

A Two-site Pilot Randomized 3 Day Trial of High Dose Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Suicidal Inpatients

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ABSTRACT

Background: Suicide attempts and completed suicides are common, yet there are no proven acute medication or device treatments for treating a suicidal crisis. Repeated daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) for 4–6 weeks is a new FDA-approved treatment for acute depression. Some open-label rTMS studies have found rapid reductions in suicidality.

Design: This study tests whether a high dose of rTMS to suicidal inpatients is feasible and safe, and also whether this higher dosing might rapidly improve suicidal thinking. This prospective, 2-site, randomized, active sham-controlled (1:1 randomization) design incorporated 9 sessions of rTMS over 3 days as adjunctive to usual inpatient suicidality treatment. The setting was two inpatient military hospital wards (one VA, the other DOD).

Patients: Research staff screened approximately 377 inpatients, yielding 41 adults admitted for suicidal crisis. Because of the funding source, all patients also had either post-traumatic stress disorder, mild traumatic brain injury, or both.

TMS methods: Repetitive TMS (rTMS) was delivered to the left prefrontal cortex with a figure-eight solid core coil at 120% motor threshold, 10 Hertz (Hz), 5 second (s) train duration, 10 s intertrain interval for 30 minutes (6000 pulses) 3 times daily for 3 days (total 9 sessions; 54,000 stimuli). Sham rTMS used a similar coil that contained a metal insert blocking the magnetic field and utilized electrodes on the scalp, which delivered a matched somatosensory sensation.

Main outcome measure: Primary outcomes were the daily change in severity of suicidal thinking as measured by the Beck Scale of Suicidal Ideation (SSI) administered at baseline and then daily, as well as subjective visual analog scale measures before and after each TMS session. Mixed model repeated measures (MMRM) analysis was performed on modified intent to treat (mITT) and completer populations.

Results: This intense schedule of rTMS with suicidal inpatients was feasible and safe. Minimal side effects occurred, none differing by arm, and the 3-day retention rate was 88%. No one died of suicide within the 6 month followup. From the mITT analyses, SSI scores declined rapidly over the 3 days for both groups (sham change −15.3 points, active change −15.4 points), with a trend for more rapid decline on the first day with active rTMS (sham change −6.4 points, active −10.7 points, $P = 0.12$). This decline was more pronounced in the completers subgroup [sham change −5.9 (95% CI: −10.1, −1.7), active −13 points (95%

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Conflicts of interest: *Relationship with the vendor:* Although the equipment was loaned for this trial from one vendor (Neuronetics), significant firewalls existed between the vendor and the trial, similar to the NIH OPT-TMS trial. None of the investigators has any financial conflict of interest with the vendor, other than other TMS research studies, nor have they for the past 5 years. Second, the equipment was loaned for the trial but the study design, conduct, data, data analysis and manuscripts to emerge are independent of the vendor and did not involve the vendor. The vendor was notified of safety issues and device malfunctions as they must notify the FDA about this regarding their device.

Dr. George has no equity stake in any TMS device manufacturer and does not accept speaker or consultant fees from TMS device manufacturers. He has had research studies within the past three years with Neuronetics, Brainsway, Cervel, Neosync, St. Jude's, Medtronic and MECTA.

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CI: $-18.7, -7.4$); $P = 0.054$]. Subjective ratings of 'being bothered by thoughts of suicide' declined non-significantly more with active rTMS than with sham at the end of 9 sessions of treatment in the mITT analysis [sham change -31.9 (95% CI: $-41.7, -22.0$), active change -42.5 (95% CI: $-53.8, -31.2$); $P = 0.17$]. There was a significant decrease in the completers sample [sham change -24.9 (95% CI: $-34.4, -15.3$), active change -43.8 (95% CI: $-57.2, -30.3$); $P = 0.028$].

Conclusions: Delivering high doses of left prefrontal rTMS over three days (54,000 stimuli) to suicidal inpatients is possible and safe, with few side effects and no worsening of suicidal thinking. The suggestions of a rapid anti-suicide effect (day 1 SSI data, Visual Analogue Scale data over the 3 days) need to be tested for replication in a larger sample.

Trial registration: ClinicalTrials.gov Identifier: NCT01212848, TMS for suicidal ideation.

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Introduction

Suicide is the 10th leading cause of death for Americans of all ages and is the number two killer of US young adults [1,17,23,27,37]. More Americans now die from suicide than die from car accidents [2,3]. Someone in the US dies by suicide every 13 min [3]. Suicide is a major problem in the military [4]. For the past several years more soldiers have died by suicide than were killed in combat [5,6]. Eighteen US veterans die each day by suicide [7].

Despite these grim statistics, clinicians have no truly effective treatment for acute suicidal crisis. Much of the research in the area of suicide has focused on understanding risk factors and trends, while perhaps undertaking large initiatives to reduce overall rates. Much less attention has been paid to developing new treatments for patients who are actively struggling with thoughts of suicide or who have recently tried to kill themselves. Recently there is renewed interest in acute treatments that have anti-suicide effects such as electroconvulsive therapy (ECT) [8], clozapine, lithium [9–11] and ketamine [12]. While suicide is common, it remains relatively rare, requiring large samples with extended followup to show an effect [13]. However studying enriched samples – patients who have recently attempted suicide – is particularly difficult, and these patients are often deemed too sick to study [14]. Thus, there have been relatively few controlled studies of interventions in the acute setting of a recent suicide attempt; what we refer to in this manuscript as a 'suicidal crisis.' Patients attempting suicide and those at high risk are routinely hospitalized in order to keep them from killing themselves and to remove them from the stresses in their lives that may be aggravating the situation. Hospital admission, with its structure and counseling, does result in reductions in suicidality [15,16]. Commonly medications are adjusted or changed; however, the effect of antidepressant medications requires several weeks and thus is unlikely to quickly treat the suicidal crisis [17].

Repeated daily left prefrontal rTMS is a non-invasive approach to treating depression, differing from medications and electroconvulsive therapy (ECT) [18,19]. The FDA has now cleared two devices for treating depression. Recent studies suggest that stimulating the prefrontal cortex non-invasively with transcranial magnetic stimulation (TMS) might rapidly reduce suicidal thinking [20]. Other open-label studies have demonstrated the feasibility of delivering higher doses of TMS in a short timeframe [21].

Daily prefrontal TMS is thought to treat depression by improving cortical-limbic regulatory control over emotional drive [18]. Some researchers have conceptualized suicidal crisis as a dysfunctional brain event (like a stroke). Although patients are not routinely psychotic, there is clear evidence that the governing prefrontal cortex is unable to do its job of regulating emotional drive, put problems in context, and plan for the future [22].

We therefore conducted this study to test the safety, feasibility, and potential efficacy of delivering high doses of rTMS to suicidal inpatients. As mentioned above, studying these patients is difficult, for both regulatory and administrative reasons. We sought inpatients either who recently attempted to kill themselves or who

were hospitalized because their thoughts of suicide were so intense that they were not safe. Because no prior data existed about the safety of using TMS in this setting, or of this high dose of TMS to a vulnerable population such as patients in suicidal crisis, we could only conduct this first study in an inpatient setting. Moreover, as there were no efficacy data for treating suicidality with rTMS, and because patients were in a critical, life-threatening condition, we were ethically compelled to conduct this study in an adjunctive fashion such that subjects also received their prescribed anti-suicidal treatments, which allowed subjects to get the full benefits of hospitalization, medication changes and counseling.

Methods and materials

Study overview

The study was conducted at 2 study sites in the United States: Ralph H. Johnson VA Medical Center (RHJVAMC) associated with the Medical University of South Carolina, Charleston, SC; and Walter Reed National Military Medical Center (WRNMMC), Bethesda, MD. Active enrollment extended from December 2010 through March 2013, with 6 month followup complete by August 2013. This study was part of the INjury and TRaumatic STress (INTRuST) Consortium, coordinated through the University of California, San Diego (UCSD) funded by the Department of Defense. Because of this funding source and the desire to integrate these data with the larger consortium database, patients had to have post-traumatic stress disorder (PTSD) or traumatic brain injury (TBI) or both, in addition to being suicidal. The Institutional Review Board (IRB) at each center approved the protocol (as did the UCSD and US Army Medical Research and Materiel Command (USAMRMC) Human Protection Research Office (HRPO)), and all subjects provided written informed consent. An independent Data and Safety Monitoring Board (DSMB) through the INTRuST Consortium reviewed participant safety and progress of the study. The data were processed, managed and organized by the INTRuST Informatics Core at UCSD, with primary statistical analyses conducted by independent statisticians (RR, SJ, and XS) from the INTRuST Biostatistics Core. Site monitoring was conducted by the INTRuST Consortium.

The study was designed as an acute intervention delivered during the first few days of hospitalization as an adjunctive intervention in addition to all other interventions, including workup for ECT but not including active ECT treatment (see Fig. 1). In fact, no subjects went on to receive ECT in the index admission. Additionally, after discharge patients were followed up for 6 months, with standard clinical care and without additional study intervention (extended safety phase).

Subjects

Patients were recruited from the inpatient wards at the two sites. Two investigators (CGP, GGG) were inpatient psychiatrists and would thus monitor admissions for eligible patients. The attending

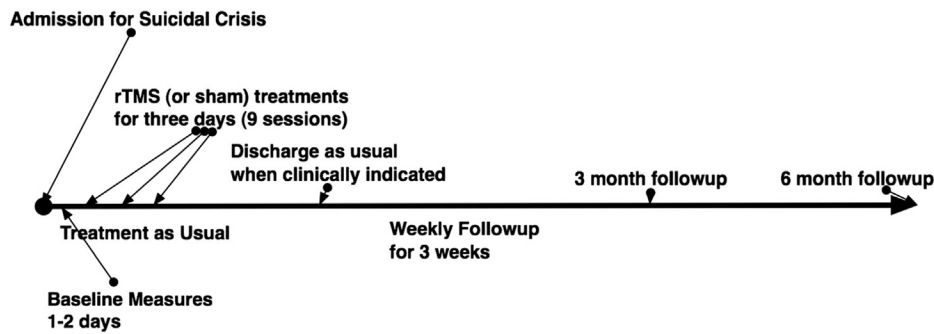


Figure 1. Design of the study – Inpatients admitted for suicidal crisis were consented within the first few days of admission, given ratings, and then had three days of treatment with either active or sham TMS. Participation in this study was done adjunctively. That is, patients stayed on their current medications and had other counseling and adjustments made by the clinical staff.

physician (or another physician if there was a conflict) would then approach the patient about participation, and if they agreed, then patients were screened by study staff.

We enrolled inpatients who were admitted because of suicidal ideation (or attempt), aged 18–70 years, with a Beck Scale of Suicidal Ideation (SSI) score ≥ 12 [23], and a score of at least 3 on Question #3 of the Hamilton Rating Scale for Depression [24]. Patients must have been in a depressive episode (unipolar or bipolar II, non-psychotic), as defined by Diagnostic and Statistical Manual (DSM)-IV. Because of the funding source and the desire to merge these data with other clinical trials within the consortium, they must also have had a diagnosis of post-traumatic stress disorder (PTSD), or mild traumatic brain injury (TBI), or both. The diagnosis of PTSD was made according to DSM-IV by clinical history, and then confirmed by the overall study PI. The diagnosis of mTBI was also made clinically in accordance with the American College of Rehabilitation Medicine (ACRM) criteria [25]. Women must have had a negative urine pregnancy test. Patients must have been able to speak English and have been competent to give informed consent. We excluded patients who had clinically unstable medical illnesses, metal in their head, a history of seizures, borderline personality disorder, or homelessness (at the Charleston site only, defined as having no address), those were committed to the hospital under court order, and those with schizophrenia or psychosis, bipolar disorder type I, or dementia. We excluded subjects who had repeatedly abused or were dependent upon drugs within 6 days of study entry. We allowed patients who had been drinking alcohol to participate, but only after their vital signs were stable with no signs of alcohol withdrawal, as documented by a clinical institute withdrawal assessment for alcohol (CIWA protocol). Patients were allowed to remain on their current medications or to have medications changed or added with the exceptions of theophylline, stimulants such as methylphenidate, or the antidepressant bupropion (as these raise the potential risk of a TMS-induced accidental seizure).

rTMS treatment sessions

We used a Model 2100 magnetic stimulator (Neuronetics, Inc., Malvern, PA; NS 0226 A 15VAC-C) consisting of a controller/power supply and three solid iron core coils (active labeled, active not labeled and sham not labeled) that were placed in a support platform for consistent coil position and repositioning. This same TMS system was used in the OPT-TMS trial [26]; however, a slightly different active sham system was controlled by a “smart card,” which is a preprogrammed credit card-sized plastic card with a flash memory chip imbedded. After randomization at UCSD, each subject was assigned an initial smart card (active or sham), which

sensed whether the appropriate TMS coil for that patient (sham or active) was attached and then drove the TMS device appropriately. Active and sham coils were labeled randomly as either *b* or *c*, varying across sites and throughout the trial. Both active and sham coils were unmarked and appeared identical. An open label coil was used to determine a subject’s motor threshold using the parameter estimation with sequential testing (PEST) algorithm and visible movement in the right hand [27–29]. The sham system is the same as that used in the OPT-TMS trial, where the sham antidepressant response rate was only 5%. We thus theorize that the sham system does not itself have any biological antidepressant or anti-suicidal activity. This sham is not the same as tDCS, as the stimulation is only intermittent, coordinated with the firing of the TMS device [30]. The active sham setup consisted of a transcutaneous electrical nerve stimulation (TENS) unit connected through a splitter device attached to electroconvulsive therapy (ECT) electrodes positioned directly under the TMS coil [31]. The TMS machine sent out a transistor–transistor logic (TTL) pulse trigger to the splitter device at which point the device was toggled to either coil *b* or *c*. For those assigned to real TMS, the sham system was inactive. For a subject randomized to sham, the splitter device allowed the TENS unit stimulation to pass to the electrodes while the sham TMS coil fired. The sham coil mimics the noise and placement of the active coil [32,33]. The coil was not actively cooled and did in fact get hot during some treatments.

For treatments, subjects were seated in a semi-reclined chair with a foam headset in a head-holder. This chair was located either in a separate room on the inpatient unit (WRNMMC) or in a laboratory just outside the door of the unit (RHJVAMC).

TMS treatment parameters

Repetitive TMS (rTMS) was delivered to the left prefrontal cortex, defined as a location 6 cm (cm) anterior to the right hand motor thumb area. Trained treaters, who were not raters, delivered the treatments. rTMS was delivered with a figure-eight solid core coil at 120% motor threshold, 10 Hertz (Hz), 5 s (s) train duration, 10 s intertrain interval for 30 min (6000 pulses) 3 times daily for 3 days (total 9 sessions, 54,000 stimuli). These parameters are slightly greater than the published safety guidelines (10 Hz at 120% for only 4.2 s is within) [34]. The safety guidelines also do not address the total dose of stimulation, or the number of stimuli in a given day or week. Variations were allowed in the dosing schedule to accommodate the patient’s inpatient schedule and staffing needs, with at least 1 h between sessions. Treatments were done on consecutive days, with the goal to deliver 9 sessions over three days. Some patients required a 4th day to get all 9 treatments done. Adverse events were assessed at each treatment session as well as daily.

Prior to and then immediately after each TMS session, subjects completed visual analog scales (VAS) on a desktop computer located next to the TMS chair. Patients wore earplugs and were not allowed to sleep. Counseling or other conversation during treatment was discouraged. At both sites following an adverse event described below at about 30% final enrollment, a small foam insert was placed between the coil and the scalp. Additionally, the coil was monitored with an external thermostat and then replaced within a session if the temperature exceeded 42 °C (Table 1).

Concomitant treatments

Inpatient medical staff were told to continue to adjust medications and perform all 'treatment as usual,' including counseling, support and workup for electroconvulsive therapy (ECT) if indicated.

Efficacy assessments

Trained and blinded study staff (raters) administered the Beck Suicidal Scale Inventory (SSI) to subjects at baseline and then at the end of each day during their three treatment days. A custom-developed Visual Analog Scale (VAS) questionnaire was administered on a laptop computer pre and post each treatment session. Subjects were asked to rate their treatment experiences using the following descriptors: happy, irritable, angry, excited, confused, calm, sad, anxious, nervous, bored, relaxed, tired, distracted, pain, discomfort, and suicidality. VAS scores were converted to a scaling of 0–100 points. On post treatment questions only, subjects were asked about the painfulness of the procedure at the beginning, middle and end of each treatment. Appendix 1 provides the questions. The program presents all questions at each session, but in a constantly-changing random order across different sessions. As part of the planned statistical analysis protocol devised before unblinding, we decided to perform analyses on 3 suicide-related questions, 3 mood questions, and 2 anxiety/irritability questions. We also analyzed the painfulness questions. Other secondary efficacy outcomes include the HRSD, MADRS, C-SSRS and CAPS which were collected at baseline, before discharge from the index admission, and at followup visits at month 3 and 6.

Safety assessments

Research staff used the MedDRA System Organ Class (SOC) and preferred term (PT) to document adverse events, which were assessed at each treatment, and at followup visits.

Integrity of the blind

At the end of the first day of TMS treatments (Day 1) and at the end of Day 3 (last rTMS treatment) subjects, TMS treaters and clinical raters were asked to indicate their best guess (forced) as to which treatment group a subject was assigned and their

confidence in their guess (extremely, considerably, moderately, slightly, not at all).

Statistical methods

The primary outcome (SSI) was analyzed using an MMRM (mixed model repeated measures) approach based on a modified intent-to-treat (mITT) population. The mITT population was defined as randomized subjects who started at least one treatment. Participants from the mITT population who were included in the MMRM model also required both a baseline and at least one post-baseline SSI score. The model included as the dependent variable change from baseline in SSI total score at each post-baseline visit during the acute phase. Independent variables in the MMRM model included treatment, visit, treatment-by-visit interaction, SSI total score at baseline, gender, age at baseline and diagnosis. Visits (Days 0, 1, 2, 3) were treated as a categorical variable. Unstructured variance-covariance structure was used. This same analysis was also repeated on the completers population, defined as subjects who completed 3 days of treatment with the scheduled maximum 6000 pulses per session.

Analyses of VAS data were conducted using a similar MMRM approach. Each VAS item was analyzed separately. For the suicide, mood and anxiety items, the model included as the dependent variable change scores from pre-session 1 (session prior to intervention) to each post-session (sessions 1–9) during the acute phase. Independent variables included treatment, session, treatment-by-session interaction, VAS score at pre-session 1, gender, age at baseline, and diagnosis. Painfulness questions collected only at each post-session were analyzed using an MMRM approach with post-session scores as the dependent variable. Independent variables remained the same.

Descriptive analyses were performed to compare baseline data between treatment groups. Categorical variables were evaluated using Fisher's exact test. Continuous variables were analyzed with Wilcoxon's rank sum test.

Safety data were summarized overall and by treatment groups. Fisher's exact test was used to compare the number of subjects between groups who experienced any adverse events. Length of hospital stay was compared using Wilcoxon Rank Sum test. Time to re-admission was analyzed with log-rank test.

Other secondary efficacy outcomes (HRSD, MADRS, CAPS and SSI) for the extended safety phase were analyzed with MMRM model. The model included the change from baseline at each follow-up visit as the dependent variable. Independent variables included treatment, visit, treatment-by-visit interaction and baseline score.

The integrity of the blind was analyzed by tables and Fisher's exact test.

All statistical analyses were performed in R version 2.14.0. Because this is an early phase study, no adjustments were made for multiple comparisons, and a *P*-value of 0.05 was considered to be statistically significant.

Table 1
rTMS parameters used in this study.

Study	# Pulses/session	# Pulses/day	Total pulses	% Motor threshold	Hz	Intertrain interval (s)
George (1997) [59]	800	800	8000 (in 2 weeks)	80%	20	58
O'Reardon (2007) [36]	3000	3000	60,000 (in 4 weeks)	120%	10	26
George (2010) [26]	3000	3000	45,000 (in 3 weeks)	120%	10	26
Zangen, in press	1980	1980	39,600 (in 4 weeks)	120%	18	20
Andersen (2006) [35]	12,960	12,960	38,880 (in 3 days)	80–120%	1–20	Varied
Holtzheimer (2010) [21]	1000	5000/10,000	15,000 (in 2 days)	100%	10	25
This study	6000	18,000	54,000 (in 3 days)	120%	10	10

Results

Patients

377 patients were screened (98 WRNMMC; 279 RHJVAMC), and 78 were found eligible (37 WRNMMC; 41 RHJVAMC). 42 subjects were randomized; however, one was removed from analysis due to incorrect consent. Thus 41 were randomized correctly (14 WRNMMC; 27 RHJVAMC; 21 sham, 20 active). True completers were those subjects who completed three days of treatment with the maximum 6000 pulses per session. Only 27 of the 41 were true completers (9 WRNMMC; 18 RHJVAMC; 17 sham, 10 active). 5 subjects were acute phase early discontinuations [2 prior to treatment, 2 withdrew consent before completion of treatment, and 1

subject was discontinued due to a heat induced burn (see below)] (Fig. 2).

Table 2 shows that basic demographic variables are similar between the two groups. Table 3 shows the concomitant medications patients were taking. Many patients were taking multiple medications. The only large differences between the two groups are that the active TMS patients were taking more benzodiazepines than the group randomized to sham, and that the active group had higher rates of current substance abuse.

SSI change scores

The MMRM statistical analysis on the mITT population indicates that both groups improved over the 3 days of treatment (mean

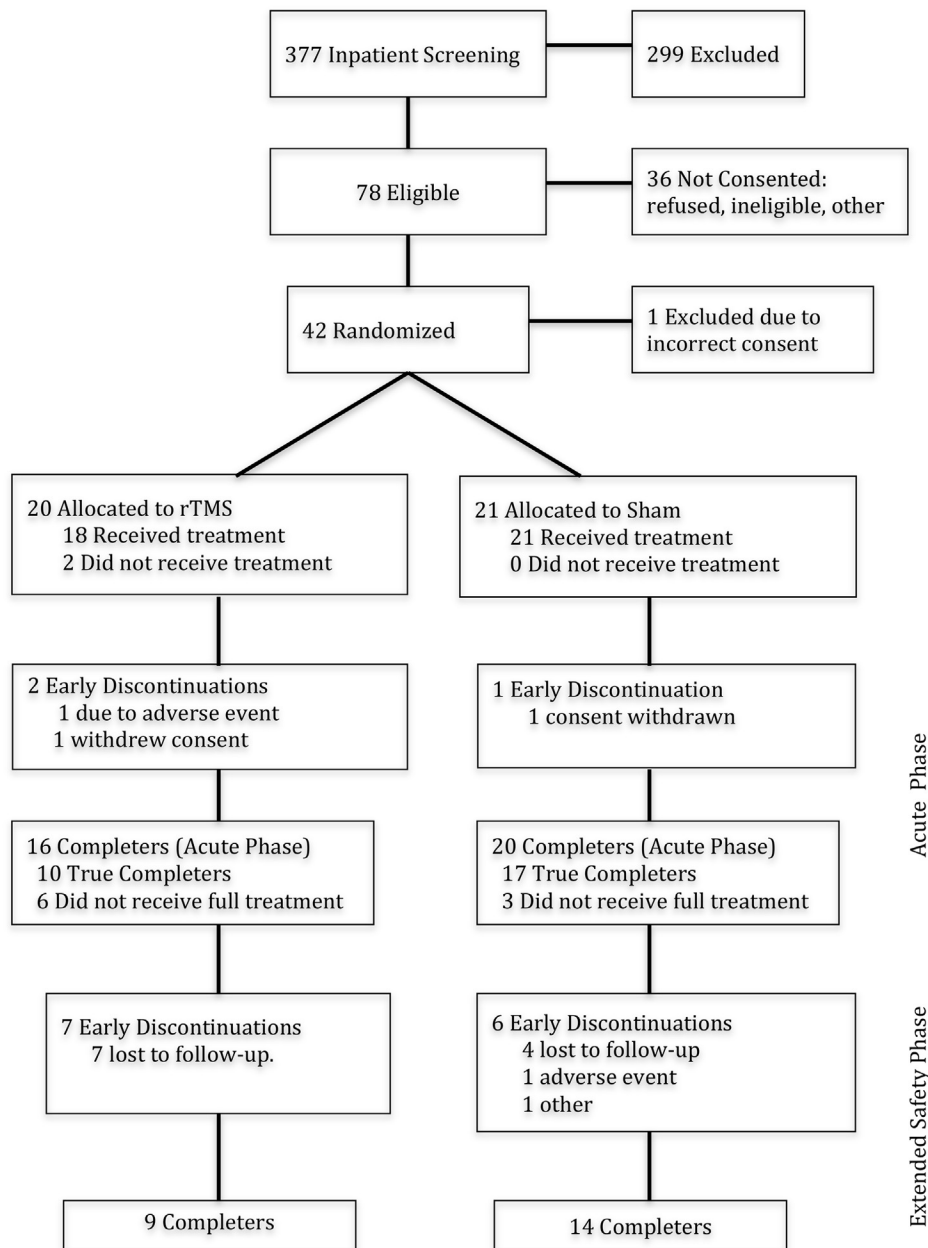


Figure 2. Consort diagram – Virtually all patients admitted to the two wards during the enrollment period were indirectly screened for potential inclusion, but many did not qualify for obvious reasons such as not being suicidal, or being psychotic or having a substance abuse disorder. 42 patients were randomized to either active [18] or sham [21] TMS. This is the modified ITT sample. There were 10 active completers versus 17 sham completers who comprise the completer sample. The extended phase of the study is still under datalock and is not reported in this manuscript.

Table 2
Baseline characteristics of the study participants.^a

Variable	Sham (N = 21)	rTMS (N = 20)	Total (N = 41)
Age (yr)	46.1 ± 15.9	38.7 ± 15	42.5 ± 15.7
Male sex – no. (%)	17 (81%)	18 (90%)	35 (85%)
White race – no. (%)	14 (67%)	15 (75%)	29 (71%)
Education (yr)	13.5 ± 1.9	13 ± 1.8	13.3 ± 1.9
Diagnosis – no. (%)			
mTBI only	1 (5%)	0 (0%)	1 (2%)
PTSD only	10 (48%)	7 (35%)	17 (42%)
Both mTBI and PTSD	10 (48%)	13 (65%)	23 (56%)
Past substance	6/19 (32%)	7/13 (54%)	13/32 (41%)
Abuse/dependence			
Current substance	2/19 (11%)	6/13 (46%)***	8/32 (25%)
Abuse/dependence			
SSI total ^b	20.8 ± 5.3	21.7 ± 5.7	21.2 ± 5.5
Length of stay before start of treatment (days) ^c	4 (2, 6)	2 (2, 3.75)	2 (2, 5)

*** $P < 0.05$.

^a Plus-minus values are means ± SD. There were no significant differences between groups with regard to baseline characteristics.

^b SSI total ranges from 0 to 38, and higher scores indicate greater suicidal ideation. SSI Total score is only available for 19 of the rTMS subjects at baseline.

^c Length of stay is reported with median (inter-quartile range).

change from baseline at day 3 = −15.3 and −15.6 for sham and rTMS groups, respectively), however there is no significant treatment difference (see Fig. 3). There is a trend toward more improvement in the TMS group versus sham at day 1 ($P = 0.12$ in the mITT analysis; $P = 0.054$ in the completers' analysis); however, this difference normalized at days 2 and 3. The SSI scoring algorithm assumes that the total score equals to 0 if someone responds no to the first five questions. It thus quickly goes to 0, and does not have full range at low amounts of suicide. We thus also examined how many subjects scored zero after day 1 [mITT (active 4/16, 25%, sham 2/20, 10%, NS) and day 3 (active 6/14, 43%, sham 8/20, 40%, NS), completers, active 4/10, 40%, sham 2/17, 12%, NS) and day 3 (active 4/9, 44%, sham 8/17, 47%, NS)].

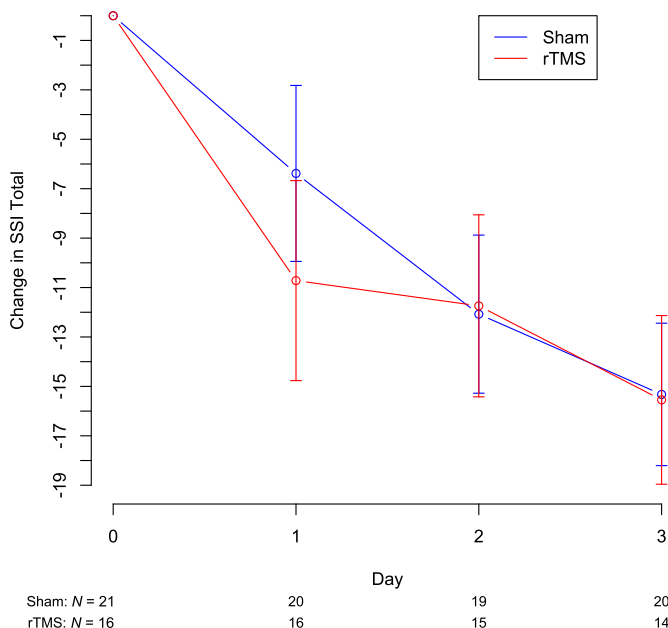
Subjective visual analog scores

VAS examined participants' current suicidal ideation as well as moods, such as sadness, happiness, tiredness, irritability and anxiety; painfulness of treatment was also assessed.

Table 3
Concomitant medications.

Medication class	Total	Active	Sham
Antipsychotic			
Haloperidol	3	1	2
Olanzapine	2	2	
Quetiapine	7	4	3
Aripiprazole	2	2	
Benzodiazapine	15	11	4**
Tricyclic	1	1	
SSRI	20	10	10
NSRI	8	3	5
Trazodone	10	6	4
Mirtazapine	8	5	3
Mood stabilizer			
Gabapentin	14	8	6
Valproic acid	2	1	1
Carbamazepine	2	2	
Lamotrigine	4	1	3
Topiramate	3	2	1
Lithium	2		2
	103	59	44

A SSI Change from Baseline from MMRM - mITT



B SSI Change from Baseline from MMRM - Completers

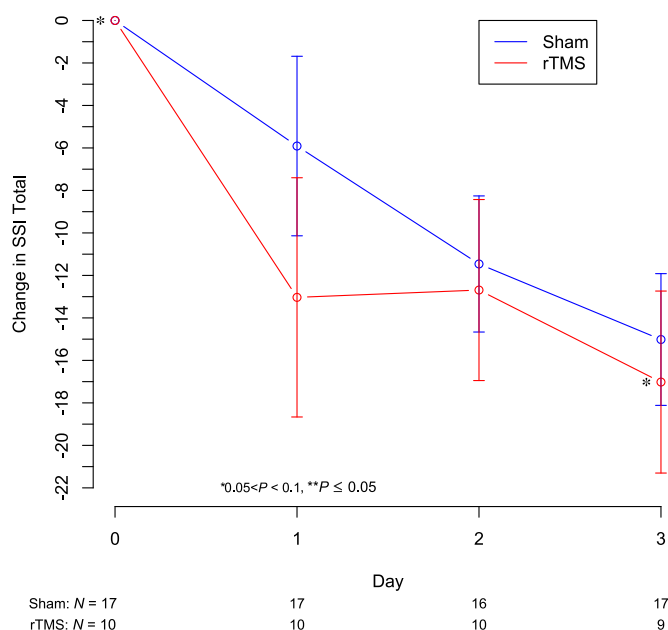


Figure 3. SSI Overall Scores (A. mITT, B. completers) These are changes from baseline in the Beck Suicidal Ideation Score by group. In the completer analysis (B) there is a marked reduction in scores on the first day ($P < 0.05$).

Current suicidality

Figure 4 shows the change in score from pre-session 1 at each post-session by treatment groups. The mITT analysis indicates that although there is more decline in the TMS group as compared to the sham group, the difference is not statistically significant. The completers' analysis demonstrates a significant decline in the TMS group at the end of 9 sessions [sham mean change = −24.9 (95%

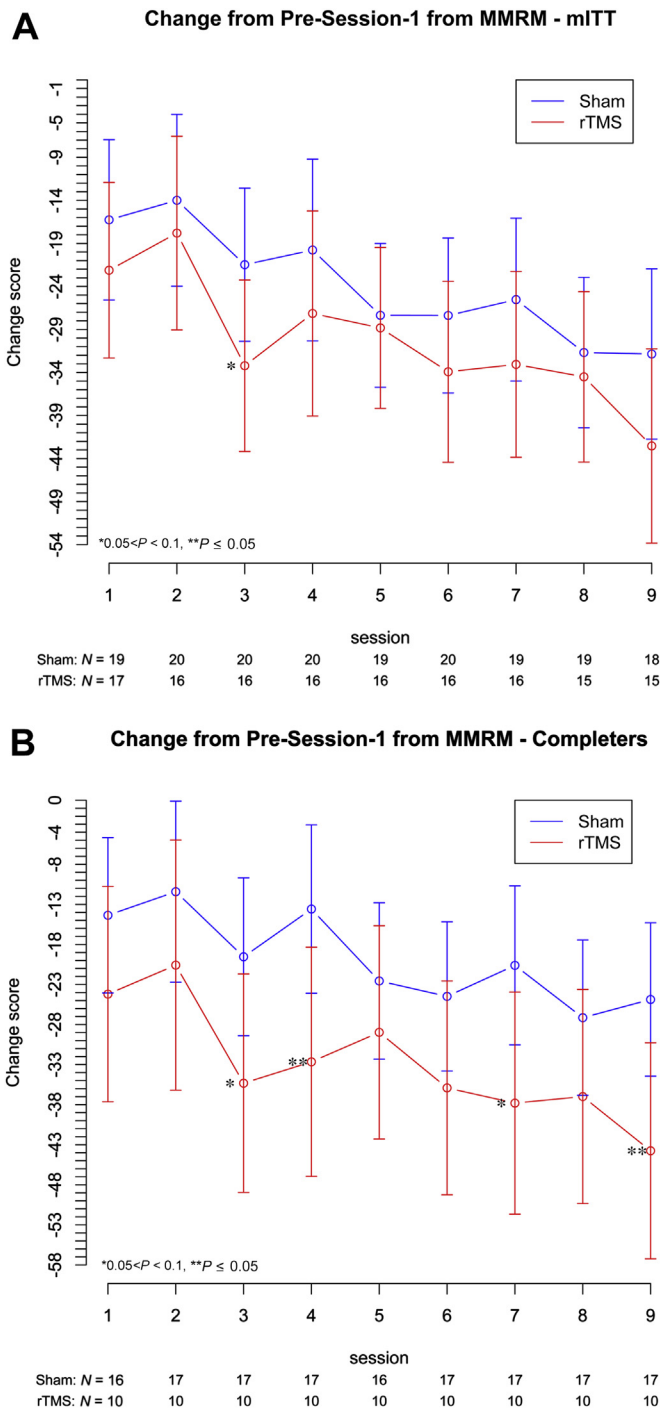


Figure 4. These are visual analog responses by patients to the question, 'I am currently bothered by thoughts of suicide.' The data are presented as change from their response immediately before the first treatment, and are graphed by each of the 9 treatments and by group (active, sham). Note that in the completer analysis there is a significant reduction in suicidal thinking, particularly after the third treatment, or the first full day of treatment (A. mITT, B. completers).

CI: $-34.4, -15.3$), TMS mean change = -43.8 (95% CI: $-57.2, -30.3$); $P = 0.028$].

There were no significant group differences in response to the question, 'It is likely I will attempt suicide someday,' and 'I think of harming myself often.'

Mood

The 3 questions relating to mood (sadness, happiness, tiredness) did not reveal a significant difference between groups. Interestingly, for the two anxiety related questions probing anxiety or irritability ('At the present moment I feel anxious,' or '... I feel irritable'), there was a significant between group difference in change scores from baseline to the end of the treatment, with the sham group reporting greater reductions in anxiety and irritability over time (Fig. 5).

Painfulness

Figure 6 shows responses by group to the questions regarding pain experienced during TMS treatment. Note that the active, but not the sham, group indicates a significant reduction in the rated painfulness of the procedure.

Safety outcomes

TMS as delivered in this protocol was safe both acutely and long-term. There were no suicide attempts and no serious adverse events in the acute phase. There were 33 adverse events (AE) overall (21 sham, 12 active), with 13 subjects experiencing at least one adverse event (6 sham, 7 active; $P = 0.74$). Table 4 lists the AEs overall and by group.

Two adverse events that were rated both as 'definitely device related' appeared in the active arm, while 2 adverse events rated 'probably related' emerged in the sham arm. In the active arm, 1 subject acquired and subsequently recovered from a headache (rated 'moderate') on the first day of treatment. Another subject developed erythema at the coil stimulation site, which progressed to a second-degree burn. This subject was discontinued from the study, was treated and recovered. After this event occurred, the research team adopted the practice of placing a thin insulating pad between the coil and the scalp for all subjects, in addition to a protocol to periodically check the temperature of the coil during all treatment sessions and pausing the session if the coil became warm. In the sham arm, 1 subject developed eye pain and an eye twitch, with both symptoms subsiding without the need to stop treatment. Importantly, no between group differences appeared as a consequence of headache or other symptoms. The data safety monitoring board reviewed all adverse events and determined that two additional adverse events possibly led to withdrawals of consent. The site investigators did not think the withdrawals were related to adverse events. One subject (active) noted that the treatment was too painful behind the eye, and another (sham) had a 'shooting pain down my jaw,' and also had prior and current migraines.

Length of hospital stay, index admission

The median length of stay was 10 days with no difference between groups (sham median 11 days (IQR: 8–20), TMS median 9.5 days (IQR: 7–16)). Treatment was started on average on the 3rd day of hospitalization (range 2–20 days; sham median 5 days (IQR: 3–7), TMS median 3 days (IQR: 3–5)).

Mood, suicide and safety during the extended safety phase

A total of 11 (28%) patients (4 sham, 7 TMS) were readmitted for psychiatric reasons in the 6 month followup window, primarily for suicidal ideation or attempt. There were no completed suicides. There is no significant difference in the time to re-admission between the two groups (log rank test $P = 0.34$).

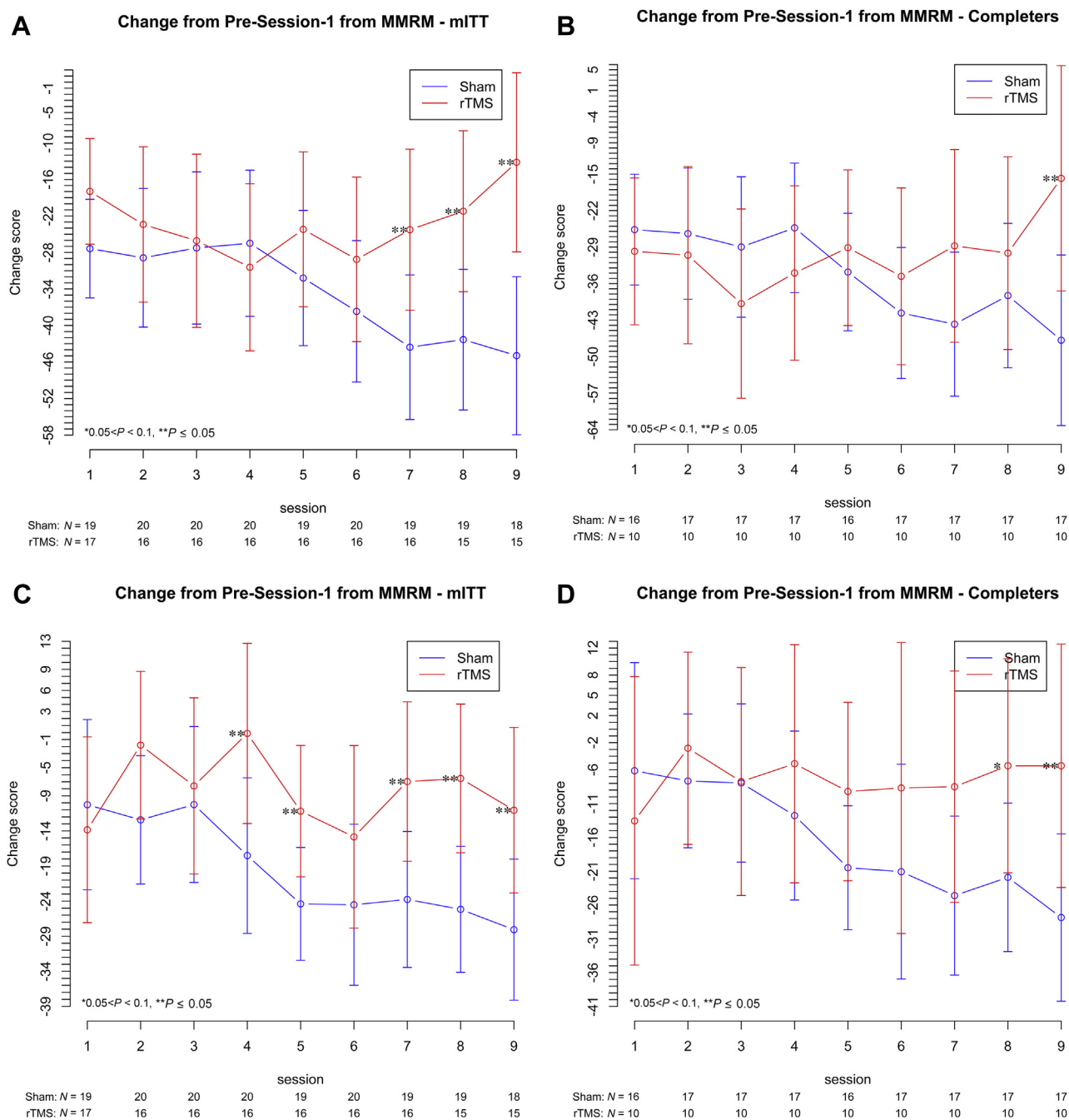


Figure 5. These are visual analog response change scores for the question, 'At the present moment I feel anxious' (A. mITT, B. completers) or 'At the present moment I feel irritable' (C. mITT, D. completers). Note that the sham group was less anxious and less irritable than those who received active TMS.

There were no statistically significant between group differences (mITT sample) in followup scores of the SSI, C-SSRS, HRSD, MADRS, or CAPS.

Integrity of the blind

Overall, patients in the study were not able to correctly guess their randomization status. The majority of the patients (75% in the sham group vs. 81% in the rTMS group on day 1, 78% vs. 86% on day 3) guessed they received the active intervention ($P = NS$). Although 13 patients (36%) rated their confidence high (extremely or

considerably), 5 of these 13 were wrong. For a full description of the integrity of the blind see [Appendix 2](#).

Discussion

This pilot study demonstrates that it is feasible and safe to administer a very large dose (number of stimuli in a given time) of prefrontal rTMS to inpatients who are admitted in a suicidal crisis. Nine treatments in 3 days were reasonably well-tolerated without major side effects, even in this severely ill cohort that is rarely studied due to their severity of illness. Additionally, although the

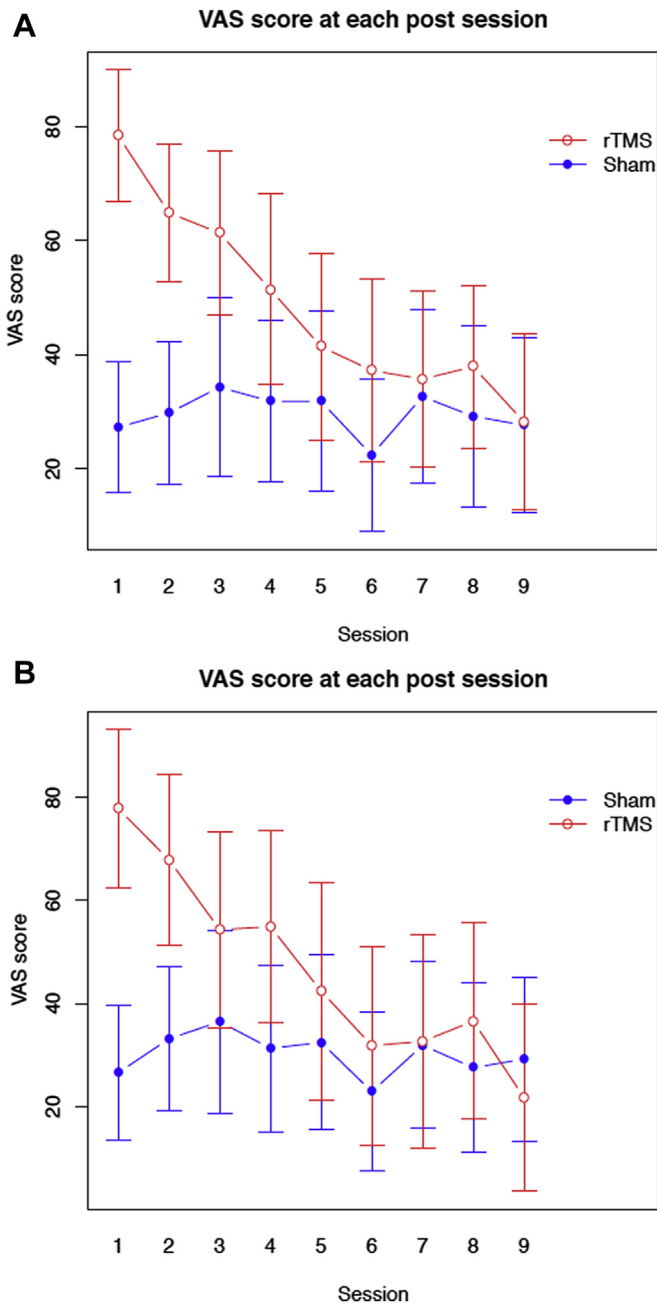


Figure 6. These are visual analog response change scores for the question, 'I felt pain during the beginning of the treatment' (A. mITT, B. completers). Note that the active TMS was rated as significantly more painful for the first few sessions, but that this difference diminished over time.

planned primary analysis was not significant, there are suggestions of a rapid anti-suicide effect with the completer sub-group on the SSI and on the VAS item about being bothered by thoughts of suicide. Below we discuss the feasibility, safety and then efficacy findings before returning to a discussion of the limitations and proper interpretation of the study.

Dose

It appears both feasible and safe to administer as many as 54,000 left prefrontal rTMS stimuli to patients within 3 days. This is the most aggressive dose of rTMS ever administered in the published

Table 4

Adverse events summarized by System Organ Class (SOC) and Preferred Terms (PT).^a

	Sham (N = 21)	rTMS (N = 20)	Overall (N = 41)
EYE DISORDER	2 (9.5%)	1 (5%)	3 (7.3%)
Diplopia	0 (0%)	1 (5%)	1 (2.4%)
Eye pain	1 (4.8%)	0 (0%)	1 (2.4%)
Vision blurred	1 (4.8%)	0 (0%)	1 (2.4%)
GASTROINTESTINAL DISORDERS	2 (9.5%)	0 (0%)	2 (4.9%)
Nausea	2 (9.5%)	0 (0%)	2 (4.9%)
Vomiting	2 (9.5%)	0 (0%)	2 (4.9%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0%)	1 (5%)	1 (2.4%)
Brain contusion	0 (0%)	1 (5%)	1 (2.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.8%)	1 (5%)	2 (4.9%)
Back pain	0 (0%)	1 (5%)	1 (2.4%)
Myokymia	1 (4.8%)	0 (0%)	1 (2.4%)
NERVOUS SYSTEM DISORDERS	5 (23.8%)	5 (25%)	10 (24.4%)
Dizziness	2 (9.5%)	1 (5%)	3 (7.3%)
Headache	4 (19%)	5 (25%)	9 (22%)
Migraine	1 (4.8%)	0 (0%)	1 (2.4%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0%)	1 (5%)	1 (2.4%)
Erythema	0 (0%)	1 (5%)	1 (2.4%)
VASCULAR DISORDERS	1 (4.8%)	0 (0%)	1 (2.4%)
Hypertension	1 (4.8%)	0 (0%)	1 (2.4%)

^a Capitals are SOC terms, lower cases are PT terms. There were no significant between group differences.

literature [35]. By comparison, the FDA clearance for the Neuro-netics machine approves 3000 stimuli per day over a course of 4–6 weeks [26,36]. Thus, this dose of 18,000 stimuli/day is a 6-fold increase in the daily dose beyond the current FDA approval and matches the maximum dose previously proven safe in healthy young adults [35]. The 54,000 stimuli in 3 days is roughly similar to the number of stimuli that are routinely given over almost 4 weeks (18 sessions) when using TMS to treat depression in outpatients. The upper safety limits of TMS in terms of the number of stimuli in total or in a given time are not known [34], and these data suggest that there is room for safely and feasibly increasing TMS dosage well above that used in current practice, if indicated clinically. The patients in general accepted the treatments, and there were no cumulative side effects. The air-cooled coil did overheat on 1 subject causing a first-degree burn; consequently this concern was monitored and a method was devised to mitigate this risk.

In terms of discomfort and tolerability, the VAS data show that there was a remarkable accommodation, in the active group only, to the painfulness of the TMS procedure. Anecdotally, patients were often uncomfortable during the first few sessions, and by Day 3, they would need to be nudged to keep from falling asleep during the procedure. Several studies have shown that a single session of prefrontal TMS similar to those given in this study has acute anti-nociceptive effects [37–41]. Blocking the endogenous opiate system with naloxone abolishes this effect [42], suggesting that prefrontal cortex mediated opiate release is critical for this TMS anti-nociceptive effect, likely mediated through brainstem regions [43]. The rapid tolerance to the painfulness of the procedure over 3 days (9 sessions) without worsening or sensitization bodes well for the feasibility of using aggressive doses like this in patients in future studies. The slope of the tolerance or accommodation over 3 days resembles the slope seen with accommodation to pain over 3 weeks in the OPT-TMS trial [44].

The painfulness ratings also reveal that sham stimulation was not as painful as active stimulation, which was also seen in the OPT-TMS trial. Complicated methods exist that allow investigators to exactly match the painfulness of TMS and the active sham [30,31,45]. These methods are quite useful and are required in

studies related to treatment of pain using TMS [37,38,46–48]. However the method requires a randomly alternating administration of sham and active TMS, which takes time and risks subject unblinding. This type of methodology is not likely feasible for use in this critically ill cohort. The overall greater painfulness of the active treatment over sham may explain partially why the sham group reported a greater overall reduction in self-rated irritability and anxiety. The real treatment hurt more. Alternatively, the active treatment may have been stimulating and activating cortical subcortical circuits in a manner that was essentially more irritating and anxiogenic than the sham.

With respect to feasibility of performing this type of research on suicidal patients immediately after their hospital admission, the research team overestimated the amount of neuropsychological and other testing that these inpatients with suicidal crisis could tolerate. Many were exhausted from little or no sleep, and they had difficulties concentrating, attending to and responding to questionnaires. Future studies on similar critically ill suicidal cohorts should recognize the limited ability of these subjects to participate in complex ratings in a short amount of time. The dropout rate in this TMS study was higher than in outpatient studies, where retention rates of 90% or greater have been seen. There was no difference in the retention rate between active and sham, suggesting that non-specific factors associated with the suicidal crisis and hospitalization were also involved. It must be remembered that this is a very ambitious dose of TMS, in a critically ill group. Finally, there have been few studies of interventions in hospitalized suicidal patients. Thus it is hard to compare the dropout rates in this study with other interventions or other TMS studies.

Turning to a discussion of efficacy, this pilot safety and feasibility study was powered only to fully detect large effects and to provide pilot data for use in a power analysis for designing later trials. These data show that the primary analysis of SSI change scores was not significantly different using the mITT analysis, and the scores were only marginally significant with the completer analysis. However, in completers on Day 1, an average 50% reduction in SSI scores emerged from the day before with active rTMS, as compared to a 25% reduction with sham. This is a rapid and moderate effect, in the same range as recent data regarding subanesthetic doses of ketamine for suicidal ideation [12]. Interestingly, and in keeping with this inpatient adjunctive study, almost all subjects had substantial reductions in suicidality by Day 3. Although it is not known whether some of this reduction is due to their inpatient stay, an outpatient study might be able to separate out this potential non-specific hospitalization effect. The data found here now support further studies using this high TMS dosing treatment regimen as a primary intervention (as opposed to adjunctive) and in an outpatient setting for suicidal patients.

The VAS results are in one sense confirmatory of the reduction in suicidality, but are puzzling in other respects. Although there was a significant reduction in how much subjects were bothered by thoughts of suicide, there was no difference in response to questions about future intent of suicide or the statement 'I think of harming myself often.' There were no significant changes in self-rated sadness, tiredness or happiness. Puzzlingly, there are greater improvements in anxiety and irritability with sham than with active TMS. This may derive from differences in painfulness of each session or an unequal distribution of comorbid anxiety or current substance abuse (as suggested by the differences in benzodiazepines across the two groups). However, these aspects should be tested for potential replication in future studies and attended to closely. Impulsivity, anxiety and irritability can often drive someone pondering suicide into action.

This was a pioneering pilot study in an understudied area where new treatments are desperately needed, and there are many

limitations. The group of patients enrolled are heterogenous with respect to their core psychiatric diagnoses [49]. Any suicidal patient who was not actively dealing with a substance abuse problem was screened. Perhaps the results would have been different if entry was restricted to a more classically homogenous population such as those with DSM-5 recurrent treatment resistant major depression. With respect to blinding, subjects were not able to accurately guess what treatment they were receiving. Treaters were able to guess above chance, but it appears this was driven more by clinical response than by any technical issues involved in administering TMS. Raters were able to guess above chance on Day 1, when the largest differences existed between groups on the SSI, but they fell back to chance ratings by Day 3, when most all subjects experienced large reductions in suicidality.

This study has shown safety and feasibility, and has clearly not established efficacy. However the putative mechanism of action that led to performing the study is as follows. The leading theory regarding how prefrontal TMS works for treating depression posits that repeated stimulation of prefrontal control circuits help re-establish a modulating role of the prefrontal cortex [18,50–54]. This has been shown in animal studies involving learned helplessness and the concept of control [50,55–58]. Although there are many factors that lead up to a suicidal crisis, it seems clear that the functions normally subserved by the prefrontal cortex (advanced planning, flexibly thinking through solutions, proper evaluation of self in the world) are not working. Although clearly psychotic patients were excluded, many patients in a suicidal crisis have a disordered manner of thinking and distorted worldview bordering on a delusion.

In summary, suicides are a major public health problem, and the world needs new acute treatments. The lack of a treatment hinders health care's ability to reverse stigma and educate the public. This study demonstrates that high doses of rTMS delivered over 3 days is feasible and is safe. Further studies are needed to determine whether, with further refinement, study and development, TMS ultimately may be a novel method to rapidly reduce suicidal thinking and prevent suicides.

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Dr. George would like to dedicate this study to the late Dr. Louisa M. Walsh (April 8, 1960–June 28, 2009) MUSC College of Medicine 1986, who died by suicide.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.brs.2014.03.006>.

References

- [1] Roy-Byrne P. Suicide: the long and winding road from research to practice. *Depress Anxiety* 2013;30:893–5.

- [2] Suicide among adults aged 35–64 years—United States, 1999–2010. *MMWR Morb Mortal Wkly Rep* 2013;62:321–5.
- [3] Gold KJ, Sen A, Schwenk TL. Details on suicide among US physicians: data from the National Violent Death Reporting System. *Gen Hosp Psychiatry* 2013; 35:45–9.
- [4] Stein MB, Ursano RJ. Suicide among United States military personnel: determining the root causes. *Depress Anxiety* 2013;30:896–7.
- [5] Injuries due to firearms and air guns among U.S. military members not participating in overseas combat operations, 2002–2011. *MSMR* 2012;19:2–6. Editorial Comment 5–6.
- [6] Deaths by suicide while on active duty, active and reserve components, U.S. Armed Forces, 1998–2011. *MSMR* 2012;19:7–10.
- [7] Kemp J, Bossarte R. Suicide data report. In: Affairs DoV, editor. Washington, DC: US Government; 2012.
- [8] Fink M, Kellner CH, McCall WV. The role of ECT in suicide prevention. *J ECT*; 2013.
- [9] Young AH. Review: lithium reduces the risk of suicide compared with placebo in people with depression and bipolar disorder. *Evid Based Ment Health* 2013;16:112.
- [10] Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *Br Med J* 2013;346:f3646.
- [11] Bluml V, Regier MD, Hlavin G, et al. Lithium in the public water supply and suicide mortality in Texas. *J Psychiatr Res* 2013;47:407–11.
- [12] Larkin GL, Beauvais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 2011;14:1127–31.
- [13] Oquendo MA, Galfalvy HC, Currier D, et al. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. *Am J Psychiatry* 2011; 168:1050–6.
- [14] Perlis RH. Hard outcomes: clinical trials to reduce suicide. *Am J Psychiatry* 2011;168:1009–11.
- [15] Madsen T, Agerbo E, Mortensen PB, Nordentoft M. Predictors of psychiatric inpatient suicide: a national prospective register-based study. *J Clin Psychiatry* 2012;73:144–51.
- [16] Troister T, Links PS, Cutcliffe J. Review of predictors of suicide within 1 year of discharge from a psychiatric hospital. *Curr Psychiatry Rep* 2008;10:60–5.
- [17] Olsson M, Gameroff MJ, Marcus SC, Greenberg T, Shaffer D. Emergency treatment of young people following deliberate self-harm. *Arch Gen Psychiatry* 2005;62:1122–8.
- [18] George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. *Curr Opin Psychiatry* 2013;26:13–8.
- [19] George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. *Am J Psychiatry* 2011;168:356–64.
- [20] Hadley D, Anderson BS, Borckardt JJ, et al. Safety, tolerability, and effectiveness of high doses of adjunctive daily left prefrontal repetitive transcranial magnetic stimulation for treatment-resistant depression in a clinical setting. *J ECT* 2011;27:18–25.
- [21] Holtzheimer 3rd PE, McDonald WM, Mufti M, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety* 2010;27:960–3.
- [22] Jollant F, Lawrence NL, Olie E, Guillaume S, Courtet P. The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. *World J Biol Psychiatry* 2011;12:319–39.
- [23] Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the scale of suicidal ideation. *J Consult Clin Psychol* 1979;47:343–52.
- [24] Hamilton M. A rating scale for depression. *J NeurolNeurosurgPsychiatry* 1960;12:56–62.
- [25] Kay T, Harrington DE, Adams R, Andersen T, Berrol S, Cicerone K. Definition of mild traumatic brain injury. *J Head Trauma Rehabil* 1993;8:86–7.
- [26] George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010;67:507–16.
- [27] Borckardt JJ, Nahas Z, Koola J, George MS. Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. *J ECT* 2006;22:169–75.
- [28] Mishory A, Molnar C, Koola J, et al. The maximum-likelihood strategy for determining transcranial magnetic stimulation motor threshold, using parameter estimation by sequential testing is faster than conventional methods with similar precision. *J ECT* 2004;20:160–5.
- [29] Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J ECT* 1998;14:25–7.
- [30] Arana AB, Borckardt JJ, Ricci R, et al. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? *Brain Stimul* 2008;1:44–51.
- [31] Borckardt JJ, Walker J, Branham RK, et al. Development and evaluation of a portable sham transcranial magnetic stimulation system. *Brain Stimul* 2008; 1:52–9.
- [32] Arana AB, Borckardt JJ, Ricci R, et al. Focal Electrical Stimulation as a Sham Control for rTMS: does it truly mimic the cutaneous sensation and pain of active prefrontal rTMS? *Brain Stimul* 2008;1:44–51.
- [33] Borckardt J, Walker J, Branham RK, et al. Development and evaluation of a portable sham TMS system. *Brain Stimul* 2008;1:52–9.
- [34] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*; 2009.
- [35] Anderson B, Mishory A, Nahas Z, et al. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *J ECT* 2006;22:49–53.
- [36] O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;62:1208–16.
- [37] Borckardt JJ, Smith AR, Reeves ST, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. *Pain Med* 2009;10:840–9.
- [38] Borckardt JJ, Reeves ST, Weinstein M, et al. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. *Brain Stimul* 2008;1:122–7.
- [39] Borckardt JJ, Smith AR, Reeves ST, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. *Pain Res Manag* 2007;12:287–90.
- [40] Borckardt JJ, Weinstein M, Reeves ST, et al. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* 2006;105:557–62.
- [41] Martin L, Borckardt JJ, Reeves ST, et al. A pilot functional MRI study of the effects of prefrontal rTMS on pain perception. *Pain Med* 2013;14: 999–1009.
- [42] Taylor JJ, Borckardt JJ, George MS. Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. *Pain* 2012;153: 1219–25.
- [43] Taylor JJ, Borckardt JJ, Canterberry M, et al. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. *Neuropsychopharmacology* 2013;38: 1189–97.
- [44] Borckardt JJ, Nahas ZH, Teal J, et al. The painfulness of active, but not sham, transcranial magnetic stimulation decreases rapidly over time: results from the double-blind phase of the OPT-TMS trial. *Brain Stimul*; 2013.
- [45] Borckardt JJ, Linder KJ, Ricci R, et al. Focal electrically administered therapy: device parameter effects on stimulus perception in humans. *J ECT* 2009; 25:91–8.
- [46] Borckardt JJ, Reeves ST, Frohman H, et al. Fast left prefrontal rTMS acutely suppresses analgesic effects of perceived controllability on the emotional component of pain experience. *Pain* 2011;152:182–7.
- [47] Borckardt JJ, Reeves ST, Beam W, et al. A randomized, controlled investigation of motor cortex transcranial magnetic stimulation (TMS) effects on quantitative sensory measures in healthy adults: evaluation of TMS device parameters. *Clin J Pain* 2011;27:486–94.
- [48] Barth KS, Rydin-Gray S, Kose S, et al. Food cravings and the effects of left prefrontal repetitive transcranial magnetic stimulation using an improved sham condition. *Front Psychiatry* 2011;2:9.
- [49] Fawcett J. Suicide and anxiety in dsm-5. *Depress Anxiety* 2013;30:898–901.
- [50] Baratta MV, Christianson JP, Gomez DM, et al. Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. *Neuroscience* 2007;146:1495–503.
- [51] Amat J, Paul E, Watkins LR, Maier SF. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. *Neuroscience* 2008;154:1178–86.
- [52] Baratta MV, Lucero TR, Amat J, Watkins LR, Maier SF. Role of the ventral medial prefrontal cortex in mediating behavioral control-induced reduction of later conditioned fear. *Learn Mem* 2008;15:84–7.
- [53] George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation and ECT. *Convuls Ther* 1994;10:251–4. discussion 255–258.
- [54] George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. *Depression* 1994;2:59–72.
- [55] Miller W, Seligman M. Depression and learned helplessness in man. *J Abnorm Psychol* 1975;84:228–38.
- [56] Seligman ME, Rosellini RA, Kozak MJ. Learned helplessness in the rat: time course, immunization, and reversibility. *J Comp Physiol Psychol* 1975;88: 542–7.
- [57] Vollmayr B, Faust H, Lewicka S, Henn FA. Brain-derived-neurotrophic-factor (BDNF) stress response in rats bred for learned helplessness. *Mol Psychiatry* 2001;6:471–4. 358.
- [58] Christianson JP, Thompson BM, Watkins LR, Maier SF. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. *Stress* 2008;1.
- [59] George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry* 1997; 154:1752–6.