maintain fixed and stable antidepressant medications (at least three weeks prior to start with no change). They had to have a moderate level of treatment resistance (1–4 medications in the current episode or intolerance to at least three trials) and have a current episode duration no greater than three years. They could not have a history of schizophrenia, schizoaffective disorder, other [non-mood disorder] psychosis, depression secondary to a medical condition, mental retardation, substance dependence or abuse within the past year

(except nicotine), bipolar disorder, psychotic features in this or previous episodes, amnestic disorder, dementia or MMSE ≤24, delirium, obsessive-compulsive disorder, post-traumatic stress disorder, or panic disorder. They could not have current vagus nerve stimulation (VNS) therapy, electroconvulsive therapy (ECT), or TMS within three months or a history of non-response to ECT. They could not have safety contraindications to MRI scanning. They must have been medically stable and without active suicidal intent or plan or suicide attempt within the past 12 months.

Prior to the clinical trial, all patients had two MRI scans after obtaining consent but before being randomized (see Fig. 1 for more details). During the first scan on a Siemens Prisma 3T scanner, they had a short structural scan and resting state fMRI. If they could tolerate this and were not claustrophobic, they then had a longer fNET scan where the person's individual alpha and synchronization phase were identified using the method described in Faller supplemental material S.1 [21]. The 15 subjects in the blinded analysis (Faller et al., 2022) are also included in this current manuscript as part of the completer samples (as well of course as ITT), with their clinical scores and group assignment.

After every five treatment sessions (sometimes roughly referred to as a 'week', but this is not always true to the calendar) (described in Fig. 1), patients had the following assessments performed by a qualified individual who was blinded to the patient's assigned treatment group: Hamilton Depression Score (Ham-D 28 item), Inventory of Depressive Symptomatology Self-Report (IDS-SR), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF), and Clinical Global Impression (CGI).

2.2. EEG preparation, TMS system, TMS delivery, randomization, blinding

For a detailed description of the clinical TMS-EEG system, see Ref. [21]. All subjects had 32-channel EEG setups for each of the 30 rTMS sessions (see Fig. 2). Briefly, the SYNC and UNSYNC treatment groups received the following dose of rTMS delivered over the left prefrontal cortex**:** 6–13 Hz (at individual IAF), 120 % Motor Threshold, 40 pulses per train, average 4-s pulse train, 3000 pulses per session, one session per weekday as the train length varied by frequency (e.g., it takes 4 s at 10 Hz to get 40 pulses, but 5 s at 8 Hz) we adjusted the intertrain off time (8–12 s) so that all treatment sessions were the same length regardless of the IAF. Treatments were delivered for a fixed 6-week interval. Interruptions during the treatment were allowed as needed for patient comfort or convenience by using the "pause" selection on the device. However, incomplete treatments were recorded. When a treatment was missed, the count continued into the subsequent week to complete the missed days. Clinical evaluations occurred after every five treatments regardless of calendar day although we commonly lump 5 treatments into a batch and loosely use the term 'week' for each of these.

In the SYNC group only, the initial TMS pulse in each rTMS train was systematically phase-locked to the individual's optimum phase (as determined by a prior fET session), and in the other group (UNSYNC) the initial TMS pulse in the train was applied randomly. In the UNSYNC group, the start of each train was random (from a uniform distribution), and thus, a small fraction of starts could be at the subject's preferred phase. We did not exclude this possibility. Nonetheless, the random nature of the phase triggering in the UNSYNC group meant that there was never a systematic repeat of phase-locking in this group. The only difference between the two groups was the presence or absence of systematic phase-locking of the initial pulse in each train for all 75 trains in all 30 sessions (2250 phase-locked pulses over the six weeks). IAF was re-determined prior to each treatment session (at 0.1 Hz accuracy) because IAF may vary slightly from day to day, and stimulation at a non-IAF frequency would result in loss of phase-locked synchronization with endogenous alpha oscillations. Phase-locked stimulation was hypothesized to maximize target engagement as reflected by activation in the dorsal ACC (previously demonstrated and reported by Refs. [20,21]) and, in turn, to increase the antidepressant effect (investigated in this clinical trial).

2.3. EEG phase entrainment

In our previous work with a subset of these patients [21], but without clinical outcomes which were still blinded, we found that the degree of phase entrainment, as measured by the inter-trial phase coherence (ITPC), increases across treatment sessions for patients who received the synchronized rTMS treatment (SYNC group). Such an effect was not observed for patients who received the non-synchronized rTMS treatment (UNSYNC group). In addition to the degree of phase entrainment,

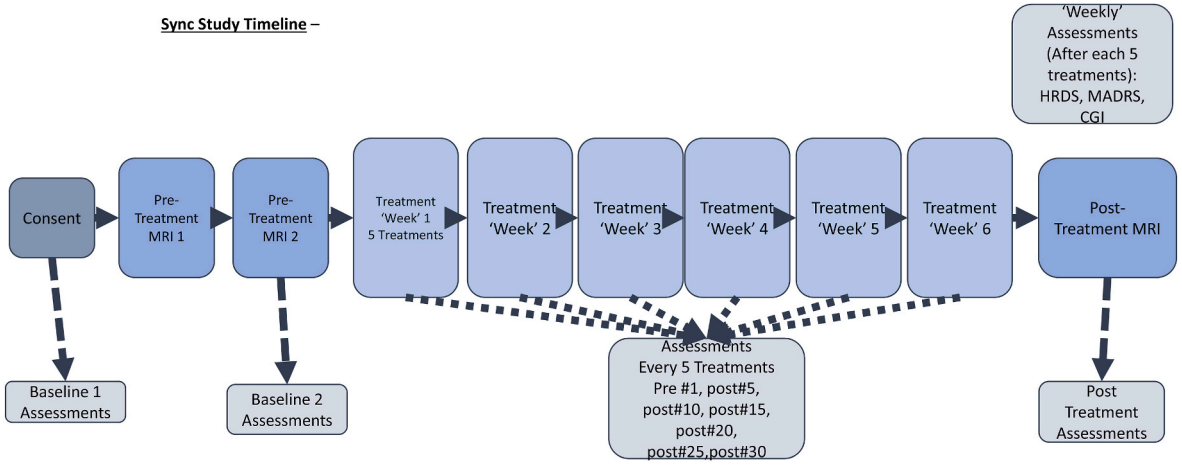

Fig. 1. Study Timeline
After consent and baseline screening assessments, subjects had 2 MRI scans performed. These MRI's were concurrent TMS/EEG/BOLD fMRI (fET). Subjects were then randomized to SYNC or UNSYNC and were treated for 30 TMS sessions over six weeks, followed by a post-treatment course concurrent TMS/EEG/BOLD fMRI (fET). Immediately before the first TMS session, and then after every five treatment sessions (sometimes roughly referred to as a week, but this is not always true to the calendar), patients had the following assessments performed by a qualified individual who was blinded to the patient's assigned treatment group: Hamilton Depression Score (Ham-D 28 item), Inventory of Depressive Symptomatology Self-Report (IDS-SR), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF), and Clinical Global Impression (CGI). For data analysis, the pre#1 scores were used as the baseline for calculating clinical response data, as this was closer to the actual start of treatment.The time between the last TMS treatment and the post MRI scan varied from the next day to 14 days, depending on the MRI scanner.. (This entire trial was done during the COVID pandemic.)

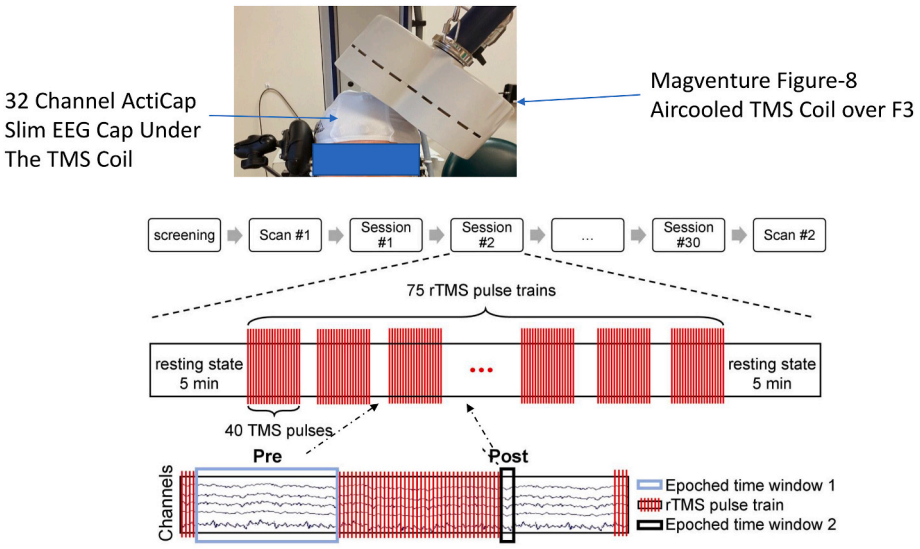

Fig. 2. Synchronized rTMS system
The TMS EEG system is shown on a volunteer. For all treatment sessions, each subject had the 32-channel Actichamp ActiCap slim EEG placed, with a covering cap, and then the Magstim coil was placed over F3. Bottom panel: Subjects wore earplugs and had a 5-min eyes open EEG, followed by the TMS session with another 5-min resting EEG at the end. During the rTMS session, the real-time EEG analysis system calculated their individual alpha frequency (IAF) and delivered the initial pulse in each train either synchronized or random. EEG was acquired for all subjects and all sessions, and continuously within sessions, including before, during, and after each TMS train. For a complete system description, see Faller et al., 2022, *Brain Stimulation* [21].

as measured by the ITPC, we also considered the entrainment phase φ_{ent}, defined as the corresponding phase of the post-stimulation ITPC value in circular space (i.e., the phase at which the first maximum ITPC after the rTMS pulse train).

Here, we report the relationship between phase entrainment and clinical outcome. For each treatment session where the first post-stimulation ITPC peak is detected, there is a corresponding entrainment phase φ_{ent}. We plot the distribution of φ_{ent} using a polar histogram (with twelve phase bins where each bin has a 30-degree range; see example in Fig. 3) of each patient's entrainment phases. All calculations are done at the near target region which includes electrodes FP1, F3, and F7. With the polar histogram, we calculate a metric that characterizes how frequently the same/similar φ_{ent} are seen throughout the 6-week treatment. One such metric is the maximum percentage of the entrainment phases across the phase bins—i.e., the phase bin with the highest peak. To test whether the distribution of entrainment phases is related to clinic outcome, we tested the correlation between this peak in the circular histogram (i.e., the bin having the maximum percentage) and the rTMS treatment effect for both SYNC and UNSYNC groups. We represent the rTMS treatment effect by the percentage decrease in the Hamilton Rating Scale for Depression (HRSD) between session#1 (recorded immediately before the first actual treatment, and thus a true baseline).

In addition to calculating the peak of the entrainment phase distribution, we also use an unsupervised clustering algorithm to divide the entrainment phases into two groups. Specifically, we used the Fast Optimal Circular Clustering (FOCC) algorithm to cluster the entrainment phases into two groups [22]. The circular data clustering problem can be defined as grouping N points on a circle into K clusters via minimizing the within-cluster sum of squared distances. This can be done by applying the K-means algorithm repeatedly, however this takes quadratic time and becomes impractical for large circular datasets. The FOCC algorithm overcomes this issue by providing a reproducible

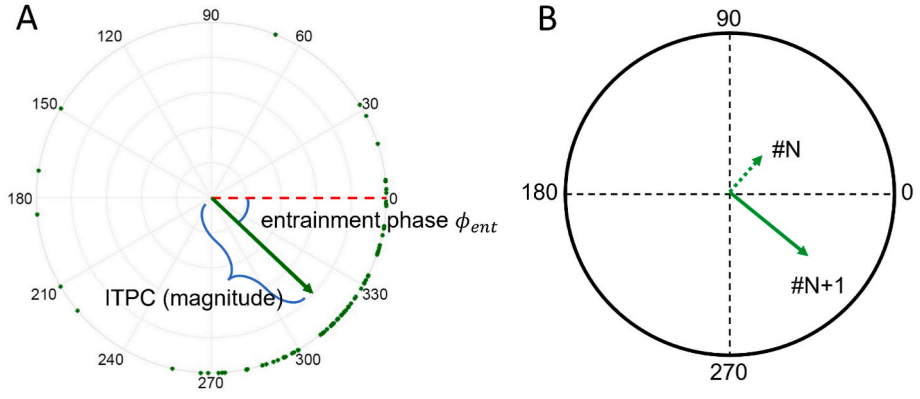

Fig. 3. A: An example of the intertrial phase coherence (ITPC) and entrainment phase φ_{ent} measured at the target electrode (F3) from one session of one SYNC patient. The green points are the phase points for each trial (i.e., 75 rTMS pulse trains) of one session, plotted in polar coordinates (r = 1). The green vector is the trial-weighted average of these points. The length of the green vector defines the ITPC value, while the corresponding angle defines the entrainment phase φ_{ent}. In this example, the ITPC value is 0.7945 and the entrainment phase φ_{ent} is 316° (i.e., using the acute angle definition). **B:** An example of an increased ITPC value from session #N (green dash vector) to session #N+1 (green solid vector). As we can see, an increase in ITPC can be observed regardless of whether the entrainment phase is consistent—i.e., an increase in entrainment magnitude (ITPC) does not imply that the entrainment phase is the same and the two can vary independently. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

algorithm for the worst-case O ($KNlog^2$ N) and it is optimal based on its property of monotonic increasing cluster borders over frames on linearized data. By repeating the same circular clustering analysis for each patient, we obtain the number of sessions classified into each cluster, with the cluster having more sessions considered to be the entrained phase. Moreover, we would expect that the circular standard deviation of phases within the entrained class would be smaller compared to the other (outlier) class (i.e., those phases belonging to the entrained class would be more likely to have similar phase angles in the circular space). We thus calculate the difference between the circular standard deviation of two classes by subtracting the standard deviation of the cluster with fewer sessions from the cluster with more sessions (i.e., $SD(C1) - SD(C2)$). Negative values of this difference would be expected to be indicative of a robust entrained phase (i.e., $SD(C1) < SD(C2)$, see Fig. 4) whereas more positive values would indicate less reliable or poor entrainment, since fewer sessions would have a more consistent entrained phase.

2.4. Clinical trial statistical analysis

Clinical unblinding was done only after all data was checked and locked. For primary outcomes we used the 28 item Hamilton Rating Scale for Depression (HRSD). Those with a final HRSD score <10 were labeled remitters. Response was defined as >50 % reduction in HRSD from baseline. Thus, all remitters are also responders, although for ease of understanding, we report responders but not remitters as a separate group. We collected HRSD28 at the screening baseline as well as immediately before the first TMS treatment session. For all efficacy results we use the scores immediately before the first treatment (pre#1) as it was the closest to the start of the trial. The main clinical analysis focuses on the intent-to-treat (ITT) sample, which is defined as all randomized patients who received at least one rTMS clinical treatment. For the purposes of testing EEG-related outcomes, only the completer sample was used. The completer and fully adherent samples were identical.

For testing categorical clinical remission data, we performed a chi-square test on the IIT and completer sample using Graph-Pad Prism.

To evaluate changes in Hamilton Depression Ratings over time, we performed a two-way repeated measures ANOVA with time and group as factors.

3. Results

As shown in Fig. 5 (consort diagram), we screened 54 patients and consented 34. Two patients withdrew before, or could not complete, the MRI scan to determine their optimum alpha phase, leaving 28 patients for randomization. Fifteen were randomized to SYNC, with three patients not completing 30 treatment sessions, and 13 to UNSYNC, with 1 not completing 30 treatment sessions, leaving 12 completers within each group. Full demographics are shown in Table 1. There were no differences between the two groups in age, gender, or length of current depression episodes.

3.1. MRI determined best alpha phase

Fig. 6 displays the best target phase for each patient grouped by responder and SYNC or UNSYNC. The best target phase was that phase that produced the largest BOLD increase in the ACC during the pre-treatment fET session. [Note that apparently many of the UNSYNC responders cluster near the negative peak. The UNSYNC patients received rTMS at their IAF unsynchronized to this best phase information.]

3.2. System performance

The system performed well with few failures (delay in treatment or stopping treatment for the day early before all trains). The system sampled the EEG between each train and recalculated the correct timing. The mean time for the intertrain interval was 15.6s, 8.1s std, median 13.48 s. Problems encountered out of a total of 769 sessions were – system failure and immediate restart with no problem with treatment – 3/769; unable to get a reasonable EEG signal, used previous day's value – 4/769; ran the pre study resting EEG twice in order to get a root mean square error (RMSE) value – 7/769. In 45/769 sessions the RMSE increased because the system could not obtain 10 locks in 5 min.

3.3. Integrity of the blind

We asked patients to best guess (forced choice) their randomization status after the initial session and then again after the last session. They gave a confidence level from 1 (not confident) to 6 (very confident). At baseline, 7/12 guessed correctly in the SYNC group (1.9 confidence), and 2/12 correctly in the UNSYNC group (2.6 confidence). At the end of the trial, 5/12 guessed correctly in the SYNC group (2.75 confidence), and 8/12 correctly in the UNSYNC group (2.3 confidence). These are not above chance and there was no frank unblinding of patients, treaters, or raters.

3.4. Depression outcomes

In contrast to the study hypothesis, we failed to find a significant between group difference in either categorical (remission) or continuous measures of the (HRSD), for either the ITT or completer analyses. There were 2 remitters in the SYNC and 3 in the UNSYNC group (two-sided chi-Square 0.253, df 1, z 0.5, p = 0.6, NS).

Table 2 shows the distribution and percentage of clinical outcomes

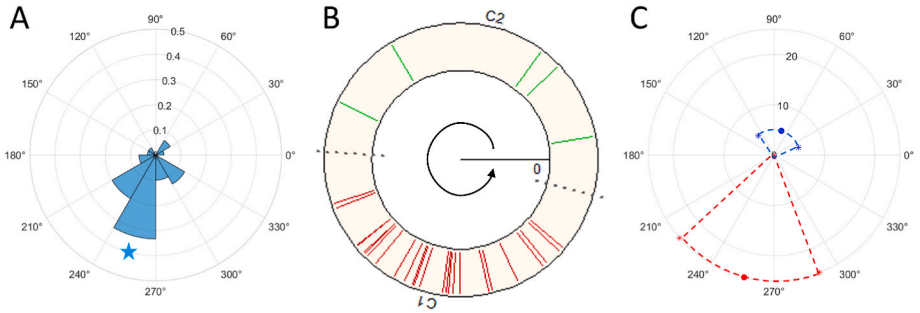

Fig. 4. Clustering entrainment **A:** An example of a polar histogram with twelve phase bins (30° range for each bin) for one patient. The peak (i.e., maximum percentage) in the histogram for this patient is 0.33 (10 sessions out of 30 sessions located at the phase bin between 240 and 270°, marked as a blue star). **B**: Example of circular clustering (with two classes) for data in A. Clustering this patient's entrainment phases into two classes (C1 and C2), results in 25 sessions clustered into C1 (red) and 5 sessions clustered into C2 (green). **C**: Example of circular standard deviation for the clustering. Given the clustering in B, the circular standard deviation (SD) of the two classes is calculated, where $SD(C1) = 0.6109$ and $SD(C2) = 0.9829$. A smaller SD corresponds to a more consistent φ_{ent} (i.e., less variation) across the 6-week treatments. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

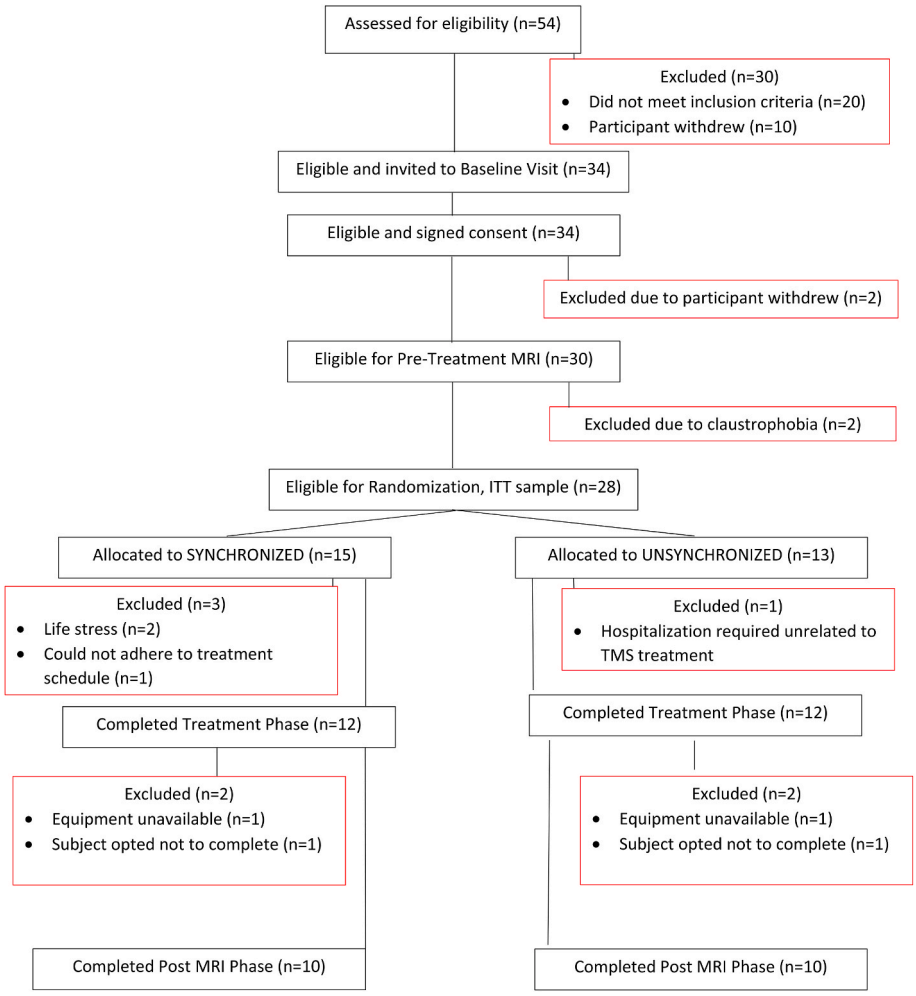

Fig. 5. Consort Diagram
This entire study took place during the COVID pandemic in an outpatient hospital setting which remained open. All subjects and treaters and raters wore masks at all times. We screened 54 subjects and then invited to consent 34 who were eligible for screening, all of whom met full inclusion and exclusion criteria and were consented. Two patients withdrew after consenting but before starting the study. We attempted to scan 30 subjects but 2 developed claustrophobia in the scanner and withdrew. Thus 28 patients were randomized, 15 for SYNC and 13 with UNSYNC. Over the 6 weeks of treatment 4 patients withdrew (3 SYNC, 1 UNSYNC). Three (SYNC) felt they could not handle the daily commuting during COVID, and one patient (UNSYNC) had a medical illness requiring hospitalization unrelated to depression. This left 12 completers in each group. We asked patients to have a full EEG/fMRI TMS scan at the end of the treatment course, but with COVID sometimes this occurred several weeks later, or was simply not available. For MRI pre and post analyses we only had 10 in each group.

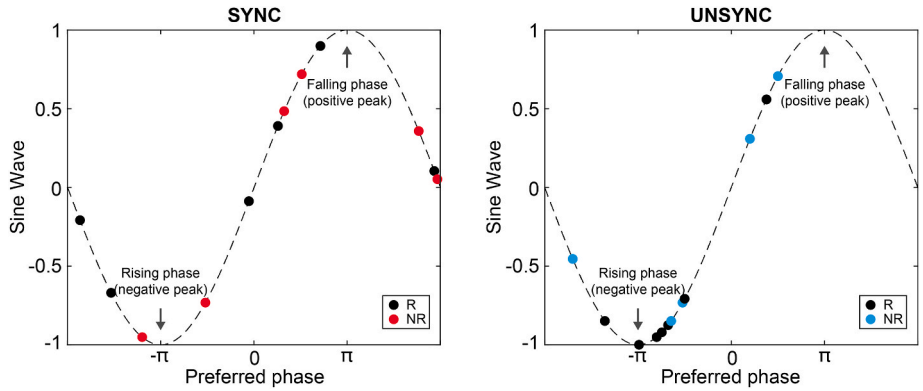

Fig. 6. Distribution of the estimated target phase at the first scan (i.e., the MRI scan before the entire treatment course) for all completers (n = 12 for each group) for the SYNC group (left panel) and UNSYNC group (right panel). Each point represents one patient (black dots are responders, red dots are SYNC nonreponders, blue dots are UNSYNC non-responders), and the dashed line is the referenced sine wave. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Subject demographics for all patients (ITT) and divided by treatment group.

	All	SYNC	SYNC	UNSYNC	UNSYNC	p-value
	Patients	(All)	(Comp)	(All)	(Comp)	
Age (years)	45 ± 13	43 ± 12.6	42 ± 12.1	45 ± 12.2	44 ± 12.4	NS
Sex (F; M)	19 F; 9 M	10 F; 5 M	9 F; 3 M	9 F; 4 M	8 F; 4 M	–
Duration of Illness (weeks)	87 ± 124.3	110 ± 123	91 ± 79.3	61 ± 48.5	60 ± 50.4	NS
Baseline HRSD	30.4 ± 5.2	30.1 ± 4.3	29.7 ± 4.3	30.2 ± 7.2	29.9 ± 7.0	NS
IAF (Hz)	9.2 ± 1.8	9.4 ± 1.9	8.9 ± 1.9	9.2 ± 1.8	9.1 ± 1.6	NS

Table Legend: Statistics (mean ± standard deviation) of age (years), sex, duration of illness (weeks), Hamilton Rating Scale for Depression, 24-item (HRSD) measured at the baseline immediately prior to the first treatment, and individual alpha frequency (IAF, Hz) at the first treatment are reported. All patients are the ITT sample, and Comp are the Completer Sample. [The exact IAF numbers for the UNSYNC (All) and for All patients are not a typographical error. They are different when expressed to more decimal points.].

Table 2
Distribution (N,%) in three non-overlapping clinical outcome categories: Intent to treat (ITT) and completer samples.

	Intent to Treat			Completer		
	All	SYNC	UNSYNC	All	SYNC	UNSYNC
Remitter	8 (28 %)	2 (13 %)	6 (46 %)	5 (21 %)	2 (17 %)	3 (25 %)
Response but Not Remission	6 (21 %)	5 (33 %)	1 (7 %)	8 (33 %)	4 (30 %)	4 (30 %)
Non-Responders	14 (50 %)	8 (53 %)	6 (46 %)	11 (46 %)	6 (50 %)	5 (42 %)
Total	28	15	13	24	12	12

(categorical, HRSD rating) at the end of the treatment course for both the Intent to Treat and the Completer Samples. These outcomes in terms of response and remission are roughly similar to other published studies using rTMS for treatment resistant depression. There is no significant difference in clinical outcomes between the SYNC and UNSYNC groups.

Fig. 7a shows the weekly HRSD scores for the SYNC and UNSYNC before and after the 30 treatments for the completer sample. Overall, there are no significant between group differences (two-way repeated measures ANOVA, group, SYNC, UNSYNC, and Time. Time, $F(2.97, 65.3)$, $p < 0.0001$, Group NS and Group by Time NS). Based on the result of Fisher's exact test on the response of completers ($p = 1$, NS), we report that there is no significant difference between treatment groups (6 out of 12 SYNC subjects are responders and 7 out of 12 UNSYNC subjects are responders).

Fig. 7B shows the consistency over time in HRSD improvements in the UNSYNC group, while the SYNC group is inconsistent over time and fluctuates, with some patients even worsening. As we were interested in whether the EEG entrainment was linked to clinical improvement, this motivated and guided the analysis tracking the consistency and precision of the stimulation across sessions. That motivated the next analysis that suggests if there is high phase precision that is consistent across sessions, we can cleanly predict responders vs non-responders in the SYNC group.

3.5. Entrainment outcomes correlating with clinical outcomes

We then investigated the relationship between the maximum percentage phase angle (i.e., the histogram peak in the circular space of phases) and the HRSD changes across sessions. Pearson correlation was used to quantify their linear relationship and direction of association. This maximum percentage was our first measure of the robustness of φ_{ent} across the six weeks of treatment. We found a significant positive correlation between this maximum percentage and percent HRSD decrease across the SYNC treatment group ($p = 0.023, R^2 = 0.420$, see Fig. 8). In other words, the more consistent a SYNC participant's entrainment phase was across sessions, the more likely they had a better clinical improvement. This relationship was not, however, seen in the UNSYNC group, ($p = 0.113, R^2 = 0.285$, see Fig. 8).

The second measure we considered for assessing the relationship between φ_{ent} and the clinical outcome was based on our cluster analysis (see Materials and Methods), with results plotted in Fig. 9. For the SYNC group, all the clinical responders (defined based on the decrease between the baseline and post-treatment HRSD measurement) are patients whose entrainment phases are clustered in a similar direction, or more consistent, across the entire treatment (across sessions) as depicted in the joint space of the number of sessions clustered into the entrained class (i.e., # of sessions in the entrained class) and the difference in the standard deviation between the entrained and outlier classes (i.e., ΔSD (entrained-outlier)). In fact, in Fig. 9A, for the SYNC group, we see clear separation in this space with patients who had more sessions (x-axis) entrained at similar direction (y-axis) relative to the outlier cluster all being clinical responders. This suggests again, as in Fig. 8 using a different metric, that the more often patients entrain to a similar phase across the 6-week treatment, the more likely they are to be clinical responders. Analysis of the UNSYNC group did not show any separation in the joint space (see Fig. 9B). Additionally, we tested the association between entrainment and clinical outcomes by combining the result between two groups (see Fig. 9C). Although 9 clinical responders are on the side indicating greater entrainment effect, there is no significant association between them regardless of groups (Fisher's exact test: $p = 0.675$).

4. Discussion

Here, we describe how synchronizing the first pulse in rTMS trains with underlying brain rhythms is feasible and can be done in a clinical setting without much additional time and effort. This clinical EEG-rTMS system works well in real-time, can be delivered in an effective double-blind fashion, and is safe. In this small sample proof of concept clinical trial, we found that patients who received TMS synchronized to their prefrontal alpha phase showed progressive entrainment. Importantly, the degree of this entrainment correlated with their clinical improvement. Moreover, we find a relationship between EEG entrainment and clinical response within the synchronized patients. This relationship can cleanly divide responders from non-responders.

These exciting brain biomarker results linking EEG synchronization with progressive entrainment did not result in a measurable clinical difference. It is somewhat puzzling that the SYNC patients overall did not have a superior clinical outcome than UNSYNC patients, as we had predicted. There are several potential explanations for this lack of a clinical difference. It is important to remember that to keep the study blinded, we treated all patients at their IAF, and few studies have done this, so it is hard to compare these results with general clinical TMS results for depression. Based on our secondary analysis result of global cortical excitability (reported in our other publication under review), we find that there is a significant positive relationship between the decrease of excitability and clinical improvement regardless of the group assignment, which further helps to explain this non-significant clinical difference between groups. Therefore, we think the synchronized rTMS might cause a more systematic changes in brain dynamics compared to the non-synchronized stimulation and help us to design/adjust individualized treatment protocol (please see more details in the preprint). This is the reason why we think the association observed only within the

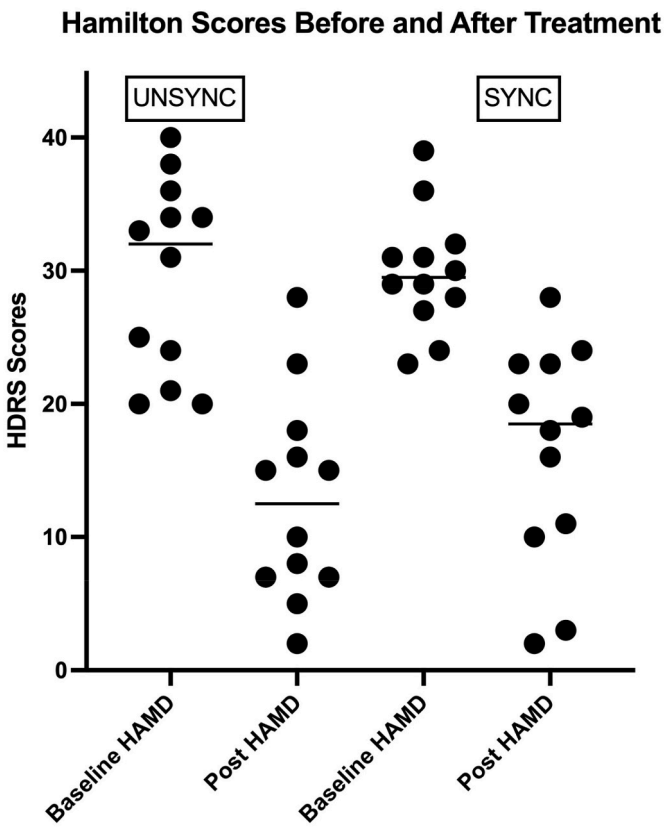

Fig. 7. A Entry and Exit Hamilton Scores by Group. Although subjects improved over the 30 treatment course, there was no statistically significant difference between groups.

B

Hamilton Scores again broken out by groups across sessions/weeks. Each color in each subfigure indicates one subject and clinical responder is plotted with cross marks while non-responder is plotted with circle marks. The consistency of group-level clinical improvement is observable with the changes of the boxplot (mean was highlighted with red bar), where UNSYNC group shows a generally linear trajectory. This display provides insight into the potential need to track the consistency and precision of the stimulation across sessions. This motivated our analysis, showing if there is high phase precision that is consistent across sessions, we can perfectly predict responders vs non-responders in the SYNC group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

SYNC group would be important.

Additionally, for the 'correct' synchronization phase, we chose the phase that maximally increased BOLD activity in the cingulate. One wonders if we should have chosen the phase that maximally decreased cingulate activity [23–28]. That would be an important next study. Unfortunately, our UNSYNC group had their phase chosen at random and not the opposite phase (i.e., with 180° shift) of the SYNC group.

Moreover, we assumed the preferred phase was the one chosen during the MRI session at the beginning of the study. However, the preferred phase may not have been constant and might have needed to be updated during the trial. Does the preferred phase change over time, and did we thus keep entraining at a phase that was no longer the preferred phase in the SYNC group? We found that the precision of reproducibility of the entrainment, particularly the entrainment phase, is a factor that correlates with treatment outcomes for the SYNC group. A preliminary analysis of post-treatment MRI scans shows that some subjects shifted in their preferred phase over the treatment course. We may need to make periodic adjustments to the preferred phase over the course of the six weeks.

5. Limitations

This small proof-of-concept study has limitations, including having only two arms and a relatively small sample size. We did not have funding to add a third arm of conventional standard clinical TMS, to have a synchronized group with their initial pulse given at the individual's worst timing, or to synchronize to the timing that maximized decreases in cingulate BOLD activity. This study shows that clinical trial synchronization building on EEG-TMS-fMRI analyses is feasible, and future studies will hopefully examine these important next questions in this area.

5.1. Further work

This system worked well in terms of delivering pulses and inducing entrainment. However, in this study, entrainment was not easily sustained across multiple treatment sessions, and even if entrainment could be maintained, it is not clear how significant the clinical effect would be. These data suggest but do not prove that EEG synchronization may correlate with antidepressant outcome. This overall approach of EEG phase synchronized TMS is not limited to a specific disease (depression), scalp location (DLPFC) or EEG rhythm or phase. More work is needed to understand how frequently the optimal within individual phase changes if it does. To this end, we are incorporating combined TMS-EEG and fNIRS for less expensive and more frequent assessment of the optimum phase. We are also investigating more global EEG-synchronized TMS-induced network effects that might correlate with clinical outcomes and serve as biomarkers for future studies.

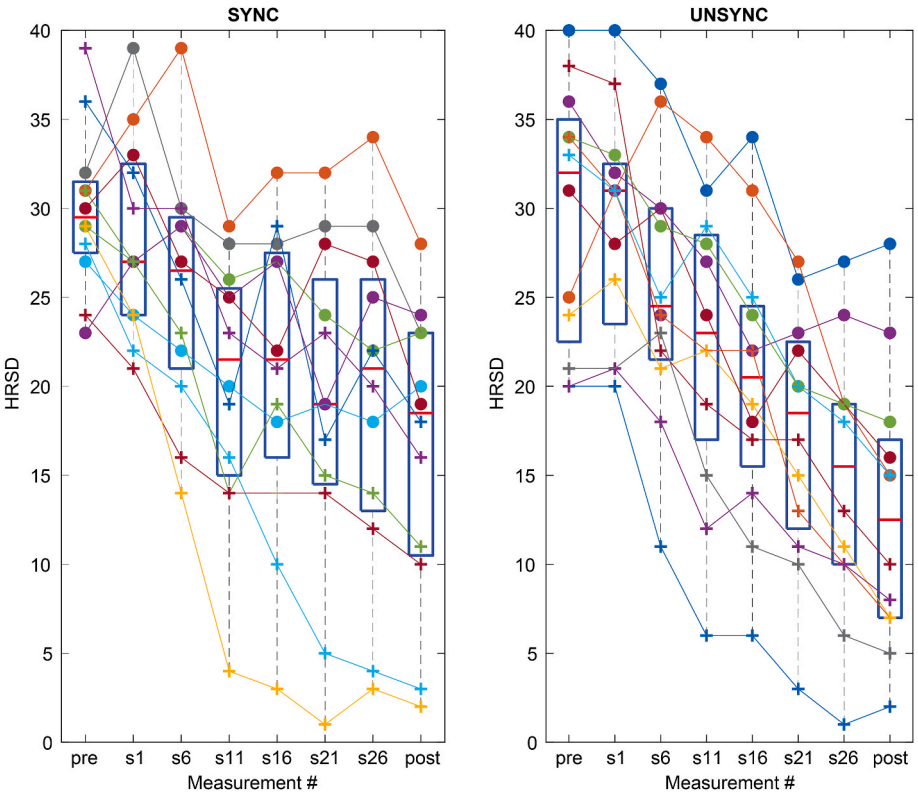

Fig. 7. (*continued*).

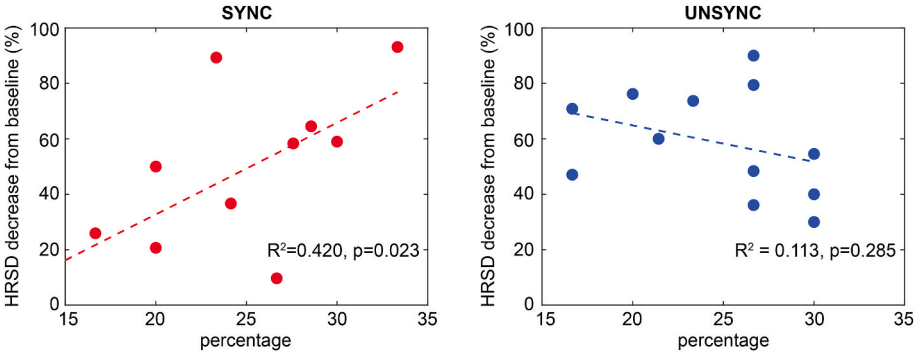

Fig. 8. Correlation between the maximum percentage phase angle (i.e., the histogram peak in the circular space of phases) and HRSD decrease (%, between the baseline and post-treatment measurement as shown in Fig. 7a) across the treatment for each group. On the left is the SYNC group ($N = 12$), and on the right the UNSYNC group (N = 12). Each point (red for SYNC and blue for UNYNC) represents one patient, and the dashed line is the fitted line across all patients. For SYNC ($R^2 = 0.420$, $p = 0.023$) and for UNSYNC ($R^2 = 0.113$, $p = 0.285$). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Funding

This work was funded by the National Institute of Mental Health (MH106775) and a Vannevar Bush Faculty Fellowship from the U.S. Department of Defense (N00014-20-1-2027).

CRediT authorship contribution statement

Mark S. George: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Sarah Huffman:** Investigation, Data curation, Visualization, Writing – review & editing. **Jayce Doose:** Methodology, Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Xiaoxiao Sun:** Methodology, Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Morgan Dancy:** Investigation, Data curation, Visualization, Writing – review & editing. **Josef Faller:** Methodology, Software, Formal analysis, Validation, Investigation, Data curation, Writing – review & editing. **Xingbao Li:** Investigation, Visualization, Writing – review & editing. **Han Yuan:** Software, Formal analysis, Investigation, Data curation, Writing – review & editing. **Robin I. Goldman:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Paul Sajda:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Truman R. Brown:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Visualization, Supervision, Project administration,

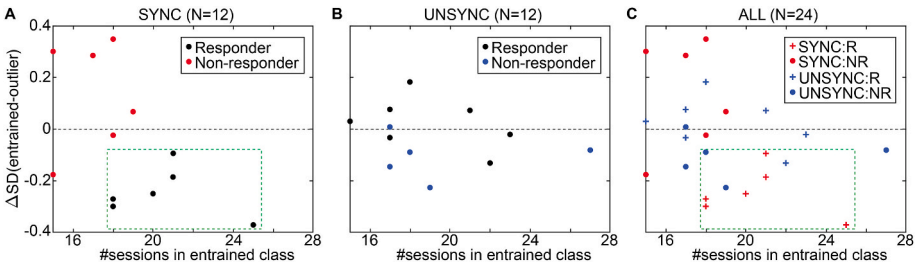

Fig. 9. Clustering of entrainment phases is linked to clinical improvement for the SYNC group. **A.** The results for the SYNC group ($N = 12$), where the x-axis is the maximum number of sessions clustered in the two classes (i.e., the number of sessions in the entrained phase group, greater number of sessions indicates greater entrainment), and the y-axis is the difference of the circular standard deviation between two defined classes (entrained class minus the outlier class, so being less than zero indicates greater entrainment). Each point represents one patient (red: clinical non-responder, black: clinical responder). All clinical responders are clustered on the bottom right corner where the maximum number of sessions in the cluster is large and the difference in the circular standard deviation is small/negative (region of separation highlighted with green dash line box). **B.** The results for the UNSYNC group ($N = 12$) show no such separation in this space. **C.** The results for all completers ($N = 24$) show no such separation regardless of the group assignment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Columbia University (Prof Sajda) along with MUSC (Profs Brown and George) have filed a record of invention for using EEG phase synchronized TMS for treatment of brain diseases. No patents have been issued yet.

Dr. George reports the following: paid consultant – Abbott (Boston Scientific), Sooma, Neurolief; unpaid consultant – Brainsway, Magnus medical. Research grants to MUSC – Livanova, Magnus Medical.

Acknowledgements

We would like to thank: Minnie Dobbins for administrative help, Daniel Cook for help with initial data collection with closed-loop EEG-rTMS, Michael Milici for help building the safety circuit box and ActiChamp testing, DeeAnn Guo for help with ActiChamp testing and initial EEG data collection, Drs. A.J. Mannet and Greg Sahlem for help with clinical trial management. We are also grateful to the patients who participated in this trial. We thank Magstim for an equipment loan for this trial. Magstim was not involved in trial design, management, data analysis or interpretation.

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