Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression (SAINT-TRD)

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Abstract

Background: Current treatments for depression are limited by suboptimal efficacy, delayed response, and frequent side effects. Intermittent theta-burst stimulation (iTBS) is a non-invasive brain stimulation treatment which is FDA-approved for treatment-resistant depression. Recent studies suggest several improvements could be made to iTBS by 1) precision targeting of the left dorsolateral prefrontal cortex (L-DLPFC) to subgenual anterior cingulate cortex (sgACC) circuit, 2) treating with multiple sessions per day at spaced intervals and 3) applying a higher overall pulse dose of stimulation.
Objective: Examine the feasibility, tolerability, and preliminary efficacy of an accelerated, high-dose iTBS protocol for treatment-resistant depression (TRD) termed 'Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)'.
Methods: Thirty-one participants with TRD received open-label SAINT. Resting-state functional connectivity MRI (fcMRI) was used to individually target the region of L-DLPFC most anti-correlated with sgACC. Fifty iTBS sessions (1800 pulses per session, 50-minute inter-session interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold depth-adjusted. Neuropsychological testing was conducted before and after SAINT.
Results: There was an average 87.24% reduction in MADRS score. 28/31 participants (90.32%) met criteria for remission (≤10 on the MADRS). All participants were remitted on measures of suicidal ideation. Neuropsychological testing demonstrated no negative cognitive side-effects. There were no seizures or other severe adverse events.
Discussion: Our highly accelerated, high-dose, iTBS protocol with fcMRI-guided targeting (SAINT) was well tolerated and safe. Efficacy was strikingly high, especially for this treatment-resistant population. Double-blinded sham-controlled trials are required to confirm the high remission rate found in this initial study.

Introduction

Depression is the leading cause of disability worldwide and approximately 800,000 suicides are completed each year [1,2]. Current FDA-approved antidepressant treatments do not achieve remission in the majority of patients with treatment-resistant depression (TRD) [3–5], are limited by tolerability [6] and have extended treatment durations which do not match the imminent risk to suicidal patients [7–9]. New antidepressant treatments are needed that are rapid-acting, more effective, durable and targeted, to reduce side-effects.

Repetitive transcranial magnetic stimulation (rTMS) delivered to the left dorsolateral prefrontal cortex (L-DLPFC) is an FDA-approved, targeted, non-invasive brain stimulation technique for TRD [10,11]. rTMS involves passing an electric current through a magnetic coil placed on the scalp, producing a high-intensity magnetic field that passes through the scalp, skull and meninges and excites neuronal tissue [12]. Repeated high-frequency excitation of the same brain region results in the successive strengthening of synapses through a process known as long-term potentiation (LTP) [13,14] causing lasting changes in functional connectivity [13,15]. The antidepressant responses induced by rTMS are predicted to be the result of strengthened indirect inhibitory connections between the L-DLPFC and sgACC [15,16].

A more efficient form of rTMS, known as intermittent theta-burst stimulation (iTBS), has been developed which has significantly shortened the duration of treatment sessions from 37 minutes to 3 minutes [17] producing equivalent antidepressant responses [18,19]. FDA-approved rTMS and iTBS courses involve daily stimulation sessions for six weeks, achieving remission in 32% of patients and response in 49%, with an open label, non-inferiority design [18]. Studies suggest that the efficacy of iTBS could be improved by accelerated delivery [20–22], higher overall stimulation doses [9,23,24] and more accurate targeting [15,25]. Furthermore, there has never been a dose-response curve for therapeutic rTMS.

This study aimed to examine the feasibility, safety and preliminary efficacy of an accelerated, high-dose iTBS protocol using functional connectivity magnetic resonance imaging (fcMRI)-guided targeting. Five consecutive days of 10-daily iTBS sessions (1800 pulses per session) were delivered to the region of the L-DLPFC that was most anti-correlated to the sgACC in each individual [26]. The individualized functional connectivity-guided targeting, accelerated delivery and high dose of stimulation were predicted to collectively result in higher response and remission rates than FDA-approved TMS protocols. This protocol was termed ‘Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)’ to distinguish this protocol from other attempts at accelerated iTBS delivery without the targeting and high dose [27,28]. We recently published a smaller series demonstrating efficacy in the most severe cohort [26].

Methods

Participants

Thirty-three participants with TRD (aged 19-78, 20 female) were recruited for this study. Twenty-four participants had a diagnosis of Major Depressive Disorder (MDD), six participants had a diagnosis of bipolar disorder (two bipolar 1) and three participants had depression in Parkinson’s Disease (DPD). Diagnoses of depression or bipolar disorder were confirmed by the study psychiatrist who performed the Mini International Neuropsychiatric Interview (MINI).

Participants were required to have a Hamilton Depression Rating Scale 17-item (HDRS-17) score higher than 20 and not have responded to at least one antidepressant medication (minimum trial duration of 6 weeks at an appropriate dose according to the Antidepressant Treatment History Form; ATHF) to be eligible for the study. Urine samples were collected to

screen for drug use and pregnancy. Participants were recruited through the Depression Research Clinic at Stanford University, Facebook advertising and clinic referrals. All participants provided written informed consent and the study was approved by the Stanford University Institutional Review Board.

One participant was excluded for having a motor threshold that was too high (>90% machine output) and one participant with a history of high anxiety dropped out after the first day of stimulation due to high anxiety levels (Young Mania Rating Scale (YMRS) and HDRS-17 scores had not increased from baseline). This resulted in a final participant sample of 31 participants (aged 19-78, 19 female). See Table 1 for participant demographic information and treatment history. Participants were required to maintain the same antidepressant regimen throughout the study enrollment (see Supplementary Table 1 for information regarding the medication participants were taking during study enrollment).

Table 1: Demographic information and treatment history for all participants (n=31)

Participant info	**Mean (SD)**
Gender (male:female)	12:19
Age	48.12 (17.05)
Age of onset of depression	22.45 (9.88)
Duration of depression	25.56 (15.86)
Number of antidepressant failures (lifetime)[1]	8.84 (6.03)
Number of adjunctive medications (lifetime)[2]	1.48 (1.39)
Number of participants attempted rTMS	14*
Number of participants attempted ECT	7**
Maudsley Staging Method Score	11.16 (2.03)

[1]Adequate antidepressant trials defined as a minimum of 6 weeks
[2]Medications defined as adequate augmentation strategies according to the Anti-depressant Treatment History Form (ATHF).
*One remitter, all other participants did not respond.
**One remitted to bilateral but did not respond to unilateral, all other participants were non-responders.

Functional magnetic resonance imaging (fMRI)
Before the stimulation course, each participant had both structural magnetic resonance imaging (MRI) and resting-state functional MRI (fMRI) scans. All participants were screened for MRI safety prior to any scanning procedures. All MRI scans were acquired using a 3T GE Discovery MR750 scanner with a 32-channel imaging coil at the Center for Cognitive and Neurobiological Imaging at Stanford, using a 3x accelerated multiband imaging sequence (TR=2 seconds). The resting state scan consisted of a single 8-minute eyes-open resting scan.
Two participants did not take part in the MRI portion of the study as one participant had a BMI which was above the limit of the scanner (BMI>35) and one participant had a spinal stimulator. For these participants, their heads were registered to the MNI brain and anatomical coordinates previously shown to result in superior clinical outcomes compared to the standard 5cm rule were used for coil placement (−46, 45, 38) [29]. This target has also shown to be more anti-correlated to the sgACC than the area identified by the 5cm rule [15].

Stanford Accelerated Intelligent Neuromodulation Therapy

A Magventure Magpro X100 (MagVenture A/S, Denmark) system was used to deliver sessions of iTBS; 60 cycles of 10 bursts of 3 pulses at 50Hz were delivered in 2 second trains (5Hz) with an 8 second inter-train interval. Stimulation sessions were delivered hourly [20–22]. Ten sessions were applied per day (18,000 pulses/day) for five consecutive days (90,000 pulses in total). Stimulation was delivered at 90% resting motor threshold [30,31]. A depth correction [32] was applied to the resting motor threshold to adjust for difference in the cortical depth of the individual's functional target compared to the primary motor cortex in order to consistently achieve 90% rMT in the intended functional target. The Localite Neuronavigation System (Localite GmbH, Sankt Augustin, Germany) was used to position the TMS coil over the individualized stimulation target.

Participants in full remission prior to the end of the five-day stimulation course, were given the option to either finish early or complete the full course. One participant with a diagnosis of Bipolar type 1 finished treatment after the first day and one participant with Parkinson's finished treatment after 3 days. All other participants completed the full five-day treatment course.

Clinical assessments

Prior to receiving any stimulation, participants' depressive symptoms and suicidal ideation were assessed using the Hamilton Depression Rating Scale-17 item (HDRS-17), Montgomery-Asberg Depression Rating Scale (MADRS) and Columbia-Suicide Severity Rating Scale (C-SSRS). A self-report measure was also used; the Beck Depression Inventory II (BDI-II). The degree of treatment-resistance was calculated using the Maudsley Staging Method (MSM[33]) and symptoms of mania were screened for using the Young Mania Rating Scale (YMRS). At the end of each day of stimulation (ten sessions), depressive symptoms were assessed using the Hamilton Depression Rating Scale 6-item (HDRS-6); participants also completed the BDI-II. The YMRS was completed daily to ensure hypomania had not been induced in any participants [34–36]. The same clinical assessments used at baseline were conducted approximately 72 hours after the stimulation course (immediate follow-up) as well as 2 weeks and one month after the stimulation course in order to assess the durability of the response.

A neuropsychological test battery was administered before SAINT, approximately 72 hours after the SAINT course and one month after the SAINT course in order to capture any neurocognitive side effects. The Hopkins Verbal Learning Test – Revised (HVLT-R) [37], the Brief Visuospatial Memory Test – Revised (BVMT-R) [38], subtests from the Wechsler Adult Intelligence Scale (4th Ed.) (WAIS-IV) [39] and various tests from the Delis Kaplan Executive Function System (D-KEFS) [40] were used. See supplementary material for a full list of neuropsychological tests that were used. These neuropsychological tests have been shown to have good psychometric properties [37,38,40,41] and assessed verbal learning and memory, visuospatial learning and memory, working memory, attention, processing speed, cognitive inhibition, cognitive switching, problem solving, and verbal fluency. See supplementary material for more details.

fMRI analysis for target generation

Personalized L-DLPFC targets were generated for each participant using the resting-state scan. All analyses were conducted in a participant's own brain space (i.e., not warped to standardized-brain space). Resting-state scans were pre-processed according to typical methods using Statistical Parametric Mapping (SPM12) software. The resting-state scans were motion corrected and resliced. The T1 weighted structural scan was then co-registered with the resting-state scans. The resting-state scans were then spatially smoothed with a 3mm Gaussian kernel, detrended using a linear model of the global signal [42], and band-pass filtered to preserve the typical resting-state frequencies (0.1Hz-0.01Hz). Next, the estimation parameters to warp the T1 weighted structural image into Montreal Neurological Institute (MNI) space was calculated using SPM segmentations based on tissue probability maps. These normalization parameters were inverted and applied to MNI space regions of interests (ROIs) for the L-DLPFC (Brodmann area 46) and the sgACC (BA25). This inverse normalization served to map the MNI space ROIs onto the individual participant's brain. The participant-space ROIs were then resliced, smoothed, and binarized to match the dimensions of the resting state scans.

The participant-space ROI for the L-DLPFC formed the search area for the optimal TMS coil placement. Two separate algorithms were used to determine coil placement. The first algorithm sorted each of the DLPFC and sgACC voxels into functional sub-units using a hierarchical agglomerative clustering algorithm. Median time series were then created for each functional subunit and the correlation coefficients were calculated between all median time series extracted from all functional subunits of the L-DLPFC and sgACC. The second algorithm determined the optimal L-DLPFC subunit to target based on three factors: the net correlation/anti-correlation of the L-DLPFC subunit with sgACC subunits, the size of the subunit and the spatial concentration of the subunit. See supplementary methods for more details on these algorithms. 3D maps of the whole brain correlation coefficient of the selected L-DLPFC subunit were then created and used to target the coil placement using the Localite TMS Navigation software (Localite GmbH, Sankt Augustin, Germany).

Clinical outcome analysis

Our primary outcome measure was percentage change in MADRS scores and these changes were used to calculate response and remission rates. Response was defined as >50% reduction in MADRS score and remission was defined as MADRS score ≤10 [43]. Reductions in HDRS-17, HDRS-6, BDI-II and C-SSRS scores were used as secondary outcome measures. Daily HDRS-6 scores were used to calculate the average number of days of stimulation required to reach responder criteria (<50% HDRS-6) and remission criteria (<5 on HDRS-6). The influence of treatment-resistance (MSM score) on the number of stimulation days required to reach responder/remitter criteria was explored using linear regression analysis.

In order to make comparisons to the response and remission rates found in both iTBS and TMS pivotal trials [44–46], all of the above analyses were also conducted with only the MDD participants (n=22). See Supplementary Table 2 for demographic information for the MDD subsample.

The number of days of stimulation required to induce response/remission in participants who had previously failed a course of rTMS were calculated in order to determine whether these participants met responder criteria after the equivalent amount of stimulation as an FDA-approved treatment course. Potential differences in duration of response for previous rTMS non-responders were examined by comparing percentage change in MADRS score at two weeks and one month after SAINT between rTMS non-responders and the rest of the participant sample. These data were not normally distributed even after being log transformed so an aligned rank transform was applied [47]. A mixed model ANOVA with time point (immediate, 2

weeks and 4 weeks) as within-subjects factor and group (TMS non-responder or rest of the participant sample) as between-subjects factor was used to analyze the transformed data. Post-hoc independent sample t-tests were then used to compare percentage change in MADRS score across groups at each time point.

Eleven participants were re-treated once their symptoms returned to baseline. The percentage change in MADRS score data were not normally distributed therefore a Wilcoxon signed-rank test was used to assess whether SAINT re-treatment was able to produce equivalent antidepressant responses.

Scores on the neuropsychological tests pre- and post-SAINT were compared using paired t-tests. Neuropsychological test data were available for 22 participants.

Results

Safety

No serious adverse events occurred. The only side-effects participants reported were fatigue and some discomfort at both the stimulation site and in the facial muscles during stimulation. The neuropsychological test battery showed no negative cognitive side-effects following SAINT. There were no significant changes in neurocognitive performance (neurocognitive data will be uploaded as a supplementary file after May 2019).

Response and remission rates

Depressive symptoms were significantly reduced following SAINT, with an average 87.24% reduction in MADRS score from 37.71 (7.24) to 4.81 (6.41). The response rate (>50% MADRS score) was 90.32% and all responders were in full remission (MADRS score ≤10). Results were similar across all clinical assessments (see Table 2). In addition to the reduction in depressive symptoms, 100% of participants were remitted on measures of suicidal ideation (C-SSRS, HDRS-Q3 and MADRS-Q10) following the course of SAINT (see Table 2).

Table 2: Clinical assessment scores for all participants n=31; mean (SD)

	Pre-SAINT	Post-SAINT	Responders (%)[1]	Remission (%)[2]
MADRS	37.71 (7.24)	4.81 (6.41)	90.32	90.32
HAMD-17	27.87 (5.23)	4.55 (5.07)	90.32	83.87
HAMD-6	15.23 (2.80)	2.39 (3.32)	87.10	83.87
BDI[3]	32.50 (12.22)	6.50 (7.10)	87.50	85.71
C-SSRS[4]	1.52 (1.29)	0.00 (.00)	100.00	100.00
HAMD-Q3	1.52 (.85)	0.03 (.18)	96.77	96.77
MADRS-Q10	2.39 (.99)	0.07 (.36)	96.77	96.77

[1]Response defined as >50% reduction in score.
[2]Remission defined <8 on HAMD-17 [48]<5 on the HAMD-6 [49], ≤10 on MADRS [43], BDI<13 [50] and C-SSRS=0 [51].
[3]n=28, four participants only had a post-SAINT BDI score so for % remission calculation n=28, and % response n=24.
[4]Current suicidal ideation subscale, n=26
The response and remission rates were very similar for the MDD subsample, see Supplementary Table 3 for response and remission rates for this subsample.

Time course of response

The average number of days of aiTBS required to elicit a response (≥50% reduction in HAMD-6 score) across all participants (n=29, daily HAMD-6 scores missing for 2 participants) was 2.46 (SD=1.26, ~25 treatments) and to achieve remission (HAMD-6 score <5) was 2.96 (SD=1.48, ~30 treatments). Similar time courses were seen for the MDD participants. See Figure 1 for percentage change in HAMD-6 score with each day of stimulation, for all participants (1A) and MDD participants (1B).

Figure 1

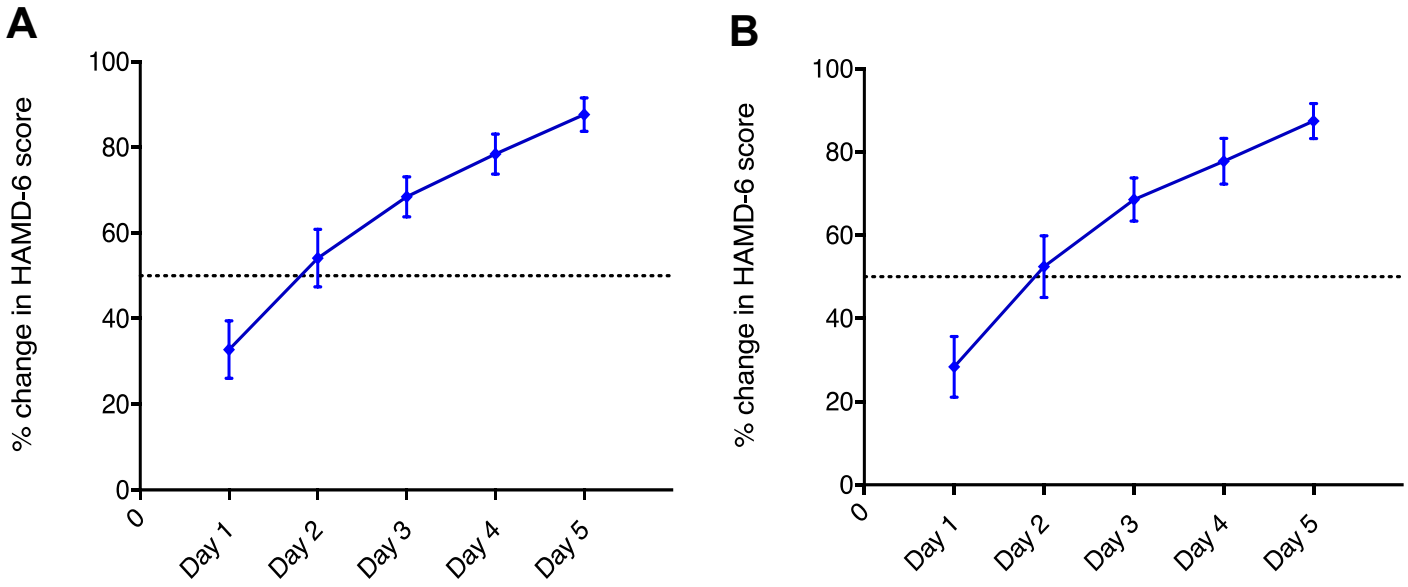

Figure 1: Average percentage change in Hamilton Depression Rating Scale score (6-item version) with each day of stimulation for A) All participants (n=29, daily HAMD-6 scores missing for two participants), diagnoses of MDD, bipolar and Parkinson's. B) MDD participants (n=21, daily HAMD-6 scores missing for one participant). Dotted lines indicate responder criteria and error bars represent standard error.

Participants who had previously not responded to a 6-week rTMS treatment course (rTMS non-responders, n=13) took longer to achieve responder criteria (M=3.08 days, SD=0.78, ~31 treatments) and remission criteria (M=3.70 days, SD=1.11, ~37 treatments; see Figure 2). None of the rTMS non-responders met responder criteria after the first day of aiTBS when the equivalent amount of stimulation as a 6-week FDA-approved iTBS course had been administered.

Figure 2

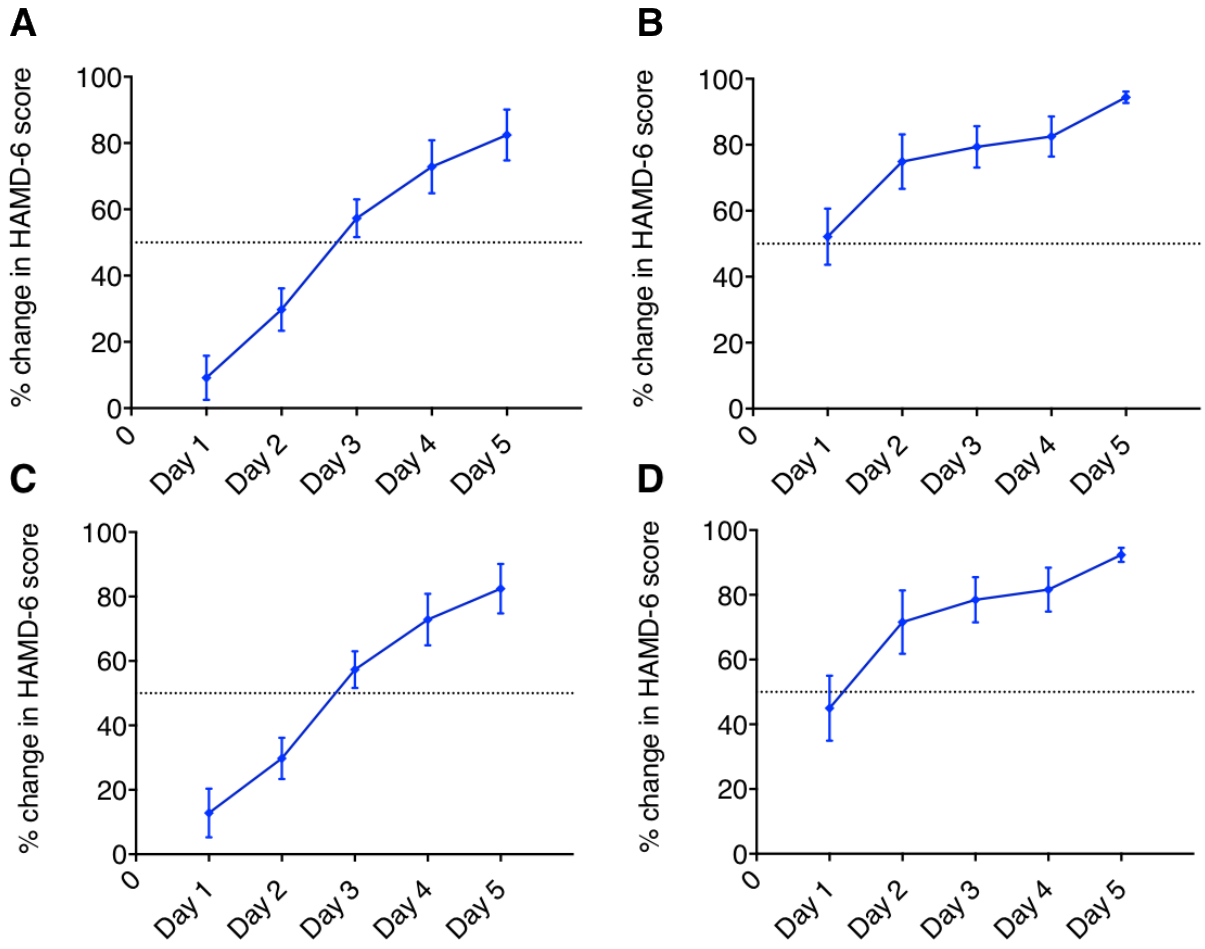

Figure 2: Average percentage change in Hamilton Depression Rating Scale score (6-item version) with each day of stimulation for A) All TMS non-responders (n=13), B) All other participants (n=16), C) MDD TMS non-responders (n= 10), D) All other MDD participants (n=11). Dotted lines indicate responder criteria and error bars represent standard error.

There was a trend towards Maudsley score predicting the number of stimulation days required to achieve remission but neither the relationship between Maudsley score and days required to achieve remission ($F(1,24)=4.01$, $p<.06$, $R^2=.14$) or response ($F(1,26)= 2.58$, $p=.12$, $R^2=.09$) reached significance. These relationships were also not significant for the MDD patients. See Figure 3.

Figure 3

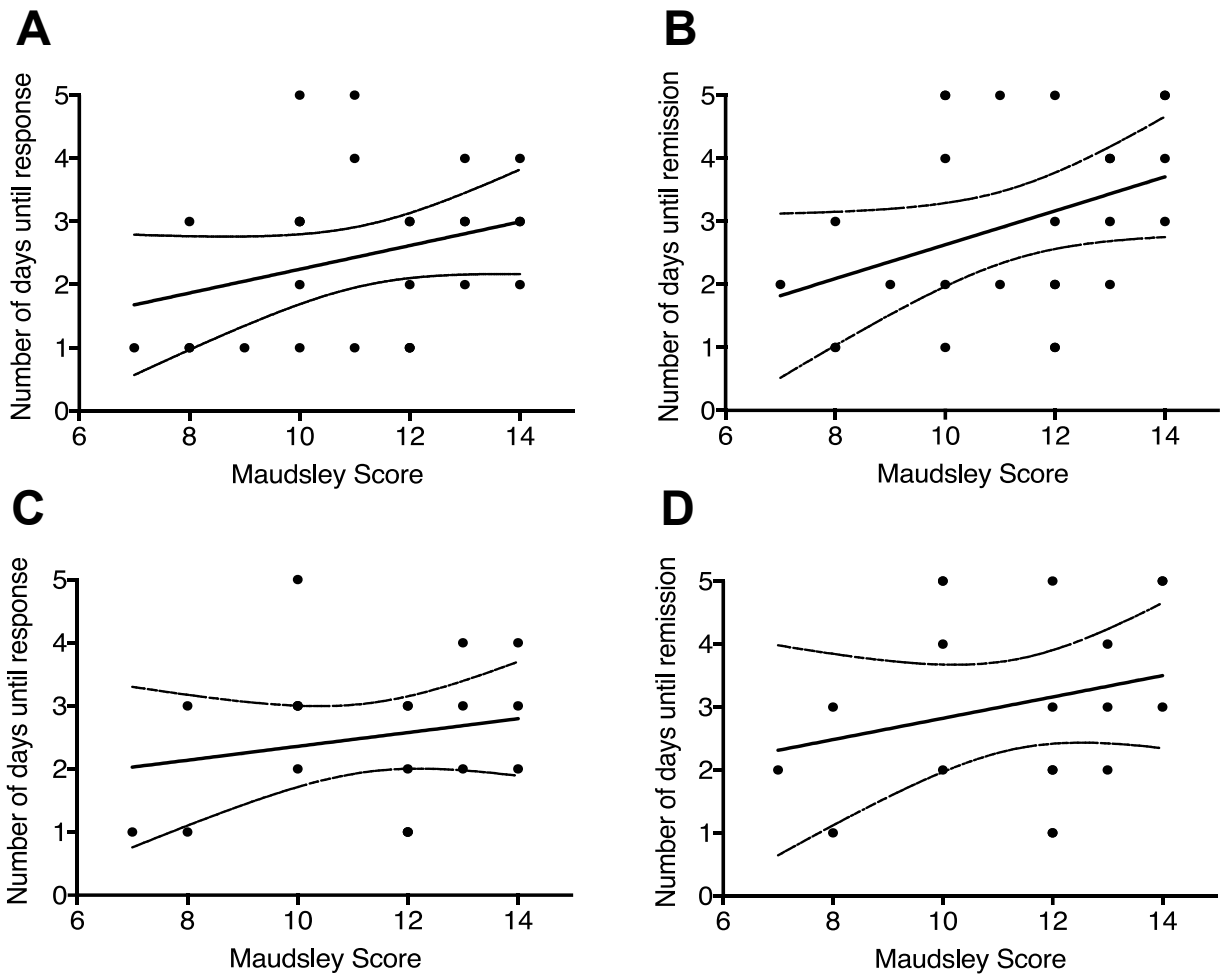

Figure 3: The relationship between Maudsley score and the number of days of SAINT needed for response (≥50% reduction in HAMD-6 score) or remission (HAMD-6 score <5) for all participants (A & B, respectively) or MDD participants (C & D, respectively). Linear regression analyses found no significant relationships between Maudsley score and the number of days to reach response/remission in all participants [response; $F(1,26)= 2.58$, $p=.12$, $R^2=.09$), remission; $F(1,24)=4.01$, $p<.06$, $R^2=.14$] and MDD participants [response; $F(1,18)=0.74$, $p=.40$, $R^2=.04$), remission; $F(1,17)=1.07$, $p=.32$, $R^2=.06$]. Dotted lines represent 95% confidence intervals.

Outcomes for previous rTMS non-responders

rTMS non-responders had significantly poorer outcomes two weeks and one month after the SAINT course compared to the rest of the participant sample (see Figure 4). A mixed model ANOVA found a significant interaction between group and time point [$F(1.48, 41.44)=4.63$, $p=.02$, $\eta^2=.14$]. Follow-up independent sample t-tests found significantly lower percentage MADRS change for rTMS non-responses at 2 weeks [$t(28)=-3.55$, $p=.001$] and one month [$t(25.71)=-5.08$, $p<.001$] but initial responses to SAINT were equivalent to the rest of the participant sample [$t(29)=-1.32$, $p=.20$]. Across all participants, 60% of participants still met

responder criteria one month after the 5-day SAINT course and 95% were still remitted on the C-SSRS suicidal ideation subscale (see Supplementary Table 4). When the rTMS non-responders were excluded from these analyses, the response rate at one month was 83.33% with 100% of participants remitted on the C-SSRS suicidal ideation subscale (see Supplementary Table 6). Similar results were seen for the one-month data for MDD participants with and without the TMS non-responders included (see Supplementary Tables 5 and 7).

Figure 4

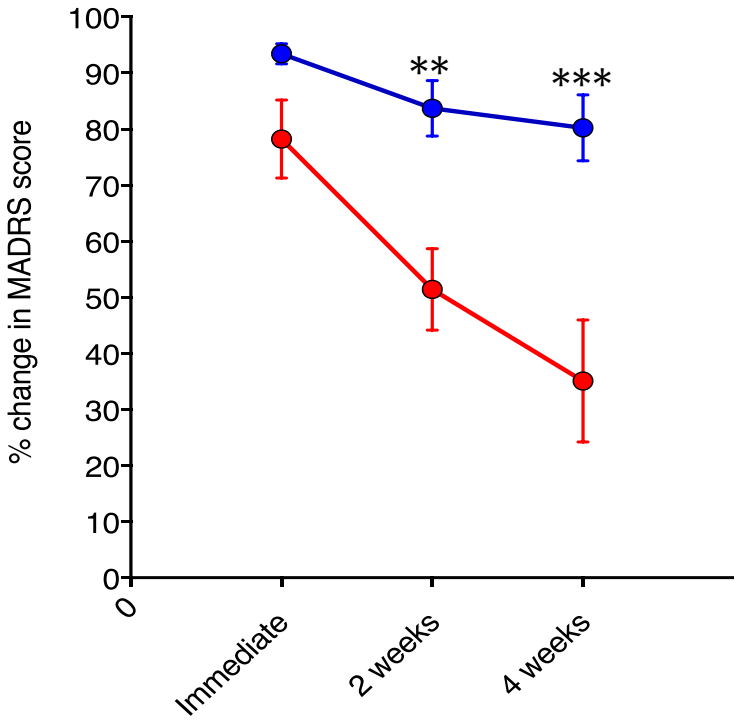

Figure 4: Percentage change in MADRS score immediately following the five-day stimulation course, 2 weeks and four weeks afterwards for TMS non-responders (red, n=13) and all other participants (blue, n=18). rTMS non-responses showed significantly lower percentage reduction in MADRS score at 2 weeks [t(28)=-3.55, p=.001] and one month [t(25.71)=-5.08, p<.001] after SAINT than the rest of the participant sample.

Re-treatment efficacy

Re-treatment data is available for eleven participants who were re-treated once they no longer met responder criteria (average time between treatments was 19.58 weeks, SD=13.49). Percentage change in MADRS score did not significantly differ between initial treatment and re-treatment (Z=.00, p=1.00 r=.00, see Table 3).

Table 3: Percentage change in MADRS score for initial and re-treatment

Participant	Diagnosis	Initial % change MADRS	Re-treatment % change MADRS
1	MDD	91.43	85.71
2	MDD	97.67	100.00
3	PD	97.50	88.89
4	MDD	100.00	100.00
5	MDD	83.64	84.44
6	BPD	100.00	100.00
7	MDD	44.12	76.47
8	BPD	100.00	100.00
9	MDD	100.00	97.44
10	PD	100.00	100.00
11	MDD	90.91	95.45

Discussion

The aim of this study was to examine the safety, feasibility and preliminary efficacy of an accelerated high-dose iTBS, fcMRI-guided treatment protocol (SAINT) for treatment-resistant depression (TRD). We found that SAINT can effectively reduce depressive symptoms and suicidal ideation in patients with severe TRD within 5 days without negative cognitive side-effects. The 90% remission rate is substantially higher than remission rates for open-label studies using standard FDA-approved treatment protocols [18,52,53]. This is also higher than ECT in TRD (~58%[54]) and in ketamine (29%-70.8%[55–57]). The extremely high remission rate in our study was found despite the inclusion of participants who had previously failed rTMS and ECT. The apparent higher efficacy of SAINT is likely due to the combination of the accelerated delivery of iTBS sessions, the high-dose of stimulation and the individualized targeting method used.

Although response and remission rates as high as those found in this study are unprecedented in TMS studies (rTMS/iTBS/cTBS), similar response rates have been found in deep brain stimulation trials for depression and Parkinson's Disease [58,59]. The apparent superior efficacy of our SAINT protocol over standard FDA-approved TMS protocols complements evidence from basic neuroscience research and human physiology data which suggest that multiple spaced daily iTBS sessions have an enhanced effect compared to the same number of single daily sessions [20–22,60,61]. Studies which have applied theta-burst protocols (cTBS/iTBS) to the motor cortex in humans have shown that two spaced stimulation sessions produce greater [62] and longer lasting [61,63] changes in cortical excitability than single stimulation sessions. Basic neuroscience research conducted using hippocampal slices have shown that multiple iTBS sessions delivered with inter-session intervals of 50-90 minutes have a cumulative effect on dendritic spine enlargement, a process involved in synaptic strengthening [20–22,60]. In comparison, iTBS sessions delivered with inter-session intervals of 40 minutes or less do not have a cumulative effect on dendritic spines[20–22]. Similarly, two iTBS sessions delivered to the prefrontal or motor cortex in humans only 15 minutes apart have shown not to increase cortical excitability further than a single iTBS session [62,64]. This could explain the limited efficacy of a previous attempt at of an accelerated iTBS protocol, which used an inter-session interval of only 15 minutes [27,28].

The individualized targeting method used in our study may have also contributed to the high response and remission rates. The L-DLPFC is a large brain area which consists of a number of different subregions, some of which are correlated and some anti-correlated with sgACC activity [63]. Superior antidepressant responses to rTMS have been shown to be associated with higher anti-correlation between the L-DLPFC and sgACC [15,65,66]. Defining L-DLPFC using common techniques such as scalp-based measurements, structural MRI scans or fMRI activation patterns could result in stimulating a subregion of the L-DLPFC which is correlated rather than anti-correlated with the sgACC and therefore not drive the desired increase in anti-correlation between L-DLPFC and the sgACC [67]. The standard '5cm rule' scalp-based measurement has been shown to miss the L-DLPFC completely in >1/3 of cases [68]. A retrospective study conducted by Fox and colleagues found that individual differences in the degree of anti-correlation between the stimulated subregion of the L-DLPFC and the sgACC accounted for over 70% of the variability in clinical efficacy [15]. A recent interleaved TMS-fMRI study showed that stimulating the subregion of the L-DLPFC which displays the greatest degree of functional connectivity with the sgACC resulted in stimulation propagation to the sgACC in all participants [69]. In comparison, in a separate study when the L-DLPFC was defined anatomically (border of BA9/BA46), stimulation propagated to the sgACC in only 44% of participants [70]. In the pivotal iTBS study [18], the aiTBS study by the Baeken group [28] and a blinded iTBS trial [71] the same anatomical target (border of BA9/BA46) was utilized, which may have contributed to the limited efficacy of the approach. By stimulating the subregion of the L-DLPFC which is most anti-correlated with the sgACC in each individual in this study, we may have reduced this variability in signal propagation and maximized treatment efficacy.

The high efficacy of our SAINT protocol also suggests that FDA-approved protocols may be under-dosing. Our protocol administered five-times the pulse dose of the FDA-approved iTBS protocol (90,000 pulses in comparison to the standard 18,000 iTBS pulses[18]). A previous study found that 61% of individuals who did not respond to the initial six weeks of stimulation, did respond with further treatment [24]. Another study utilizing double the FDA-approved number of pulses per session, demonstrated a higher remission rate [72]. Our SAINT protocol applied the equivalent amount of stimulation as a six-week treatment protocol each day of stimulation (18,000 pulses/day[18]). 31% of participants in our study met responder criteria after the first day of stimulation (n=9/29, daily HDRS-6 missing for 2 participants), this response rate is equivalent to response rates found after six-weeks of daily iTBS/rTMS sessions in individuals of this treatment-resistance level [73,74]. None of the previous rTMS non-responders in our study responded after the first day of SAINT (see Figure 3) but 87.5% of rTMS non-responders met responder criteria at the end of our SAINT protocol. These data indicate that a non-response to a standard six-week treatment protocol may reflect the need for a higher stimulation dose, for the majority of patients [24] which matches with recent trajectory data [75]. The apparent need for a higher number of pulses is consistent with other neuromodulation modalities such as deep brain stimulation in Parkinson's where an average of 500,000 pulses of stimulation are delivered to the STN or the GPi each day [76]. The need for a higher overall dose of stimulation may have also contributed to the limited efficacy of a previous attempt of an accelerated iTBS protocol which only delivered 32,400 pulses [27]. Our study administered the highest number of pulses per day and highest overall pulse-dose of any published study to date [26]. These findings are critically important for translating dosing/stimulation strategies across brain stimulation modalities [77].

Previous rTMS non-responders in our study not only required more stimulation sessions to induce a clinically significant response but also showed less-durable responses than the rest of the participant sample. It is likely that depressed individuals with a higher degree of treatment-resistance display neuroplasticity impairments [78]. This is reflected in the pathological functional connectivity work [79]. The higher number of stimulation sessions required to induce

antidepressant responses could be due to deficits in processes involved in the early stages of LTP, such as AMPA receptor phosphorylation [78,80]. The shorter duration of antidepressant responses could be the result of dysfunction in later LTP processes which results in long-lasting changes to synaptic strength [63]. These processes include the synthesis of new proteins and gene expression changes such as the activation of transcription factors (e.g. CREB) and the induction of plasticity-enhancing genes such as BDNF [78]. Highly treatment-resistant individuals may require maintenance iTBS therapy [81] or even implanted epidural cortical stimulators [77,82] to sustain antidepressant responses.

The short duration of our SAINT protocol, the apparent reproducibility of responses and the lack of cognitive side-effects, add to the potential benefit of SAINT over existing treatments. The short duration of our SAINT protocol means SAINT could provide a rapid means of ensuring the safety of suicidal patients. Currently, there are only two rapid-acting treatments for suicidal ideation. One is ketamine/s-ketamine, a form of which has just been FDA-approved for treatment-resistant depression, but approximately 11% of patients report the dissociative symptoms as very disturbing [83], the antidepressant efficacy of ketamine beyond a single infusion is not yet understood [84,85] and the opioid mechanism of action poses a potential risk [84]. The other available rapid-acting treatment is ECT, for which less than 2% of eligible patients receive due to concerns regarding cognitive side-effects and stigma [86,87]. In the majority of patients, ECT also takes 2 weeks or longer to produce remission from suicidal ideation [88].

Our study is limited by the open-label design; a double-blind control trial is required to determine the efficacy of our SAINT protocol in comparison to an identical schedule of sham stimulation sessions. However, individuals with the same degree of treatment-refractoriness as the participants included in this study (severe treatment-resistance; >11 Maudsley Staging Method), have previously shown no placebo response to iTBS sessions of 1800 pulses [71]. Additionally, the most recent deep brain stimulation (DBS) sgACC trial for TRD included individuals with similar treatment-resistance levels to the patients in this report and had a response rate of only 20% [89]. A greater degree of placebo response would be expected for DBS as placebo response has generally been related to the degree of invasiveness of the intervention [90]. Other limitations of our study include the use of fixed stimulation frequencies, fixed inter-session intervals [91,92] and the lack of state-dependent stimulation [93]. It is likely that individualized stimulation frequencies will result in quicker and potentially more durable responses [92,94]. Some individuals may require slightly different inter-session intervals due to differences in cortical excitability profiles [91,95]. Finally, recent studies have shown that applying stimulation in particular brain states using real-time electroencephalography (EEG)-triggered transcranial magnetic stimulation (EEG-TMS) can increase cortical responses to stimulation [93]. Application of simultaneous TMS-EEG will be crucial to address these limitations in future studies.

In conclusion, the high-dose of stimulation, accelerated delivery and fcMRI-guided individualized targeting method likely collectively resulted in the high antidepressant efficacy of this SAINT protocol. The extremely high remission rate was found despite the inclusion of participants who had previously not responded to rTMS and ECT. These rates are almost double those observed in TRD individuals receiving open-label ECT [4] which is currently the 'gold standard' treatment for TRD. Our data suggest that FDA-approved TMS protocols may be under-dosing, could potentially benefit from individualized targeting methods and accelerated delivery. The efficacy of SAINT at treating suicidal ideation and the short duration of the protocol suggest SAINT could provide a means of rapidly ensuring the safety of suicidal patients. Larger, double-blind, placebo-controlled trials are required to confirm the promisingly high response and remission rates found in this initial study.

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