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Focal electrical stimulation as an effective sham control for active rTMS and biofeedback treatments

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Abstract

A valid sham control is important for determining the efficacy and effectiveness of repetitive transcranial magnetic stimulation (rTMS) as an experimental and clinical tool. Given the manner in which rTMS is applied, separately or in combination with self-regulatory approaches, and its intended impact on brain states, a valid sham control of this type may well serve as a meaningful control for biofeedback studies, where efforts to develop a credible control have often been less than ideal. This study examined the effectiveness of focal electrical stimulation of the frontalis muscle as a sham technique for blinding participants to high-frequency rTMS over the dorso-lateral prefrontal cortex (DLPFC) at durations, intensities, and schedules of stimulation similar to many clinical applications. In this within-subjects single blind design, 19 participants made guesses immediately after receiving 54 counterbalanced rTMS sessions (sham, 10Hz, 20Hz); 7 (13%) of the guesses were made for sham, 31 (57%) were made for 10Hz, and 16 (30%) were made for 20Hz. Participants correctly guessed the sham condition 6% (CI: 1%, 32%) of the time, which is less than the odds of chance (i.e., of guessing at random, 33%); correctly guessed the 10Hz condition 66% (CI: 43%, 84%) of the time, which was greater than chance; and correctly guessed the 20Hz condition 41% (CI: 21%, 65%) of the time, which was no different than chance. Focal electrical stimulation therefore can be an effective sham control for high-frequency rTMS of the DLPFC, as well as for active biofeedback interventions. Participants were unaware that electrical stimulation was, in fact, sham rTMS.

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Keywords

transcranial magnetic stimulation; sham control

Repetitive Transcranial Magnetic Stimulation (rTMS), is a neuromodulatory technique that delivers multiple pulsed magnetic fields over the scalp via a stimulating coil (Hallett, 2000). As a noninvasive method for altering cortical excitability, rTMS is increasingly being used as an experimental and clinical tool to examine neuroplasticity, alter excitability in specific areas of the brain, and treat a variety of disorders including depression, mania, schizophrenia, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder (George et al., 2009). The acute effects on neuronal activity are thought to be either excitatory or inhibitory depending on the frequency of the pulses delivered (Di Lazzaro et al., 2005; George et al., 2002), although there are exceptions (Fitzgerald, Fountain, & Daskalakis, 2006). Low frequency rTMS (LF; ≤ 3 Hz) is believed to inhibit cortical excitability (Bear, 1999; Stanton & Sejnowski, 1989) and high frequency (HF; >3 Hz) to increase cortical excitability (Chen et al., 1997; Malenka & Nicoll, 1999; Pascual-Leone et al., 1998; Wu, Sommer, Tergau, & Paulus, 2000). Very HF rTMS (~ 50 Hz), called theta burst stimulation (TBS) administered intermittently at 5 Hz, is believed to increase cortical excitability; continuous TBS (cTBS) is believed to inhibit cortical excitability (Di Lazzaro et al., 2005; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Changes in cortical excitability induced by rTMS accumulate in an additive fashion as the number of sessions increases over days, but there is no evidence that the changes are maintained after rTMS is discontinued.

rTMS has recently been combined with feedback techniques and other technologies that can potentially target and/or titrate its neuromodulatory effects. For example, TMS can be implemented in a brain-computer interface (BCI) feedback system using electromyographic (EMG) or electroencephalographic (EEG) signals to provide a self-paced, engaged, human-machine feedback paradigm for use as a rehabilitation tool in movement disorders (Niazi, Mrachacz-Kersting, Jiang, Dremstrup, & Farina, 2012). rTMS also can be used to examine the effects of other modulation techniques such as real-time functional magnetic resonance imaging BCI (Sitaram et al., 2012). Additionally, co-registration of EEG during rTMS is a promising tool for experimental and clinical purposes (Bonato, Miniussi, & Rossini, 2006). Theoretically, TMS is a quick and effective method of ascertaining the effects of modulating cortical excitability in specific areas of the brain and could be used to quickly identify and characterize areas to be trained with EEG biofeedback in order to achieve long-lasting neuromodulatory effects.

While current applications of rTMS are promising, a valid sham technique is important for blinding treatment conditions and determining the efficacy and effectiveness of rTMS. A valid sham condition reliably reduces the chances of introducing systematic confounds associated with condition as well as eliminates demand characteristics associated with participants being able to correctly guess the condition; however, many rTMS sham techniques fail to reproduce all the features of active stimulation (George et al., 2009; Loo et al., 2000; Strafella, Ko, & Monchi, 2006; Wassermann & Lisanby, 2001). While the look and sound of active rTMS can be convincingly replicated using commercially available sham coils, the cutaneous scalp muscle twitching produced by active rTMS has been more challenging to replicate. Recent developments that pair timed electrical stimulation of the scalp muscles with sham coil pulse clicks hold promise. Nonetheless, some have found that brief (1-4 second), back-to-back comparisons of electrical and TMS pulses do not feel exactly the same to participants (Arana et al., 2008; Mennemeier et al., 2009; Rossi et al., 2007) while others have found participants' experience of 4-second stimulus trains of

electrical stimulation to be no different than that of the active TMS (Borckardt et al., 2008). An effective sham, however, might not need to feel identical to active TMS in order for participants to be blind to condition. Few rTMS naïve participants were actually able to correctly identify the sham stimulation even though they reported the “feel” to be different. Moreover, the procedures for many treatments in which blinding are endeavored do not require sham/active back-to-back comparisons. Most are delivered over the course of days and/or weeks with administrations separated in time by at least 24-48 hours (George et al., 2009; O'Reardon et al., 2007; Plewnia et al., 2007; Rossini & Rossi, 2007).

To our knowledge, no study has examined the effectiveness of electrical stimulation as a sham control for high-frequency rTMS of the dorsolateral pre-frontal cortex (DLPFC) when the sham and active conditions are separated by at least 48 hours over the course of weeks. We examined whether participants were able to reliably identify each of three conditions immediately after the session. The parent study examined the effects of high-frequency rTMS on delay discounting (a decision-making task). The three conditions included sham (900 pulses of repetitive, electrical stimulation of the frontalis muscles delivered at 10Hz), 10Hz (900 pulses of rTMS delivered at 10 Hz), and 20Hz (900 pulses of rTMS delivered at 20Hz). Given that previous studies indicate that rTMS naïve participants were unable to correctly identify sham stimulation even when they judged the two types of stimulation to feel different in back-to-back comparisons (Arana et al., 2008; Mennemeier et al., 2009), we predicted that participants would be unable to correctly identify electrical stimulation as the sham control condition as well as be unable to correctly identify the two active rTMS conditions beyond the level of chance (i.e., no different than if participants chose the condition at random).

Methods

Participants

Participants (n=19) were 11 men and 8 women, mean age 40.7 years (SD 11.7) who completed a total of 54 TMS sessions (19 active 10Hz, 17 active 20Hz, and 18 Sham). The mean number of sessions completed per participant was 2.8 (SD 1.8, range 1 to 6). No participants experienced any serious adverse events. Participants met the following inclusion criteria: a) age 19-55 years, b) right-handed, c) English-speaking, and c) passed the Transcranial Magnetic Stimulation Adult Safety and Screening Questionnaire. Participants were excluded if they failed any item on the TASS, had a diagnosed neurological or psychiatric disorder or tinnitus, took medications that alter seizure threshold, had claustrophobia (because a closed MRI was needed) or tested positive for drugs of abuse. All participants provided informed consent. This study was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences.

Apparatus

A Magstim Super Rapid² stimulator with sham and active air-cooled, 70-mm, figure-of-eight coils (Magstim Company, Whitland, Wales, UK) were used. The sham coil attenuated the magnetic field to 5% of the stimulator output and was identical to the active coil in appearance and the quality and intensity of the clicking sounds with the stimulator set at 45% (Mennemeier et al., 2009). Electrical stimulation was delivered with a DS3 Isolated Stimulator (Digitimer Ltd., Welwyn Garden City, Herforshire, U.K.). Conductive skin preparation gel was placed on two rectangular, carbon-impregnated rubber electrodes (4 × 5 cm). The gelled electrodes were placed firmly over the left frontalis muscle about 1 cm above the eyebrow. The first electrode was aligned roughly above the right side of the eyebrow and second was roughly aligned with the corner of the left eye (Figure 1). Electrical pulses were triggered by the TMS controller so that each pulse coincided precisely

with the clicking sounds of the sham coil. Coil targeting was achieved using the BrainSight Stereotaxic System (Rogue Research) in conjunction with an MRI obtained for each subject.

Procedure

Conditions were administered in a counterbalanced manner. Participants were blind to condition. Administrations were separated by at least 48 hours and participants could possibly undergo each of the three conditions a maximum of two times in the parent study. Immediately after the stimulation was discontinued, participants were presented with a blank form on an 8×11 sheet of paper that listed the three conditions and asked them to circle the type of stimulation that they thought they had just received. The list of conditions on the form was always the same (sham, 10Hz, and 20Hz). Participants experienced up to six stimulation sessions, providing a single guess immediately after each session.

In every condition participants were prepared by placing two stimulating electrodes over the left frontalis muscle underneath a headband that held the locator for the Brainsight system in place on the head. See Figure 1. Three recording electrodes were placed over the abductor pollicis brevis (APB) muscle to assess participants' motor threshold (MT). The MT was defined as the minimum stimulation intensity required to elicit a motor evoked potential (MEP) of 50 μ V from the APB in 3 of 6 trials. Once participants' MT was determined, the location and parameters were documented and participants were escorted out of the room. With participants out of the room, the technician attached either the active or sham coil as per the counterbalancing schedule. Once a coil was attached, participants were escorted back into the room and positioned in a dental chair for stimulation. The target site for stimulation of the DLPFC, 6 cm anterior to the MT location, was located and marked in Brainsight system. The stimulating electrodes were attached to the DS3 Stimulator which was located outside of participants' field of vision. The two active rTMS conditions consisted of 900 pulses delivered at 10 Hz (1 second on and 20 off) or 20Hz (1 second on and 20 off) both at 110% of the MT. Sham rTMS consisted of 900 pulses of electrical stimulation delivered at 10Hz (1 second on and 20 off). The mean amperage was 5.5mA (SD 2.1) similar to other studies of electrical sham stimulation (Arana et al., 2008; Borckardt et al., 2008; Mennemeier et al., 2009).

Data analysis

Analyses were conducted with the GLIMMIX procedure of SAS v9.3 software. The dichotomous outcome variable was the concordance or correctness of the guessed condition (i.e., yes, guessed correctly; no, guessed incorrectly). These binary data were modeled with a repeated measures logistic regression using a generalized linear mixed model to estimate the probability of correctly guessing each condition. Actual condition (sham, 10hz, 20Hz) was entered as a fixed effect and subject as a random effect. Within-subject correlations were assumed to be exchangeable (a.k.a. compound symmetric). Estimated probabilities and 95% confidence intervals (CIs) of correctly guessing the actual conditions are reported. The hypothesis stated that the probability of guessing any condition correctly was one out of 3 (i.e., 1/3 or 33%), thus confidence interval (CIs) that do not include 0.33 indicate significance levels less than or equal to 0.05 (i.e., greater or less than chance). We considered a condition adequately blinded if the probability of correctly identifying the condition was no different than chance (i.e., 33%, no different than if participants had chosen at random).

Results

Of the 54 guesses, 7 (13%) of the choices were made for sham, 31 (57%) were made for 10Hz, and 16 (30%) were made for 20Hz. Participants correctly guessed that they had

received the sham condition 6% (CI: 1%, 32%) of the time they were administered the sham condition, a lower probability of being correct than if they had chosen at random (i.e., the CI does not include 33% and is less than chance). Participants correctly guessed that they had received the 10Hz condition 66% (CI: 43%, 84%) of the time they were administered 10Hz, a higher probability of being correct than if they had chosen at random (i.e., the CI does not include 33% and is greater than chance). Participants correctly guessed that they had received the 20Hz condition 41% (CI: 21%, 65%) of the time they were administered 20Hz, which was no different than if they had chosen at random (i.e., the CI includes 33% and is thus no different than chance).

Discussion

This study examined the use of focal electrical stimulation of the left frontalis muscle as an effective sham control for multiple sessions of high frequency rTMS stimulation of the DLPFC. Participants were unable to correctly identify the sham and 20Hz stimulation conditions beyond the level of chance. In fact, participants were significantly less likely than chance to correctly identify the sham stimulation indicating that most participants were fairly certain they were receiving an active condition when they were, in fact, receiving sham stimulation. These findings indicate that this sham technique can be used to effectively establish and maintain active versus sham single blind designs.

Curiously, however, participants were more likely than chance to correctly identify the 10Hz condition. This suggests that the 10Hz condition was not effectively blinded, which in the context of the 20Hz being effectively blinded is somewhat peculiar, especially because the sham condition was delivered at 10Hz. Given the difference in Hz, one might expect participants to be able to correctly identify the 20Hz condition and confuse the 10Hz and the sham. However, after a careful analysis of the procedures, we believe that these results are derived from both the effectiveness of the sham to convince participants that they were receiving an active condition and the manner in which the choices were presented to participants. The sham condition is often experienced as being at least as intense as rTMS. Our findings suggest that participants are less likely than chance to correctly identify sham and are thus fairly certain they received an active condition. The 10Hz choice was always the first *active* stimulation condition on the list (sham was listed first, 20Hz last). Thus, we believe participants selected the 10Hz condition 2/3rd of the time and were thus more likely than chance to correctly identify the 10Hz condition simply because it was listed and selected as the first (default) active condition (i.e., not-sham choice). Nonetheless, we cannot conclude that the 10Hz condition was effectively blinded even though the sham and the 20Hz conditions were effectively blinded.

Participants' ability to correctly identify conditions is likely to be related to the length of time between stimulations, the length of the stimulations, and/or the intensity of the sham stimulation. Both active rTMS and electrical stimulation are often perceived to be somewhat painful, but most participants habituate to the experience as a stimulation session progresses. The ability to perceive the difference between sham and active rTMS might also increase or decrease as the individual habituates to stimulation. These parameters have not yet been explored. Our findings are similar to those found in other studies with different rTMS frequencies and lengths of administrations, but similar electrical stimulation intensities (Borckardt et al., 2008; Mennemeier et al., 2009; Rossi et al., 2007) where TMS naïve participants are unable to correctly identify electrical stimulation as sham TMS. Also, similar to these studies, using active single pulse TMS to determine the MT prior to each stimulation condition did not appear to provide an expectation of what active rTMS should feel like and affect the ability of electrical stimulation to work as an effective sham.

This sham technique could also be adapted to be combined with feedback techniques and other technologies that titrate the neuromodulatory effects of brain or other stimulation including BCI feedback systems using EMG or EEG signals to provide a self-paced, engaged, human-machine feedback paradigm for use as a rehabilitation tool in movement disorders (Niazi, Mrachacz-Kersting, Jiang, Dremstrup, & Farina, 2012). Theoretically, using feedback mechanisms with stimulation techniques has the potential to quickly modulate cortical excitability in specific brain areas and/or quickly identify and characterize areas to be trained with EEG biofeedback in order to achieve long-lasting neuromodulatory effects.

The interpretation of these findings is limited by the selection of particular study procedures. The parent study required that stimulation sessions be separated by at least 48 hours. Although unlikely, a shorter length of time between stimulation sessions might lessen the effectiveness of this sham technique to effectively blind participants. Additionally, although the conditions were counterbalanced, the presentation of the condition choices was not counterbalanced and produced what we believe to be a presentation order effect among the active choices. Future studies should randomize or counterbalance the condition choices on the response forms.

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References

- Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, et al. George MS. 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 Stimulation*. 2008; 1(1):44–51. Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S. 10.1016/j.brs.2007.08.006 [PubMed: 19424459]
- Bear MF. Homosynaptic long-term depression: a mechanism for memory? *Proceedings of the National Academy of Sciences*. 1999; 96(17):9457–9458.
- Bonato C, Miniussi C, Rossini PM. Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. *Clin Neurophysiol*. 2006; 117(8):1699–1707. Research Support, Non-U.S. Gov't. 10.1016/j.clinph.2006.05.006 [PubMed: 16797232]
- Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, et al. George MS. Development and evaluation of a portable sham transcranial magnetic stimulation system. *Brain Stimulation*. 2008; 1(1):52–59. Evaluation Studies. 10.1016/j.brs.2007.09.003 [PubMed: 19424444]
- Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*. 1997; 48(5):1398–1403. [PubMed: 9153480]
- Di Lazzaro V, Pilato F, Saturno E, Oliviero A, Dileone M, Mazzone P, et al. Rothwell JC. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *The Journal of Physiology*. 2005; 565(Pt 3):945–950. Research Support, Non-U.S. Gov't. 10.1113/jphysiol.2005.087288 [PubMed: 15845575]
- Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*. 2006; 117(12):2584–2596. Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Review. 10.1016/j.clinph.2006.06.712 [PubMed: 16890483]
- George MS, Nahas Z, Kozel FA, Li X, Denslow S, Yamanaka K, et al. Bohning DE. Mechanisms and state of the art of transcranial magnetic stimulation. *The Journal of ECT*. 2002; 18(4):170–181. [PubMed: 12468991]

- George MS, Padberg F, Schlaepfer TE, O'Reardon JP, Fitzgerald PB, Nahas ZH, Marcolin MA. Controversy: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-compulsive disorder, panic, posttraumatic stress disorder). *Brain Stimul.* 2009; 2(1):14–21. Review. 10.1016/j.brs.2008.06.001 [PubMed: 20633399]
- Hallett M. Transcranial magnetic stimulation and the human brain. *Nature.* 2000; 406(6792):147–150. Review. 10.1038/35018000 [PubMed: 10910346]
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron.* 2005; 45(2):201–206. Clinical Trial Research Support, Non-U.S. Gov't. 10.1016/j.neuron.2004.12.033 [PubMed: 15664172]
- Loo CK, Taylor JL, Gandevia SC, McDarmont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some “sham” forms active? *Biological Psychiatry.* 2000; 47(4):325–331. Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't. [PubMed: 10686267]
- Malenka RC, Nicoll R. Long-term potentiation--a decade of progress? *Science.* 285(5435):1870–1874. doi: 7846 [pii]. [PubMed: 10489359]
- Mennemeier M, Triggs W, Chelette K, Woods A, Kimbrell T, Dornhoffer J. Sham Transcranial Magnetic Stimulation Using Electrical Stimulation of the Scalp. *Brain Stimulation.* 2009; 2(3):168–173. 10.1016/j.brs.2009.02.002 [PubMed: 20160893]
- Niazi IK, Mrachacz-Kersting N, Jiang N, Dremstrup K, Farina D. Peripheral electrical stimulation triggered by self-paced detection of motor intention enhances motor evoked potentials. *IEEE Transactions on Neural Systems and Rehabilitation Engineering.* 2012; 20(4):595–604. Research Support, Non-U.S. Gov't. 10.1109/TNSRE.2012.2194309 [PubMed: 22547461]
- O'Reardon JP, Solvason HB, Janicak PG, Sampson HA, Isenberg KE, Nahas Z, et al. Sackeim HA. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biological Psychiatry.* 2007; 62(11):1208–1216. Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't. 10.1016/j.biopsych.2007.01.018 [PubMed: 17573044]
- Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology.* 1998; 15(4):333–343.
- Plewnia C, Reimold M, Najib A, Reischl G, Plontke SK, Gerloff C. Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomised, controlled pilot study. *Journal of Neurology, Neurosurgery, and Psychiatry.* 2007; 78(2):152–156. Randomized Controlled Trial Research Support, Non-U.S. Gov't. 10.1136/jnnp.2006.095612
- Rossi S, Ferro M, Cincotta M, Olivelli M, Bartalini S, Miniussi C, et al. Passero S. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clinical Neurophysiology.* 2007; 118(3):709–716. Clinical Trial Comparative Study Research Support, Non-U.S. Gov't. 10.1016/j.clinph.2006.11.005 [PubMed: 17188568]
- Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. *Neurology.* 2007; 68(7):484–488. Review. 10.1212/01.wnl.0000250268.13789.b2 [PubMed: 17296913]
- Sitaram R, Veit R, Stevens B, Caria A, Gerloff C, Birbaumer N, Hummel F. Acquired control of ventral premotor cortex activity by feedback training: an exploratory real-time fMRI and TMS study. *Neurorehabilitation and Neural Repair.* 2012; 26(3):256–265. Case Reports Research Support, Non-U.S. Gov't. 10.1177/1545968311418345 [PubMed: 21903976]
- Stanton PK, Sejnowski TJ. Associative long-term depression in the hippocampus induced by hebbian covariance. *Nature.* 1989; 339(6221):215–218. 10.1038/339215a0 [PubMed: 2716848]
- Strafella AP, Ko JH, Monchi O. Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. *NeuroImage.* 2006; 31(4):1666–1672. Clinical Trial Research Support, Non-U.S. Gov't. 10.1016/j.neuroimage.2006.02.005 [PubMed: 16545582]
- Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clinical Neurophysiology.* 2001; 112(8):1367–1377. Review. [PubMed: 11459676]

Wu T, Sommer M, Tergau F, Paulus W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neuroscience Letters*. 2000; 287(1):37–40. doi: S0304-3940(00)01132-0 [pii]. [PubMed: 10841985]

Figure 1.

In all conditions participants were prepared by placing two stimulating electrodes over the left frontalis muscle underneath the Brainsight system headband. A demonstrates the electrode placement. B and C are reflect the set-ups for active and sham rTMS, respectively.