Brain Stimulation (2008) 1, 44–51

ELSEVIER

BRAIN
STIMULATION

www.brainstimjrnl.com

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?

Ashley B. Arana, BA[a], Jeffery J. Borckardt, PhD[a], Raffaella Ricci, PhD[a], Berry Anderson, RN[a], Xingbao Li, MD[a], Katherine J. Linder, BS[a], James Long, BA[b], Harold A. Sackeim, PhD[c], Mark S. George, MD[a]

[a]*Brain Stimulation Laboratory (BSL), Psychiatry Department, Medical University of South Carolina (MUSC), Charleston, SC*
[b]*James Long Company, New York, NY*
[c]*Department of Biological Psychiatry, Columbia University, New York, NY*

Background

Repetitive transcranial magnetic stimulation (rTMS) is a novel, noninvasive method of stimulating selected regions of the brain that has both research applications and potential clinical utility, particularly for depression. To conduct high-quality clinical studies of rTMS, it is necessary to have a convincing placebo (or sham) treatment. Prefrontal rTMS causes cutaneous discomfort and muscle twitching; therefore, an optimal control condition, ie, sham condition, would mimic the cutaneous sensation and muscular discomfort of rTMS without stimulating the brain. Ideally, the quality and intensity of the sham condition would feel identical to the quality and intensity of the rTMS condition, except that the sham would have no effect on cortical activity. We designed and built a focal electrical stimulation system as a sham rTMS condition. Although this electrical sham system is superior to methods used in previous studies, little is known about how the new electrical sham system compares with active rTMS in terms of the level of discomfort and type of sensation it produces.

The Brain Stimulation Laboratory is supported in part by the Stanley Foundation, the National Alliance for Research on Schizophrenia and Depression (NARSAD), NINDS grant RO1-AG40956, and NIMH grant RO1 MH069887, 1K08MH070915-01A1 (NAHAS), J.J.B. A.A. was funded through the NASA Summer Undergraduate Research Grant of MUSC.

Correspondence and reprint requests to: Ashley Arana, Psychiatry Department, Medical University of South Carolina (MUSC), 67 Presidents, Charleston, SC 29425.

E-mail address: arana@musc.edu

Submitted June 13, 2007; revised August 24, 2007. Accepted for publication August 27, 2007.

1935-861X/08/$ -see front matter
doi:10.1016/j.brs.2007.08.006

Methods
We hypothesized that the electrical sham system may not mirror the experimental condition sufficiently. We studied this hypothesis under single-blind conditions in 15 healthy adults by administering either the real or sham rTMS at high and low intensities while subjects, who were unaware of condition, rated subjective qualities of the stimulation (such as tingling, pinching, and piercing), the scalp location of the perception, and the painfulness of the stimuli.

Results
At low-intensity stimulation, the two techniques (active and sham) differ with respect to the subjective quality of the sensation. The differences between real and sham rTMS were less dramatic at higher intensities. The best sham condition that most closely mimics real prefrontal rTMS requires individual titration of the intensity of electrical stimulation across a broad range. Performing this titration without unblinding patients is likely possible, but technically challenging. We propose a new approach to do this.

Conclusion
We conclude that it is possible to create a truly indistinguishable sham condition (with appropriate acoustic masking as well), but more work is needed beyond these initial attempts.

Keywords transcranial magnetic stimulation; sham; blinding; methods

Most recent studies of daily repeated left prefrontal repetitive transcranial magnetic stimulation (rTMS) over several weeks have found that it reduces depression symptoms,[1-4] although earlier studies that used low doses or treated for short durations are not effective.[1,5-6] rTMS uses a powerful magnetic pulse that is generated by passing electricity through a metal coil placed against the head. This focused magnetic pulse passes through the skull and causes neuronal depolarization.[7] In the studies that used TMS as a potential antidepressant, the coil is typically targeted over the left-prefrontal cortex, which has been found to have abnormalities in functional neuroimaging studies of depression[8-10] and serves in a connected and regulatory role with other infralimbic regions involved in mood regulation.

An important issue for developing rTMS as a treatment has been the development of different sham techniques. A commonly used sham design has been to tilt the coil either 45 or 90 degrees. However, tilting the coil 45 degrees was proven to stimulate the cortex, likely contributing to the variability between some early studies.[11] Moreover, even though tilting the coil 90 degrees does not elicit motor-evoked potentials (MEPs), this sham may feel less intense.[12] A more recent sham system involves the use of specially created rTMS sham coils, which are true rTMS coils that have an aluminum plate inserted between the coil and the scalp surface. This effectively blocks most of the magnetic field from interacting with scalp and cortex. These sham systems visually resemble the actual coil, and produce a sound during an rTMS pulse and some percussive stimulation of the scalp. However, the active and sham rTMS coils sound different, and likely produce different scalp sensations, and the sham coil does not produce superficial muscle twitching in the same manner as the active coil, especially when placed over the prefrontal cortex, a location that typically causes facial twitching. Thus, although these sham coils are an improvement, they are useful only for single-blind studies as the rTMS operator quickly becomes unblinded for each patient. An ideal sham TMS system would resemble real rTMS both visually and acoustically and create a comparable cutaneous sensation without producing cortical stimulation. Although we have been grappling with these issues, another group has developed yet another sham device referred to as the real electromagnetic placebo (REMP) coil, which involves inverting a real TMS coil, and placing 3 cm of compact wood over the coil to prevent brain activation and then inserting scalp electrodes to produce scalp sensations similar to real TMS.[13] Although this sham mimics the acoustic and sensational effects of TMS, at intensities higher than 80% motor threshold (MT), the REMP coil is not sufficiently able to mimic the depth or greater area of sensation of real TMS. Because clinical trials on depression use intensities greater than 100% MT, mimicking the cutaneous sensation experienced during rTMS has been a challenging aspect of developing an optimal sham condition. Much of the cutaneous sensation is caused when rTMS stimulates scalp muscles producing a twitch in the scalp or upper face that can be uncomfortable for some, painful for others.[14]

We also wondered whether focal electrical stimulation would create a similar sensation to rTMS without causing brain activation. This current is delivered by an electrical stimulator, which produces an electrical pulse coincident with the sham magnetic pulse. We designed and implemented this system in ongoing trials, but it remains unclear what amount of electrical stimulation delivered to those receiving sham would best mimic the active rTMS treatment. In addition, at the time we launched several studies, there was no way to devise a method of titrating the electrical stimulation independent of rTMS in a way that would not jeopardize the blind. After experimenting in