Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial

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Objective: Depression is the leading cause of disability worldwide, and half of patients with depression have treatment-resistant depression. Intermittent theta-burst stimulation (iTBS) is approved by the U.S. Food and Drug Administration for the treatment of treatment-resistant depression but is limited by suboptimal efficacy and a 6-week duration. The authors addressed these limitations by developing a neuroscience-informed accelerated iTBS protocol, Stanford neuromodulation therapy (SNT; previously referred to as Stanford accelerated intelligent neuromodulation therapy, or SAINT). This protocol was associated with a remission rate of ~90% after 5 days of open-label treatment. Here, the authors report the results of a sham-controlled double-blind trial of SNT for treatment-resistant depression.

Methods: Participants with treatment-resistant depression currently experiencing moderate to severe depressive episodes were randomly assigned to receive active or sham SNT. Resting-state functional MRI was used to individually target the region of the left dorsolateral prefrontal cortex most functionally anticorrelated with the subgenual anterior cingulate cortex. The primary outcome was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 4 weeks after treatment.

Results: At the planned interim analysis, 32 participants with treatment-resistant depression had been enrolled, and 29 participants who continued to meet inclusion criteria received either active (N=14) or sham (N=15) SNT. The mean percent reduction from baseline in MADRS score 4 weeks after treatment was 52.5% in the active treatment group and 11.1% in the sham treatment group.

Conclusions: SNT, a high-dose iTBS protocol with functional-connectivity-guided targeting, was more effective than sham stimulation for treatment-resistant depression. Further trials are needed to determine SNT's durability and to compare it with other treatments.

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Major depressive disorder is the leading cause of disability worldwide (1, 2), and approximately 50% of patients meet criteria for treatment-resistant depression (3). Repetitive transcranial magnetic stimulation (rTMS), a brain stimulation treatment approved by the U.S. Food and Drug Administration (FDA) for treatment-resistant depression (4–6), targets the left dorsolateral prefrontal cortex (DLPFC), a key area in neural circuitry underlying depressive symptoms that has been shown to be hypoactive in major depressive disorder (7–9). Contemporary FDA-approved protocols for stimulation of the left DLPFC are limited by the long duration of treatment course (6 weeks) (10) and have been only modestly effective, inducing remission after 4–6 weeks of treatment in ~17% of patients who have not shown response to three prior antidepressant treatments (11).

We developed an accelerated, high-dose, patterned, functional connectivity MRI (fcMRI)–guided rTMS protocol aimed at optimizing the treatment of treatment-resistant depression using neuroscience-informed stimulation parameters (12, 13). Our protocol, previously referred to as Stanford accelerated intelligent neuromodulation therapy (SAINT) and now entitled Stanford neuromodulation therapy (SNT), includes 1) an efficient form of rTMS, termed intermittent theta-burst stimulation (iTBS) (14); 2) treatment

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with multiple iTBS sessions per day at optimally spaced intervals (15–18); 3) application of a higher overall pulse dose of stimulation (19, 20); and 4) personalized targeting for application of the stimulation of the left DLPFC to subgenual anterior cingulate cortex (sgACC) circuit (21–26).

Open-label trials of our SNT protocol have shown a remission rate of ~90%, even in treatment-resistant individuals (12, 13), which is almost double the remission rate of ECT for treatment-resistant depression (~48%), the current gold-standard treatment (27). However, the efficacy of SNT has not been investigated in a randomized sham-controlled trial. In the present study, we investigated the antidepressant efficacy of SNT in comparison to an identical schedule of sham stimulation to determine the contribution of the placebo effect.

METHODS

Study Design

We conducted a double-blind randomized controlled study using a 1:1 ratio in a parallel design. The trial was prospectively registered in the U.S. Clinical Trials registry (NCT03068715). All procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. The study was approved by the Stanford University Institutional Review Board. All participants provided written consent before taking part in any study procedures.

On the basis of a power analysis, we aimed to recruit 60 participants for this trial (see the online supplement for power analysis details). We planned an interim analysis after 30 participants had been treated.

Participants

The study was carried out in the Department of Psychiatry at Stanford University from March 2017 to December 2019. We recruited individuals for this study who had a primary diagnosis of major depressive disorder, were currently experiencing a moderate to severe depressive episode (scores ≥20 on the 17-item Hamilton Depression Rating Scale [HAM-D] and the Montgomery-Åsberg Depression Rating Scale [MADRS]) (6, 28), were between 22 and 80 years old, and had moderate to severe levels of treatment resistance as measured by the Maudsley Staging Method (29, 30). Participants were required to maintain a stable antidepressant medication regimen, or remain medication free, for 4 weeks prior to treatment and to remain on this regimen throughout the study (including all follow-up assessments after the 5-day treatment protocol). Potential participants were excluded if they had any primary psychiatric diagnosis other than major depressive disorder or any condition that would increase the risk associated with receiving iTBS (see the online supplement for details). Participants with prior exposure to rTMS, nonresponse to ECT, or a history of psychosurgery for depression were also excluded.

Imaging

Before receiving SNT, each participant underwent both structural MRI and resting-state fMRI. See the online supplement and our previous report on open-label SNT (12) for more detailed information.

Clinical Assessments

Assessments were administered at screening, at baseline, on the next working day after the final day of SNT (immediately after treatment), and 1, 2, 3, and 4 weeks after the final day of SNT. The primary outcome was MADRS (31) score 4 weeks after treatment (week 5), normalized to baseline (week 0). Participants were excluded if their total MADRS score changed by 30% or more from screening to the baseline assessment.

Secondary clinical outcome scales included the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) (32) and the 6- and 17-item Hamilton Depression Rating Scales (HAM-D) (33). The Young Mania Rating Scale (YMRS) (34) and the Scale for Suicide Ideation (35) were administered at all primary time points to assess for safety related to mania and suicidality, respectively. Potential neurocognitive side effects were assessed with a test battery administered at baseline and immediately after treatment, which included the Hopkins Verbal Learning Test–Revised (36) and subtests from the Delis-Kaplan Executive Function System (37): the Trail Making Test and the Color-Word Interference Test. (See the online supplement for detailed information.)

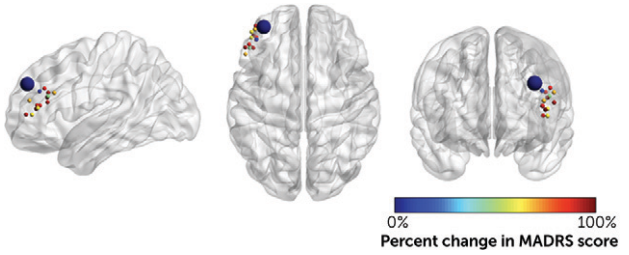
SNT Protocol

Participants were randomly assigned to receive active or sham SNT. All treatments were delivered with a MagVenture MagPro X100 system (MagVenture A/S, Denmark) equipped with a double-sided MagVenture Cool-B65 A/P coil. A Localite neuronavigation system (Localite GmbH, Sankt Augustin, Germany) was used to position the TMS coil over the individualized stimulation target at each session. Ten sessions of active or sham iTBS were delivered daily, for a total of 18,000 pulses per day, on 5 consecutive days (see our previous report on open-label treatment for details [12]). Stimulation was delivered at 90% of resting motor threshold (rMT), adjusted for depth of the identified fcMRI target (38). The personalized targets created for each individual were located at varying cortical depths. Since the strength of the induced electric field decreases with increasing distance from the TMS coil (38–41), depth-corrected intensities were used, with the aim of delivering the equivalent of 90% of rMT to all individualized targets. For safety, stimulation intensity never exceeded 120% of rMT.

Blinding Procedures

All participants, clinical assessors, treatment providers, and other study staff were blinded to treatment assignments. Clinical assessors and treatment providers were separate individuals. Participants were instructed not to discuss

FIGURE 1. Individualized functional connectivity MRI–guided target locations for Stanford neuromodulation therapy in relation to an average F3 coordinate[a]



[a] The location of the F3 coordinate (shown in dark blue) is based on the work of Okamoto et al. (59). The colors of the targets represent the maximum percentage change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) score.

stimulation sensation with study staff. All iTBS sessions utilized the same stimulation coil, with no indication of active or sham orientation. Disposable hydrogel adhesive pad electrodes ("sham pads") were used to deliver synchronous direct current stimulation to simulate the feel of active stimulation. The first seven participants received sham pad stimulation placed directly under the treatment coil; however, this was discontinued because of incompatibility with electroencephalogram equipment. The remaining 22 participants wore noise-canceling earphones (Sennheiser CX300S with memory foam tips) connected to a sham noise generator (MagVenture A/S) to simulate the stimulation noise pattern for each participant at their greatest level of tolerable noise intensity. Additionally, lidocaine was applied to the stimulation site to reduce sensation. To maintain TMS operator blinding, a covering was fixed to the side of the coil before the start of each iTBS session and positioned to restrict the view of any potential facial muscle or jaw movement as a result of active stimulation. All participants were able to view a monitor displaying their fcMRI-guided targeting during and throughout each stimulation session. If multiple study participants were in the outpatient clinic at the same time, they were seated in separate waiting areas and instructed not to speak with each other.

Analysis of the Integrity of the Blind

Participants were asked to guess their treatment allocation and to report their confidence in their guess (on a of scale 1 to 5) on the last day of treatment. A guess metric was created that ranged from 0 (full confidence that the participant received the sham treatment) to 1 (full confidence that the participant received the active treatment). Chance guessing would result in a mean score of 0.5. Departure from chance was assessed with one-way t tests. Because not all participants indicated their confidence, binomial tests were also used to determine whether the number of correct guesses exceeded chance. Finally, linear regression analysis was used to assess the relationship between the guess metric and the change in depression severity, as indicated by percent change in MADRS score from baseline.

fMRI Analysis for Target Generation

Each participant's individualized left DLPFC target was generated utilizing baseline resting-state scans in the same manner as previously reported (12; see also the online supplement). See Figure 1 for target locations.

Clinical Outcome Analysis

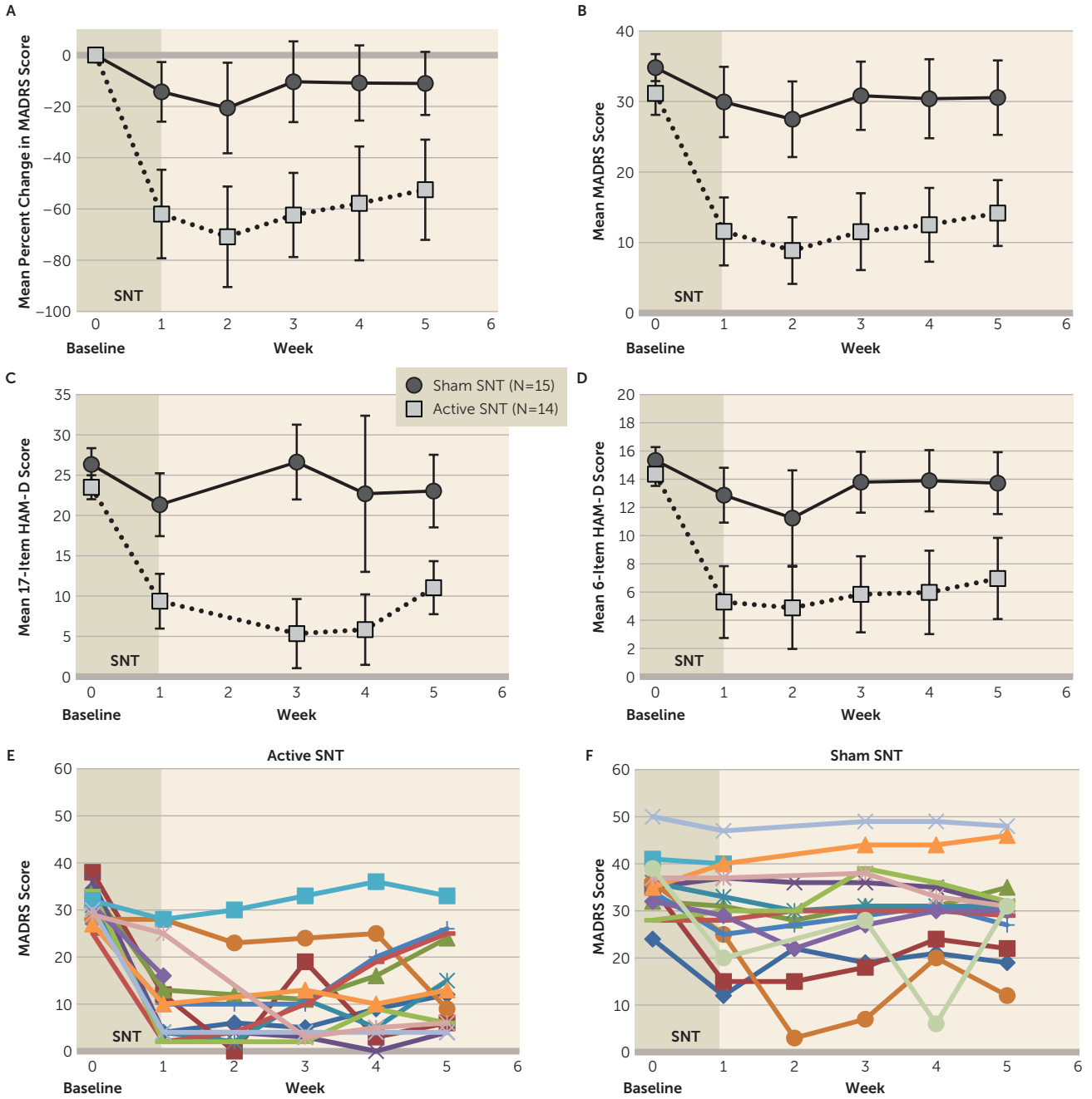
All statistical analyses were conducted using SPSS, version 27 (IBM, Armonk, N.Y.). Our primary outcome measure was the MADRS score 4 weeks after treatment, normalized to baseline. MADRS scores were used to calculate response and remission rates in each group. Response was defined as a reduction ≥50% in MADRS score, and remission was defined as MADRS score ≤10 (42). Participants were identified as responders or remitters if they met these specific criteria at any point during the 4-week follow-up. This method was chosen rather than response or remission at a single time point to allow for different response trajectories (43). This approach to calculating response and remission rates was chosen specifically as part of developing a rapid treatment for major depressive disorder that is bridged into a comprehensive long-term treatment to maintain participants in a state of remission. Thus, the most relevant measure of remission rates for this approach is the proportion of individuals who enter remission at any point in the month following treatment, regardless of whether they enter remission immediately after treatment or after a delayed-response trajectory, as maintenance treatment would be engaged irrespectively of treatment trajectory. Changes in scores on the 6-item HAM-D, the 17-item HAM-D, and the QIDS-SR were used as secondary measures of depression severity. Initial linear mixed models produced residuals that were not normally distributed (as assessed by the Shapiro-Wilk test). Thus, changes in scores on the MADRS, 6-item HAM-D, 17-item HAM-D, and QIDS-SR were assessed with generalized linear mixed models that used Satterthwaite approximation of degrees of freedom and robust estimation of coefficients to handle violations of model assumptions. Fixed effects of time, treatment group (sham versus active), and their interaction were assessed. Compound symmetry covariance structure was used for all analyses except cases in which the models failed to converge or converged on nonreal solutions. In these cases, autoregressive covariance structures were used. All post hoc pairwise comparisons were Bonferroni corrected. Similar generalized linear mixed models were used to analyze potential neurocognitive side effects (see the online supplement for details).

RESULTS

Participant Characteristics

The trial was halted at the midpoint because the planned interim analysis demonstrated a large effect size of active

FIGURE 2. Depression scores before and after active or sham Stanford neuromodulation therapy (SNT) in participants with treatment-resistant depression[a]



[a] The x-axis starts at baseline, just before the initiation of treatment, which is indicated between weeks 0 and 1 by shading. Error bars in panels A–D indicate 95% confidence intervals. Panels E and F show MADRS raw scores for individual participants in the active and sham treatment groups, respectively. Bonferroni-corrected post hoc testing indicated significant differences between groups at all posttreatment time points ($p<0.005$) for all assessments. HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale.

compared with sham treatment (Cohen's $d>0.8$). The results reported here are therefore from the sample of participants who entered the trial up to the interim analysis.

A total of 182 people were assessed for eligibility through an online screening database, of whom 54 underwent in-person screening (see Figure S1 in the online supplement). Thirty-two participants underwent randomization; however, two of these participants were not enrolled, one for no longer meeting inclusion criteria and one who withdrew because of an aversion to potentially being assigned to

TABLE 1. Characteristics of participants in a double-blind randomized controlled trial of Stanford neuromodulation therapy (SNT)[a]

Variable	Active SNT (N=14)		Sham SNT (N=15)		
	N	%	N	%	p
Male	9	64	10	67	0.75
Currently employed	7	50	6	40	
	Mean	SD	Mean	SD	p
Age (years)	49	15	52	16	0.58
Years of education	17	3	17	4	0.99
Duration of illness (years)	30	17	23	16	0.32
Duration of current depressive episode (years)	8	14	10	13	0.65
Adequate antidepressant trials, lifetime[b]	5	2	5	2	0.94
Adequate augmentation trials, lifetime[b]	1	1	1	1	0.76
Adequate antidepressant trials, current episode[b]	2	1	1	1	0.29
Adequate augmentation trials, current episode[b]	1	1	0	1	0.30
Maudsley Staging Method score	9	2	9	2	0.42
Baseline MADRS score	31	4	35	6	0.06
Baseline 6-item HAM-D score	14	2	15	2	0.15
Baseline 17-item HAM-D score	24	3	26	4	0.04
Baseline QIDS-SR score	15	3	17	3	0.21
Motor threshold	51	8.4	52	10.6	0.92
Treatment intensity (% of machine output)	52	6.9	51	9.9	0.92
Treatment intensity (% of motor threshold)	102	8.5	101	12.4	0.79

[a] HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Report.
[b] Data on past antidepressant and augmentation trials are from the Antidepressant Treatment History Form.

a sham treatment group. The 30 remaining participants were assigned in a 1:1 ratio to receive active or sham SNT. After enrollment, another participant was found not to meet inclusion criteria. Thus, the final sizes of the two groups of participants who met inclusion criteria, enrolled in the trial, and agreed to receive active or sham treatment were 14 in the active SNT group and 15 in the sham SNT group (Figure 2). Demographic characteristics were similar in the two groups (Table 1). The number of prior antidepressant trials (mean=5, SD=2) and the Maudsley Staging Method total score (mean=9, SD=2; moderate treatment resistance) were the same for both groups. All participants completed the full treatment and the immediate posttreatment assessments. One patient in each group did not complete the 4-week follow-up. One participant in the sham treatment group started a new medication (a serotonin-norepinephrine reuptake inhibitor) after study enrollment, 2 weeks before the SNT treatment week, which was maintained at a subtherapeutic dosage level throughout the trial. This participant was included in all the analyses.

Efficacy

The a priori primary outcome was MADRS score 4 weeks after the end of the 5-day SNT protocol. Scores were normalized to pretreatment baseline, that is, expressed as percentage of the baseline values. The mean percent reduction in intention-to-treat MADRS scores 0, 1, 2, 3, and 4 weeks after treatment were 62.0%, 70.9%, 62.4%, 57.8%, and 52.5% of baseline in the active treatment group and 14.3%, 20.6%, 10.4%, 10.9%, and 11.1% in the sham treatment group, with effect sizes (Cohen's d) of 1.7, 1.4, 1.8, 1.5, and 1.4, respectively. The response and remission rates varied across follow-up time points as a result of the participants' different response trajectories (see Figure 2E for individual response trajectories, and Table S5 in the online supplement for response and remission rates at each time point). Overall, across the 4-week follow-up, 12 participants (85.7%) in the active SNT group met the criterion for response (a reduction ≥50% in MADRS score), and 11 (78.6%) met the remission criterion (a MADRS score ≤10) in at least one of the five posttreatment assessments. In the sham treatment group, four participants (26.7%) responded and two (13.3%) remitted at some point during the 4-week follow-up. Remission and response rates, respectively, 0, 1, 2, 3, and 4 weeks after treatment in the active treatment group were 57.1% and 71.4%; 66.7% and 77.8%; 53.8% and 84.6%; 61.5% and 69.2%; and 46.2% and 69.2%. Remission and response rates, respectively, in the sham treatment group were 0% and 13.3%; 10.0% and 20.0%; 7.1% and 7.1%; 7.1% and 7.1%; and 0% and 7.1%.

Generalized linear mixed models revealed significant main effects of treatment group ($F=24.8$, $df=1, 14$, $p<0.001$), time ($F=16.1$, $df=5, 24$, $p<0.001$), and the interaction between treatment group and time ($F=6.1$, $df=5, 24$, $p=0.001$) on MADRS scores. Participants in the active treatment group showed significantly greater posttreatment reductions in MADRS scores at all follow-up time points (Bonferroni-corrected $p<0.05$). Equivalent results were found for the secondary outcomes (change in scores on the 6-item HAM-D, the 17-item HAM-D, and the QIDS-SR) as well as in models with missing data imputed using the last-observation-carried-forward method and when raw scores were used rather than change from baseline. (See the online supplement for all results.)

Integrity of the Blind

Twenty-three participants provided guesses as to which treatment they received, and 19 indicated their confidence in their guess. One-way t tests indicated no significant

differences from chance (chance guess metric=0.50) in the sham (mean guess metric=0.39, p=0.56) and active (mean guess metric=0.43, p=0.52) treatment groups. Because not all participants indicated their confidence in their guess, binomial tests were also used to determine whether the number of correct guesses exceeded chance. Binomial tests indicated no significant differences from chance in proportion of correct guesses in the sham (6 of 10 correct, p=0.38) and active (7 of 13 correct, p=0.50) treatment groups. There was no relationship between the guess metric and the magnitude of proportional change in MADRS scores (r=0.11, p=0.66). Because two sham methods were used (see the Methods section), we also tested for a difference between these two methods in the proportion of participants who correctly guessed that they were in the sham treatment group, and we found no significant difference (Fisher's exact test, p=0.12). Moreover, including sham type in the generalized linear mixed model did not change outcomes, nor was the sham type or the sham type-by-time interaction a significant factor (sham type: F=0.2, df=1, 21, p=0.68; treatment group: F=26.6, df=1, 19, p<0.001; time: F=13.2, df=5, 38, p<0.001; treatment group-by-time interaction: F=5.8, df=5, 33, p=0.001; and sham type-by-time interaction: F=1.9, df=4, 29, p=0.14).

Safety

No severe adverse events occurred during the trial. Spontaneous side effects were recorded daily and were categorized by common rTMS side effects (see Table S1 in the online supplement). "Discomfort at treatment site" was recorded if the discomfort occurred only during stimulation and did not persist after SNT, and "post-SNT headache" was recorded if the discomfort persisted after treatment. The only side effect that had an incidence approaching statistical significance in the active treatment group over the sham treatment group was headache (Fisher's exact test, p<0.06; see Table S1). All headaches either self-resolved or resolved after nonprescription pain relief (e.g., ibuprofen). The most common side effect in both groups was fatigue. In a separate trial, we had a participant who experienced a chipped tooth, after which we changed the dental safety protocol for all trials in the laboratory, including the present trial (see the online supplement for more details).

Both the active and sham treatment groups demonstrated stable cognitive test performance from baseline to the immediate-posttreatment assessment. A significant interaction between time and group (F=4.7, 1, 21, p=0.04) was detected for verbal processing speed (Color Word Reading completion time), and follow-up Bonferroni-corrected post hoc comparisons showed a significant improvement in the active (F=5.5, df=1, 21, p=0.03) but not the sham (F=0.4, df=1, 21, p=0.54) treatment group. All other measures showed nonsignificant group-by-time interactions. (See Table S3 in the online supplement for the statistical results of neurocognitive tests.)

DISCUSSION

The aim of this study was to investigate the antidepressant efficacy of SNT, an accelerated, high-dose, patterned, fcMRI-guided iTBS protocol, for treatment-resistant depression. Participants tolerated the treatment well; all participants completed the 5-day treatment course, and the side effect profile was similar to that of conventional daily rTMS, with a greater incidence of headache in the active SNT group compared with the sham treatment group. Headache is one of the most common side effects with TMS treatment protocols, so this was an anticipated side effect; the incidence of headache in our active treatment group (57%) is similar to that reported for the standard FDA-approved iTBS protocol for treatment-resistant depression (65%) (10).

We observed a large antidepressant effect of SNT. After 5 days of treatment, 79% of participants in the active SNT group (11 of 14 participants) achieved remission from their depressive episodes at some point during the 4-week follow-up, compared with 13% (two of 15 participants) in the sham treatment group. The short treatment course and the high antidepressant efficacy of SNT present an opportunity to treat patients in emergency or inpatient settings where rapid-acting treatments are needed.

The large effect size of SNT may be due to several factors. The SNT protocol was designed from neuroscience-informed stimulation parameters and was selected to optimally modulate the targeted neural circuitry. First, fcMRI-guided targeting was used to stimulate the region of the left DLPFC most anticorrelated with the sgACC in each individual (21–26). Second, stimulation sessions were delivered hourly, because intersession intervals between 50 and 90 minutes have been shown to produce a cumulative effect on synaptic strengthening. In contrast, sessions with intersession intervals of 40 minutes or less do not produce a cumulative effect (15–18). Third, we delivered stimulation sessions at an intensity of 90% of resting motor threshold (rMT), adjusted for individual differences in cortical depth at the target, rather than the FDA-approved intensity of 120% of rMT, because iTBS sessions of 1,800 pulses delivered at 90% of rMT may be more effective in inducing changes in cortical excitability (18) and the resultant functional connectivity changes (44). Fourth, 1,800 pulses per iTBS session were delivered rather than the typical 600 pulses per session, as 1,800 pulses of iTBS at 90% of rMT has been shown to produce greater changes in cortical excitability (18). Additionally, a blinded iTBS trial using sessions of 1,800 pulses produced effective antidepressant responses in only 2 weeks (30), which is faster than standard FDA-approved iTBS protocols using sessions of 600 pulses (10). Finally, the SNT protocol was designed to deliver a higher overall pulse dose than standard iTBS protocols (90,000 versus 18,000 pulses), because higher pulse doses are associated with greater antidepressant efficacy (19, 20). SNT parameter

choices were discussed in detail in our previous publications (12, 13).

The large antidepressant effect size of SNT was observed despite the high severity of depressive symptoms and the level of treatment resistance in our participant sample as well as calculation at 1-month follow-up. Greater severity of depressive symptoms (45, 46) and higher levels of treatment resistance (4, 6, 47) have both been associated with poorer responses to rTMS. The participants in our study had an average of five previous adequate antidepressant medication trials; conventional rTMS protocols have been found to induce remission in only 17% of individuals who have shown no response to three prior antidepressant treatments (11). Additionally, 62% of our participants had recurrent depressive episodes rather than one continuous episode, which has also been shown to negatively predict outcome following rTMS treatment (46). The high level of treatment resistance in our sample may also account for the relatively low remission rate observed in our sham treatment group (13%) in comparison to remission rates typically reported for sham treatment in rTMS studies (48, 49); a previous sham-controlled iTBS study showed that individuals with moderate to severe treatment resistance exhibited minimal response to sham treatment (30).

In this report, we included response and remission rates for the entire 4-week follow-up period. This is a departure from the more common single-time-point criterion for response or remission used in other iTBS clinical trials for depression (10). We believe this approach to defining dichotomous outcomes is appropriate based on the use of SNT as a probe of the underlying neurocircuitry of depressive symptoms and the intended future clinical approach. These high overall response and remission rates provide further evidence to support that dysfunction in the left DLPFC-sgACC network is the predominant neural basis of depressive symptoms (21, 22, 24, 50). This study expands on the literature by demonstrating that when this circuitry is targeted using an optimized stimulation dose and pattern, antidepressant responses will be induced in the large majority of individuals (85.7% in the present study) for a period of time. For unknown reasons, participants display different response trajectories following a course of SNT (see Figure 2E), which has previously been reported for rTMS and iTBS (43). SNT is still being developed for use as a therapeutic tool. We propose a treatment model in which SNT is used to achieve rapid remission from depression and is then followed by a less intensive maintenance treatment that can be of any effective and acceptable modality—medication, psychotherapy, brain stimulation, and other treatments. Under this model of care, all patients who enter remission in the month after treatment would be able to transition to a maintenance treatment. Therefore, it is appropriate to calculate response and remission rates by including all participants who met these criteria at any week during the 4-week follow-up.

This study has limitations. First, the sample size was small, as the trial was ended at the planned interim analysis because of superiority of the active treatment with a large effect size; yet, the sample size is similar to those of other clinical trials in patients with severe treatment-resistant depression (51, 52). Second, as with all clinical trials for major depressive disorder, our study relied on clinical assessments to measure improvement in depressive symptoms, as there are currently no validated biomarkers of depression remission. Third, thus far our SNT protocol has been tested at a single site, in a highly educated sample. Although this limits generalizability, the absence of a significant sham response in this treatment-resistant population indicates clear efficacy of active over sham stimulation for this patient population. Fourth, 45% of our participant sample had comorbid psychiatric diagnoses (see Table S4 in the online supplement), which could have influenced the efficacy of the protocol. Comorbid anxiety in particular has been shown to reduce rTMS efficacy (4, 53, 54), perhaps because of the need for an alternative treatment target for these patients (55) or a higher incidence of benzodiazepine use in this population (56, 57). However, the number of participants with comorbid psychiatric conditions was not significantly different between the active and sham treatment groups (see Table S4). Finally, given the large effect size in comparison to other TMS protocols in similar populations, we hypothesize that the differences between SNT and standard rTMS protocols lead to high antidepressant efficacy; however, SNT remains to be tested directly against another active protocol, and the unique aspects of the SNT protocol that account for improvements in efficacy over conventional iTBS remain to be identified. Studies will be needed that compare the efficacy of SNT parameters with and without fcMRI-guided targeting to determine the importance of this targeting method (58).

In conclusion, SNT induced a significantly greater reduction in depressive symptoms than an identical course of sham stimulation after 5 days of treatment in a treatment-resistant sample. The short duration and high antidepressant efficacy of SNT presents an opportunity to treat patients in the emergency or inpatient settings, where a compressed time course is necessary.

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Examination Questions: Cole et al.

1. **SNT utilizes functional connectivity between:**
   A. DLPFC and dACC
   B. DMPFC and sgACC
   C. DLPFC and sgACC
   D. DMPFC and dACC
2. **What is the interval protocol utilized by SNT?**
   A. 15 min intersession interval
   B. 50 min intersession interval
   C. 15 min intertrain interval
   D. 50 min intertrain interval
3. **What is the stimulation dose utilized by SNT?**
   A. 1800 iTBS pulses
   B. 1800 cTBS pulses
   C. 600 cTBS pulses
   D. 600 iTBS pulses