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

Jeffrey J. Borckardt [a,b,*], Ziad H. Nahas [a,c], John Teal [a], Sarah H. Lisanby [d], William M. McDonald [e], David Avery [f], Valerie Durkalski [g], Martina Pavlicova [h], James M. Long [i], Harold A. Sackeim [j,k], Mark S. George [a,l]

[a] Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA
[b] Department of Anesthesia and Perioperative Medicine, Medical University of South Carolina, Charleston, SC, USA
[c] Department of Psychiatry, American University of Beirut, Lebanon
[d] Brain Stimulation and Neurophysiology Division, Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA
[e] Psychiatry Department, Emory University, Atlanta, GA, USA
[f] Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, USA
[g] Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA
[h] Biostatistics Department, Columbia University, New York, NY, USA
[i] James Long Company, Caroga Lake, NY, USA
[j] Department of Psychiatry, Columbia University, New York, NY, USA
[k] Department of Radiology, Columbia University, New York, NY, USA
[l] Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, USA

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ABSTRACT

Background: Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) over several weeks is an FDA approved treatment for major depression. Although rTMS is generally safe when administered using the FDA guidelines, there are a number of side effects that can make it difficult for patients to complete a course of rTMS. Many patients report that rTMS is painful, although patients appear to accommodate to the initial painfulness. The reduction in pain is hypothesized to be due to prefrontal stimulation and is not solely explained by accommodation to the stimulation.
Methods: In a recent 4 site randomized controlled trial (using an active electrical sham stimulation system) investigating the antidepressant effects of daily left dorsolateral prefrontal rTMS (Optimization of TMS, or OPT-TMS), the procedural painfulness of TMS was assessed before and after each treatment session. Computerized visual analog scale ratings were gathered before and after each TMS session in the OPT-TMS trial. Stimulation was delivered with an iron core figure-8 coil (Neuronetics) with the following parameters: 10 Hz, 120% MT (EMG-defined), 4 s pulse train, 26 s inter-train interval, 3000 pulses per session, one 37.5 min session per day. After each session, procedural pain (pain at the beginning of the TMS session, pain toward the middle, and pain toward then end of the session) ratings were collected at all 4 sites. From the 199 patients randomized, we had usable data from 142 subjects for the initial 15 TMS sessions (double-blind phase) delivered over 3 weeks (142 × 2 × 15 = 4260 rating sessions).

Results: The painfulness of real TMS was initially higher than that of the active sham condition. Over the 15 treatment sessions, subjective reports of the painfulness of rTMS (during the beginning, middle and end of the session) decreased significantly 37% from baseline in those receiving active TMS, with no change in painfulness in those receiving sham. This reduction, although greatest in the first few days, continued steadily over the 3 weeks. Overall, there was a decay rate of 1.56 VAS points per session in subjective painfulness of the procedure in those receiving active TMS.

Discussion: The procedural pain of left, prefrontal rTMS decreases over time, independently of other emotional changes, and only in those receiving active TMS. These data suggest that actual TMS stimulation of prefrontal cortex maybe related to the reduction in pain, and that it is not a non-specific accommodation to pain. This painfulness reduction softly corresponds with later clinical outcome. Further work is needed to better understand this phenomenon and whether acute within-session or over time painfulness changes might be used as short-term biomarkers of antidepressant response.

Introduction

Daily left dorsolateral prefrontal rTMS for several weeks is a new acute treatment for depression. However, some preliminary data and anecdotal reports suggest that this treatment may be painful for some patients. Recently, we found in an open label study of TMS for depression, that the painfulness of TMS stimulation decreases over time [1]. The exact cause of the focal pain of prefrontal rTMS is not known, but some have reasoned that the magnetic pulses activate nociceptors in the scalp, periosteum, and maybe meninges under the coil [2]. Because prefrontal rTMS for depression is painful for some, and requires daily visits for several weeks, we initially hypothesized that there would be high dropout rates in clinical trials. In fact, the dropout rate has been very low. For example, in recent multisite trials, the dropout rate at 3 or 4 weeks after randomization was only 7–8% [3,4], lower than in antidepressant medication trials.

There is accumulating evidence that stimulation of the left dorsolateral prefrontal cortex with TMS is associated with analgesic effects in healthy adults undergoing experimental pain methods [5], in patients with chronic pain [6], and in patients with postoperative pain [7,8]. The role of the left prefrontal cortex in pain perception is unclear, but there is some evidence indicating that its activation is negatively correlated with pain unpleasantness ratings suggesting a possible governing role of the prefrontal cortex over the affective dimension of pain [9].

To date, no one has examined whether the reduction in painfulness of the TMS procedure is a specific effect, linked only to active TMS, or is a non-specific effect of repeatedly being exposed to a noxious stimuli (general accommodation).

Methods

Study design

We analyzed data from the recently completed NIMH-funded Optimization of TMS for the Treatment of Depression (OPT-TMS) study. This was a 4 year, 4 site study of double-blinded, randomized, sham-controlled daily left prefrontal rTMS as an acute clinical treatment for major depression [5]. 199 moderately depressed adult subjects were initially enrolled in the study. Visual Analog Rating Scale data were available for 142 participants (68 in the real TMS group and 74 sham).

Phase-I of the study employed the double-blind, randomized, sham-controlled use of daily prefrontal rTMS to determine the efficacy and safety of rTMS in the treatment of depression. The first 3 weeks were double-blind, using a newly developed active electrical sham TMS system (similar to transcutaneous electrical nerve stimulation; TENS) that delivered a small electrical scalp stimulation to those receiving sham TMS, and thereby also controlled for facial twitching, scalp discomfort and noise differences (see [4] and [10,11]) between real and sham stimulation. In the trial, this system was an effective mask, and patients, raters and treaters were not able to distinguish active from sham TMS.

Study device description and rTMS treatment session procedures

rTMS was delivered using the Neuronetics Model 2100 Therapy System investigational device. Each site used three magnetic coils, identical in weight, external appearance and acoustic properties when actively pulsed. One coil was unblinded and labeled 'active', and was used to determine motor thresholds (MT). The remaining two coils were distinguishable only by external labels as 'coil B' or 'coil C', with one being the active treatment coil while the other was a sham coil. The sham coils contained a magnetic shield which limited the magnetic energy reaching the cortex to 10% or less of that of the active coil, but nevertheless allowed the active and sham coils to have the identical appearance, placement and similar but not identical acoustic properties. Triplets of coils were periodically rotated from the central core at MUSC across the four clinical sites once each during the trial to reduce the possibility that inadvertent unmasking would result in knowledge of the true nature of the "B" and "C" coils. On 4 occasions (3 Emory, 1 NYSPI), if an administrator encountered equipment problems with the TMS coils, the sham and active coils were replaced at that site and the TMS administrator was changed until that patient completed treatment. This procedure ensured that the TMS administrator was not accidentally unblinded. There were no instances when treaters were clearly unblinded and extremely confident of the patient randomization status.

The novel active sham condition consisted of the sham coil described above, noise dampening earphones for the patient and treater, and electrical pads inserted under the coil on the patient's head. Coincident with the discharge of the sham coil, a small electrical pulse (5 mA) was administered that mimicked the active rTMS sensation and also caused focal scalp twitching. Patients, treaters, local raters, offsite expert raters and all other study personnel were masked to coil functionality. The integrity of the mask was assessed immediately at Phase 1 exit. Patients, treaters and raters made "best guesses" as to the assignment to active or sham rTMS and indicated their confidence in this guess.

Treatment parameters

Treatment was standardized at 120% magnetic field intensity relative to the patient's EMG-determined resting motor threshold,
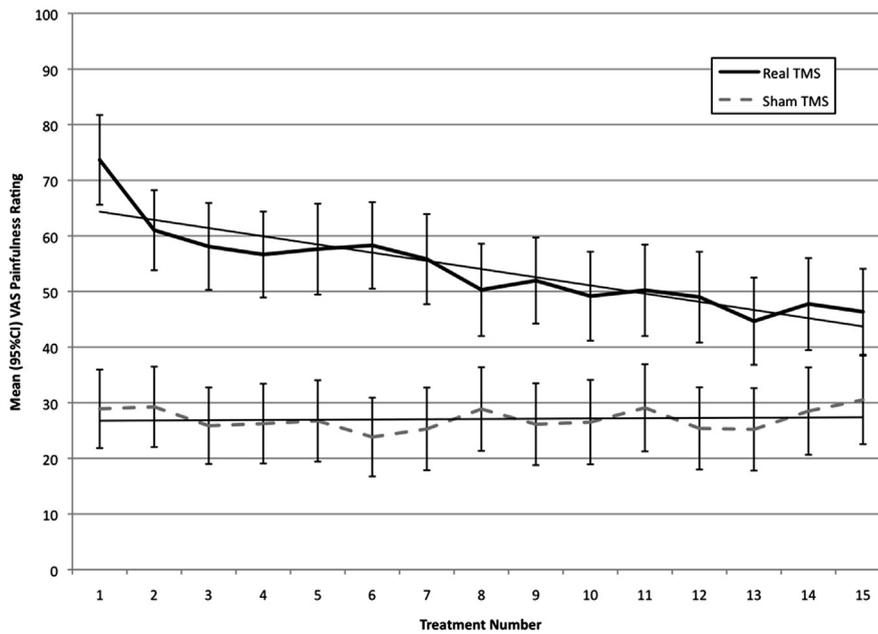
Figure 1. Graph of painfulness changes over time (beginning, middle and end of treatment) separated by active and sham groups. Note that only in the active group is there a reduction over time. Note also that the two groups differed in their overall painfulness ratings.

with a repetition rate of 10 pulses per second (10 Hz), with a stimulus train duration of 4 seconds and an inter-train interval of 26 s. During the first week of the acute phase only, treatment intensity could be reduced to 110% for tolerability, but was then required to return to 120% from week-2 onward. A treatment session lasted for 37.5 min (75 trains) for a total of 3000 magnetic pulses.

Subjects who complained of painfulness were offered the insertion of a simple sheet of packing foam. This could be folded to create 4 layers, but no more. Subjects rested in a semi-reclined chair with their head supported by a head-holder frame. The coil was positioned 5 cm anterior and in a parasagittal line from the location that maximized movement in the right hand flexor digiti indici (as measured by EMG) [12–14]. Baseline MRI scans were performed on all subjects, and approximately 1/3 of subjects had the coil positioned 6 cm forward (rather than 5 cm) based on MRI analysis of where the 5 cm-rule resulted in placement, and whether this was over prefrontal, or premotor, cortex [15]. Patients were instructed to rest quietly during the treatment, but not to fall asleep. Eyes could be open or closed.

Visual analog scales

All subjects completed a pre- and post-treatment custom-developed VAS questionnaire on a laptop computer running either MacOS or Windows (software developed using REALbasic 5.5, REAL software, Austin TX). The questionnaire consisted of 15 pre-treatment questions and 27 post-treatment questions. They were asked to rate their experience of the following descriptors: happy, irritable, angry, excited, confused, calm, sad, anxious, nervous, bored, relaxed, tired, distracted, pain, and discomfort, and the visual analog scores were converted to a scaling of 0 to 100 points. Included only in the post-treatment questionnaire were retrospective measures of pain, unpleasantness, tolerability, and discomfort for the beginning, middle and end of the treatment. Ratings of TMS-induced pain at the beginning, middle and end were the main factors examined in the present report.

Statistical analyses

We analyzed these data using proc mixed in SAS (version 9.1). Individual subject intercepts and pain-rating slopes over time were entered into the model as random effects at level-1 [16]. Patient group assignment (real or sham) was our primary level-2 predictor. The estimation method was restricted maximum likelihood, the covariance structure was "unstructured" and the degrees of freedom method was Kenward–Roger.

Results

Procedural pain over time

The mean painfulness of TMS at the beginning of the first session was 73.66 (SD = 31.31) out of 100 in the real TMS group and 28.91 (SD = 31.43) in the sham group. Findings from the two-way inter-action model (group × time) found a significant difference between groups (real versus sham) with respect to mean pain ratings at the beginning of the TMS sessions ($F(1,136) = 60.50$, $P < .0001$). The slope/time main effect was also significant ($F(1,127) = 23.39$, $P < .0001$) and so was the group by slope/time interaction ($F(1,127) = 17.16$, $P < .0001$), both after controlling for baseline differences between groups. In the sham TMS group, the slope of the TMS-painfulness ratings over time was not significantly different from zero ($t(124) = 0.51$, ns), but in the real TMS group, the painfulness ratings decreased by 1.56 (SE = .35) VAS points per treatment ($t(127) = 4.14$, $P \leq .0001$; see Fig. 1). The amount of pain at the beginning of the last TMS session during phase-I of the trial was 46.35 (SD = 29.47) in the real group and 30.53 (SD = 33.27). This represents a 37% reduction in the real TMS group and a 6% increase in the sham TMS group.

Changes in pain within a session, over time

Retrospective pain ratings decreased from the beginning to the middle, to the end of the TMS sessions in both the real group (mean

pain at beginning = 46.43, SD = 31.92; middle = 43.04, SD = 30.53; and end = 41.58, SD = 31.13) and in the sham group (mean pain at beginning = 33.58, SD = 33.26; middle = 30.33, SD = 30.73; and end = 30.22, SD = 31.70), however the mean within-TMS session change in pain ratings was significantly greater in the real TMS group than sham (t (133) = 3.41, P = .0008) collapsing across all treatments. Over time, the amount of within-session change in procedural pain decreased by 1 VAS point per session in the real group (t (128) = 3.25, P = .002), and did not significantly change in the sham group (t (125) = 0.44, ns).

Procedural pain reduction as a predictor of antidepressant clinical outcome

Among patients receiving real TMS during the 3-week double-blind phase, the slope of the TMS procedural pain (beginning of each TMS session) over time (per TMS session) significantly predicted percent change in HAM-D scores from the beginning to the end of phase-I of the trial (t (532) = 2.70, P = .007). However the amount variability accounted for by the predictive model was only 4.38%. The slope of the TMS procedural pain ratings during the first 2-weeks of treatment significantly predicted change in HAM-D scores from the beginning to the end of phase-I of the trial (t (397) = 2.38, P = .02) as well, however the pain slope during week-1 only of the trial did not predict clinical antidepressant change as measured by HAM-D (t (187) = 0.97, ns). The amount of pain reduction within each TMS session was not a significant predictor of antidepressant outcome (t (816) = 0.66, ns) nor was within-session change over time (t (805) = 1.17, ns).

Discussion

In this well-studied multisite sample of medication free unipolar depressed patients, the painfulness of left prefrontal TMS diminished drastically (37%) over 3 weeks of treatment, but only in those receiving active TMS and not in those receiving a sham treatment. Moreover, the change in TMS procedural painfulness over time modestly predicted ultimate clinical response (percent reduction in HAM-D scores) at the end of the double-blind phase of the study. Unfortunately, given the substantial baseline differences in procedural pain ratings between the real and sham groups, regression to the mean cannot be ruled-out as a potential explanation for some of the observed effect (a major limitation of the present study) even though the baseline difference was controlled in the statistical analysis. The reason for this baseline difference may be that a standard mA intensity was applied for the sham system rather than individually titrating the sham intensity to match the subjective experience of real rTMS discomfort. Future studies should consider both approaches fort further study. Nonetheless, the fact that the slope of the procedural painfulness over time is a significant predictor of ultimate clinical response does add some credence to the notion that the change in painfulness is a brain-modulated effect. Interestingly, the reduction in painfulness *within*-session was also more pronounced over time in the real TMS group compared to sham. This adds further credibility to the notion that analgesic effects of prefrontal rTMS are likely real and perhaps relevant to brain activity changes associated with antidepressant effects.

The present findings replicate the changes seen in the open label phase of this trial and reported earlier demonstrating that the patients rate the painfulness of TMS as much less painful after 1–2 weeks of treatment [1]. These findings have some clinical implications. They suggest that for patients who have difficulty tolerating rTMS in the beginning, the discomfort is likely to decrease over time, and most drastically within the first week of treatment. While the reasons for this are still unclear, efforts to reassure patients early in treatment, and efforts to encourage their continuation despite some potential discomfort in the beginning may result in less treatment dropout. greater sense of control, with a reduction in the valence of the paired stimulus.

Conclusion

We have found that the painfulness of prefrontal rTMS diminishes steadily over the course of 3 weeks in depressed patients undergoing a double-blind treatment trial and that this only occurs in patients getting active treatment. This accommodation likely contributes to the high rates of retention in rTMS depression treatment studies. Further studies are needed to understand the mechanisms behind this accommodation. Regardless of the mechanism, clinicians and researchers using rTMS should be aware of this accommodation in designing treatment studies and in working with individual patients within a trial who might find TMS initially painful.

References

[1] Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH, et al. Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-label phase of a multi-site trial (OPT-TMS). Brain Stimul 2009;2(2):88–92.

[2] Borckardt JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Anderson B, et al. Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT 2006;22(4):259–64.

[3] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, 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(11):1208–16.

[4] George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67(5):507–16.

[5] Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag 2007;12(4):287–90.

[6] Borckardt JJ, Smith AR, Reeves ST, Madan A, Shelley N, Branham R, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med 2009;10(5):840–9.

[7] Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, et al. Postoperative left prefrontal repetitive transcranial magnetic stimulation (rTMS) reduces patient-controlled analgesia use. Anesthesiology 2006;105:557–62.

[8] Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, et al. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain Stimul 2008;1(2):122–7.

[9] Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126(Pt 5):1079–91.

[10] Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, 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(1):44–51.

[11] Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, et al. Development and evaluation of a portable sham transcranial magnetic stimulation system. Brain Stimul 2008;1(1):52–9.

[12] George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, 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(12):1752–6.

[13] George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 1996;8(2):172–80.

[14] George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6(14):1853–6.

[15] Herwig U, Padberg F, Unger J, Spitzer M, Schönfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry 2001;50(1):58–61.

[16] Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. J Educ Behav Stat 1998;24:323–55.