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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

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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 ($142 \times 2 \times 15 = 4260$ rating sessions).

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Conflicts of interest: Full disclosures and listings for all authors are at the end of the manuscript. For the specific interests of this clinical trial, Dr. George, the study chair, has received no compensation from any TMS manufacturer for the past 5 years, and owns no equity stake in any device or pharmaceutical company. Following a competitive bid and request involving all known TMS manufacturers at the time, Neuronetics was selected and loaned the TMS device, head-holder and coils used in the trial and allowed the use of the safety IDE of their device, but has otherwise been uninvolved in trial conduct or analysis. The TMS sham equipment was purchased from the MECTA Corporation and the James Long Company.

Trial registration: OPT-TMS depression trial, clinicaltrials.gov # NCT00149838, http://clinicaltrials.gov/ct2/show/NCT00149838?term=magnetic+brain+stimulation+depression&rank=1.

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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 post-operative 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,