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Blinding success of sham-controlled motor cortex intermittent theta burst stimulation based on participant perceptions

Dear Editor,

Participant perceptions of treatment conditions and effects has been raised as an important aspect of blinding success [1,2]. Nevertheless, the ability to discriminate active repetitive transcranial magnetic stimulation (rTMS) from a commercially-available sham is currently unknown. Thus, we sought to determine whether intermittent theta burst stimulation (iTBS) of motor cortex (M1) could be distinguished from a sham coil similar in appearance, sound, and tactile stimulation.

Study overview

Twenty women ($n = 20$, age: 20.4 ± 1.8 years, height: 165.5 ± 6.5cm, weight: 66.8 ± 8.6kg) completed a randomized, sham-controlled, double-blind, cross-over study. Participants provided written informed consent and were screened for contraindications to rTMS [3]. After familiarization, participants completed two visits with 600 pulses of active or sham iTBS. One-hour afterwards, participants predicted the condition and indicated the presence and nature of treatment effects.

Motor hotspot and resting threshold

All TMS procedures were performed with earplugs rated at 32db. The hotspot for the non-dominant vastus lateralis (VL) was determined based on the largest response to biphasic TMS using a 70mm^2 figure-of-eight coil with the handle oriented to induce a lateral-medial/medial-lateral current along the precentral gyrus (Magstim D70^2 coil and Super Rapid^2 Stimulator, Magstim, Carmarthenshire, UK). Single pulses were applied at 70–75% stimulator output (SO) in 0.5–1.0cm increments beginning 1cm posterolateral to the vertex at 0.1–0.2Hz during low level contractions of the target knee extensor. The hotspot was marked on a tight Lycra swim cap in relation to the vertex. Resting Motor Threshold was determined using PEST [4] with SO boundaries set at 40% and 100%. Surface EMG was measured with active Ag differential parallel-bar electrodes (Delsys, Natick, MA, USA) in compliance with SENIAM guidelines. Activity was amplified with a gain of 1000, bandpass filtered from 20 to 450Hz, and digitized at 20KHz. Electrode locations were marked with indelible ink.

Theta burst stimulation

600 pulses of iTBS were delivered over the motor hotspot with an air-cooled 70mm^2 figure-of-eight or commercially-available sham equivalent (70mm Double Air Film (Sham) Coil, Magstim, Carmarthenshire, UK). Compared to the active coil, the Magstim 70mm Double Air Film Sham coil was identical in appearance, weight, and sound with a winding configuration that produced superficial nerve stimulation and a diffuse electrical field (~25%) compared to the active coil (<0.3T vs. 0.8T at 100% SO) [5]. Stimulation intensity was set at 60% RMT as determined immediately before iTBS. Participants sat attentively in a chair with head and coil support (Rogue Research, Quebec, Canada). Double blinding was maintained until the completion of data collection.

Perceived treatment effects and condition

At the end of each visit, participants were asked to describe any treatment effects and predict whether they received active stimulation by completing the following questionnaire:

1. Did you feel any effect of the treatment?
   Yes ____
   No ____

   If so, please describe:

2. Do you believe you received treatment today? If so, which of the following do you think you received:
   ___ I did not receive real treatment today
   ___ I received real treatment today
   ___ I do not know

Data analysis

Responses were analyzed using SPSS (V24; IBM Inc, Armonk, NY). For question two, “sham” and “unsure” were combined. Chi-square Monte Carlo Exact goodness-of-fit tests (CI: 99%, N = 10,000) were used to determine if condition and effects were equally well-predicted and the data were further analyzed for sensitivity, specificity, and positive/negative likelihood ratios (LR+/-). Learning effects were examined by comparing response patterns by visit order. Open-ended responses were tabulated. Significance in this study was $p \leq 0.05$ with tendencies noted at $p \leq 0.10$.

Results

Active stimulation was predicted at chance levels (55%, X^2 (1, $N = 20) = 0.20$, $p = 0.83$), with sham (or unsure) indicated 74% of

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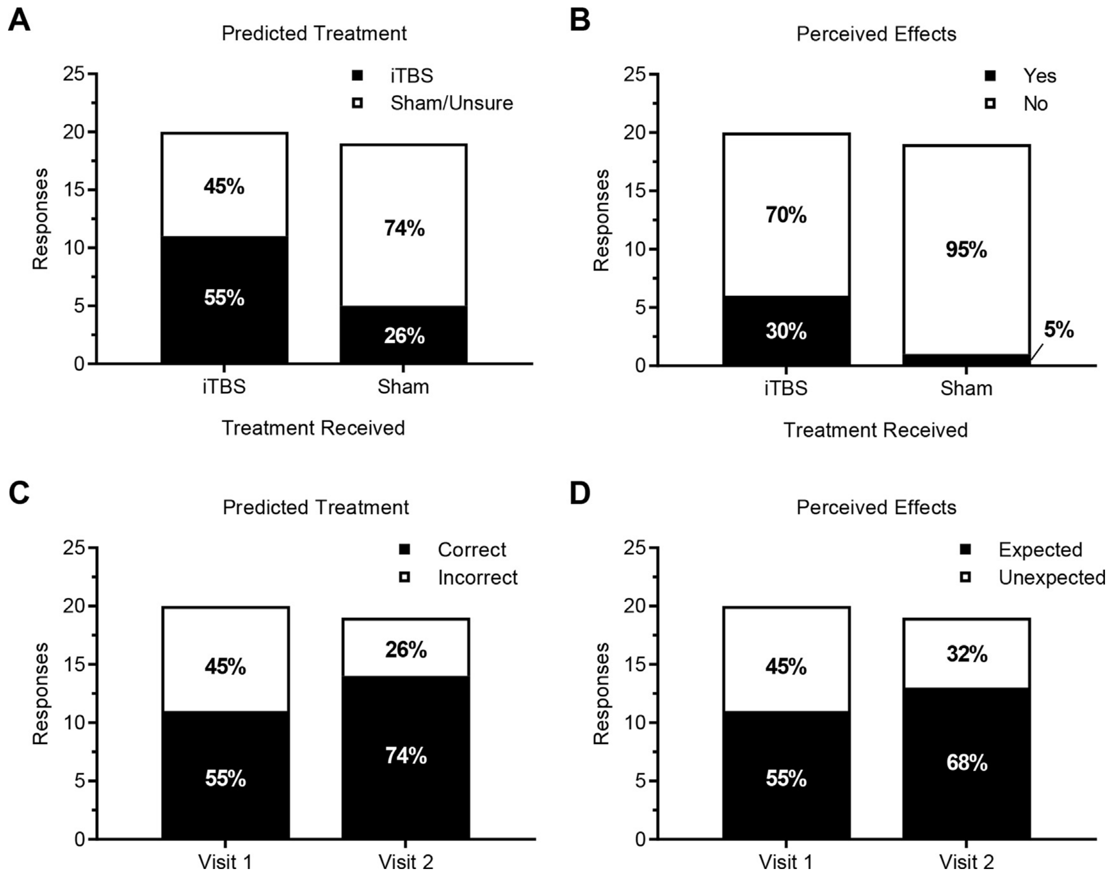

Fig. 1. Predictions and Effects by Condition and Visit Order. **A)** Participants predicted iTBS at chance levels, but sham appeared less convincing. **B)** Participants were not more likely to report treatment effects after iTBS and most indicted no effects after sham. **C)** TMS-naïve participants displayed chance accuracy; improvement was evident after the second visit. **D)** Participant beliefs about treatment effects were made in the expected direction at chance levels with no difference between visits. Values are counts and proportions of each column total (%).

the time (X^2 (1, $N = 19$) = 4.26, p = 0.06). Participants were 2.1 times more likely to correctly identify iTBS (LR+) and 0.6 times as likely to receive iTBS when sham or unknown was predicted (LR-) (Fig. 1A).

After iTBS, 30% of participants reported treatment effects (X^2 (1, $N = 20$) = 3.20, $p = 0.11$), while 5% reported effects after sham (X^2 (1, $N = 19$) = 15.21, $p < 0.00$). Participants were 5.7 times more likely to receive iTBS when effects were reported (LR+), and 0.7 times as likely to have received iTBS after reporting the absence of effects (LR-) (Fig. 1B).

Compared to the first visit when condition was correctly guessed at chance levels (55%: X^2 (1, $N = 20$) = 0.20, $p = 0.83$), accurate predictions were made 74% of the time during the second visit (X^2 (1, $N = 19$) = 4.26, $p = 0.06$) (Fig. 1C). Regardless of visit number, treatment effects matched expectations (i.e. effects after iTBS, no effects after sham) at chance levels (Visit 1: 55%, X^2 (1, $N = 20$) = 0.20, $p = 0.83$; Visit 2: 68%, X^2 (1, $N = 19$) = 2.58, $p = 0.16$) (Fig. 1D).

Analysis of written remarks revealed three instances of stimulation percept during active stimulation (e.g. "felt pulses in leg"). Stimulation percept was reported after sham in one instance. One participant noted perceived improvement in the ability to control muscle contractions after iTBS, while another reported the perception of increased strength in the target muscle after sham. Some participants reported feeling tired/fatigued after the visit ($n = 3$ after iTBS, $n = 1$ after sham).

Conclusions

Participants were unable to determine receipt of iTBS, but the sham coil appeared less convincing. There was indication of improved discrimination over time, which may reflect the discernment of attenuated sensory effects with weaker magnetic fields. Our observations confirm that participants are less likely to believe they receive active rTMS after sham [6]. Nevertheless, reduced prediction accuracy after iTBS compared to non-patterned rTMS (55% vs. 62.5%) suggests the lower intensity or brevity of patterned rTMS protocols such as iTBS may improve study blinding, an important consideration for double-blind sham-controlled trials.

Declarations of interest

Conflicts of interest: none. We affirm the consistency of this report with the Journal's guidelines on publication ethics. Funding sources were uninvolved in study design; data collection, analysis, and interpretation; manuscript preparation; and the decision to publish.

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