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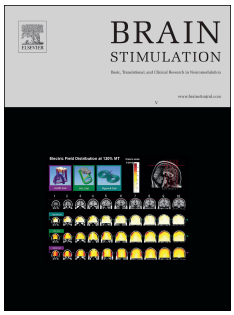

Psychophysical measurement of the effects and non-effects of TMS on contrast perception

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Title: Psychophysical measurement of the effects and non-effects of TMS on contrast perception

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Highlights

- Compared the effects of four TMS protocols on neural signals and noise.
- Single pulse TMS suppressed neural signals and repetitive TMS increased neural noise.
- Theta burst stimulation did not affect perceptual task performance.
- Participants differed in TMS susceptibility, determined by phosphene perception.
- Findings suggest systematic inter-protocol and inter-participant differences in TMS effects.

Key words

Sensory processing, neural effects, theta burst, online stimulation, psychophysics

To the editor:

Transcranial magnetic stimulation (TMS) is widely used to establish causal relationships between brain areas and behavior, but its effects on task performance are not fully understood and have rarely been directly compared between protocols. Decreases in performance on psychophysical tasks, such as those observed when applying TMS, can be attributed to either suppression of stimulus-related neural signals, increased random activity (i.e. neural noise), or a combination of both [1,2]. Indeed, evidence for all three hypotheses has been found when using differing methodologies and online stimulation protocols [3–5]. Similarly, theta burst stimulation (TBS) has been shown to have variable or bimodal effects between participants and between exact stimulation protocols [6,7]. Despite different TMS protocols (e.g. online, offline, repetitive, single pulse) potentially having vastly different effects, they are often used interchangeably in sensory and cognitive research.

We directly compared the neural effects of four commonly used TMS protocols: online single pulse (spTMS), online 3-pulse repetitive (rTMS; 50ms between pulses), offline continuous theta burst (cTBS) and offline intermittent theta burst (iTBS), during a well-understood neural computation – contrast transduction. As a secondary objective, we investigated natural TMS-susceptibility by comparing participants who could and could not perceive phosphenes to address inter-participant variability in TMS effectiveness.

We tested all stimulation protocols using the same area (occipital cortex, Supp. 2A) and a highly sensitive double-pass paradigm [8] to dissociate TMS induced changes in stimulus-related neural signal strength (i.e. suppression) and neural noise. On each trial (200 total per TMS condition) two luminance-modulated stimuli (3 deg. vis. ang.) of randomly-selected contrast were presented peripherally. Half of the trials contained a 4% contrast increment in one of the intervals (see Supp. 1A,B for examples). The exact same trials were then repeated with randomized interval order. Full details of stimuli and the double-pass paradigm be found in [9]. Using standard protocols with a Magstim Super Rapid^2 'figure of 8' coil spTMS and rTMS (Supp. 2C, 70% stimulator output) were applied 50ms after stimulus onset in each interval, and offline TBS (Supp. 2D, 30% stimulator output) was applied before the start of the task. Consistency between the first and second presentation of the trials was calculated as a direct index of neural noise. Accuracy on the task was calculated as a measure of stimulus-related signal strength.

During phosphene localization pre-screening, six participants (4 females, age 22-34) consistently perceived phosphenes and completed the main experiment (a further 19 participants were screened but did not report seeing phosphenes). Study was approved by YNiC ethics committee. All TMS protocols were tested on different days (rTMS was tested over four days due to high numbers of pulses). Phosphene localization was performed before each testing session and the location of the phosphenes (as indicated with a computer interface, Fig. 1A) was used to subsequently present stimuli.

Control trials (no TMS) were performed before stimulation for each TMS protocol separately.

We simulated predictions using a linear amplifier model (LAM). Simulations showed that if TMS reduced neural signal strength (lowered sensitivity), we would observe a steep drop in task accuracy but no change in double-pass consistency. Alternatively, if TMS increased neural noise, we would see a small reduction in accuracy and a larger drop in consistency. Finally, if TMS both reduced stimulus-related signals and increased noise, we would observe a large reduction in both measures (Supp. 1C-E).

We found a significant drop in accuracy ($t(5)=2.83$, $p=0.037$, Bayes factor (BF)=2.83) when applying spTMS compared to the no TMS condition, but no change in consistency ($p=0.601$, BF=0.29, Fig. 1B). This closely resembles our LAM model predictions for an increase in neural suppression and suggests that spTMS suppresses neural signals. Conversely, applying rTMS showed a small non-significant change in accuracy $p=0.848$, BF=0.33) compared to the no-TMS condition, and a significant decrease in consistency ($t(5)=2.74$, $p=0.041$, BF=2.38, Fig. 1C) – consistent with model predictions for an increase in neural noise. Neither protocol produced data consistent with change in both suppression and noise. This comparison between spTMS and rTMS is consistent with previous research that tested these protocols separately [4,3] and suggests suppressive and noise-inducing effects are protocol-specific.

No effects on the accuracy (p=0.790, BF=0.30) or consistency (p=0.132, BF=0.93) were observed when applying cTBS (Fig. 1D). Similarly, no changes in accuracy (p=0.773, BF=0.30) or consistency (p=0.244, BF=0.58) were observed when applying iTBS (Fig. 1E), indicating that neither protocol changed the levels of neural noise or sensory signals. This may seem to oppose the large number of successful TBS studies, particularly in the motor cortex. However, most previous research into TBS effects measured motor evoked potentials, which reflect an overall increase or decrease in neural activity (e.g. [10]). It may be that TBS changes overall neural activation but does not have particular effects on perceptually-relevant signals that would affect sensory task performance. Alternatively, the effectiveness of TBS may be overstated in the literature, as indicated by a recent large scale meta-analysis [11] which found a large positive publication bias in the TBS literature.

To investigate the effects of TMS susceptibility on task-relevant effects, a further six participants (3 females, age 23-55) who did not report seeing phosphenes also completed the experiment. For these participants, stimuli were presented at the mean location of phosphenes experienced by the other group. None of the four TMS protocols had any significant effect on accuracy or consistency scores in these individuals, indicating that the participants who did not perceive phosphenes during phosphene localization were not affected by TMS during the task. Anatomical differences in cortical folding and skull thickness may explain these individual differences in TMS susceptibility.

The inter-participant and inter-protocol differences in TMS effects found here shed light on the interpretation of findings in the existing TMS literature and inform future methodological choices. The individual differences in susceptibility and the use of different stimulation protocols in the literature may be some of the major factors in the TMS 'replication crisis' [12]. The effects of TMS are subtle and can often only be detected in reaction time data rather than task performance [13]. In this respect, the sensitivity and precision of the double-pass paradigm is a valuable tool for further investigating TMS inter-protocol and inter-participant variability in other brain areas and with larger samples.

Conflict of Interest

There is no conflict of interest relating to this manuscript.

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Figures

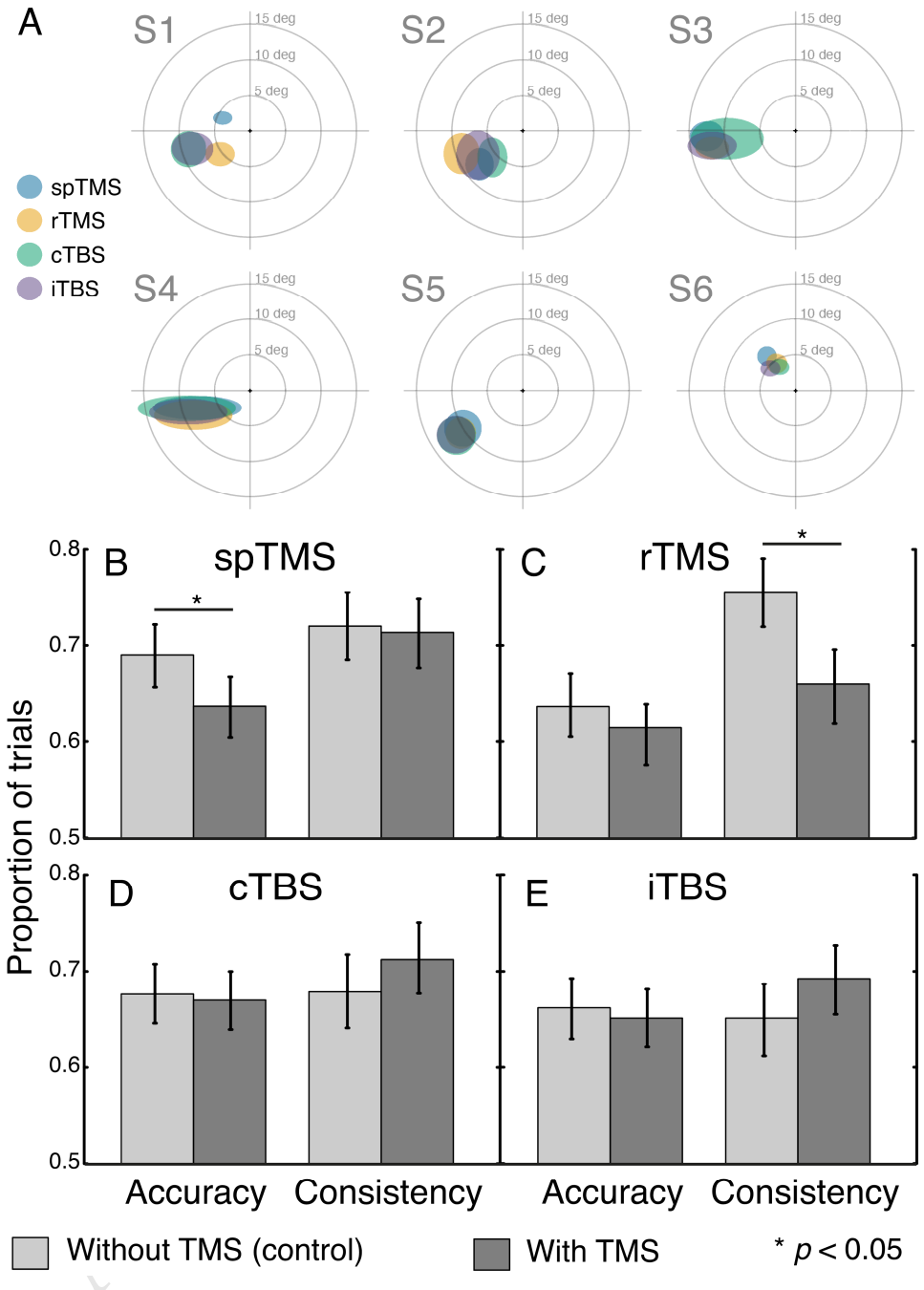
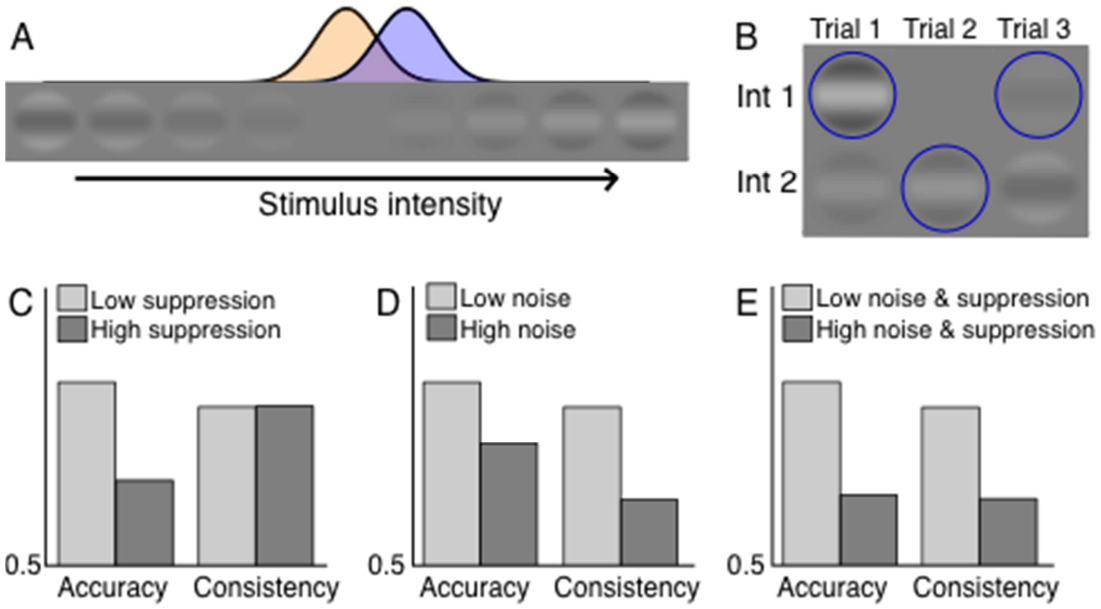


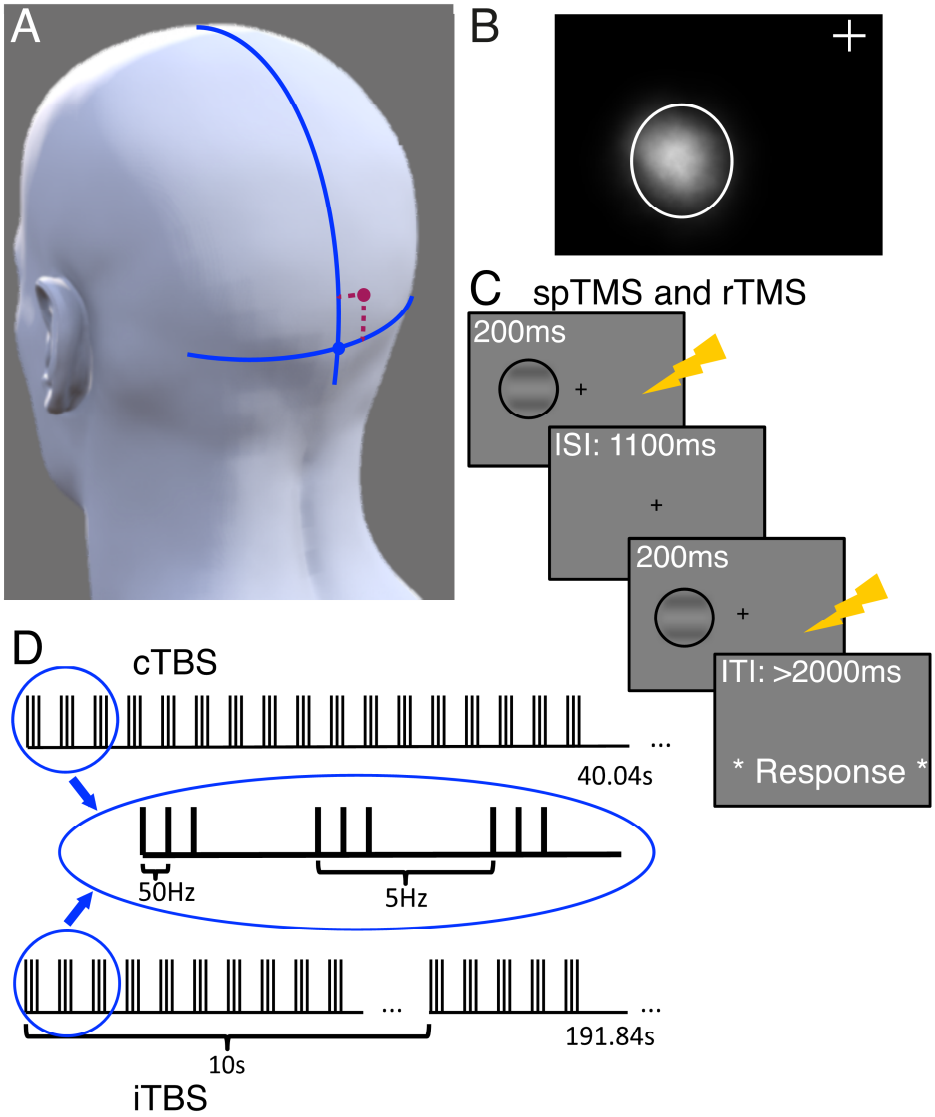
Figure 1. Phosphene locations, mean accuracy and consistency scores for the individuals seeing phosphenes. Phosphene locations were similar for all six participants, centered around the midline of the left visual field (A), within 15 degrees of the fixation cross. Phosphene locations were consistent across the four experiments using different stimulation protocols: spTMS (blue), rTMS (yellow,

averaged over four sessions), cTBS (green) and iTBS (purple), as indicated by filled ovals. In Exp 1, single pulse TMS (B) significantly reduced the mean accuracy scores (dark bars) compared to the no-TMS condition (light bars) but not consistency scores which indicates increased suppression resulting from TMS stimulation. Repetitive TMS (C) significantly reduced task consistency but not task accuracy, indicating a TMS-induced increase in neural noise. Neither cTBS (D) nor iTBS (E) produced any significant change in task performance. Error bars indicate bootstrapped 95% confidence intervals.

Supplementary materials



Supplementary figure 1. Each interval during a trial was drawn from the target (blue) and non-target (yellow) stimulus distributions (A). Participants were asked to choose the interval with the more positive contrast (B; example correct intervals are shown with a blue circle). Stochastic simulations were used to generate model predictions of double-pass data (C-E). Light bars in all panels indicate a system with low neural noise and low suppression (high sensitivity) in the system. Dark bars model an increase in either suppression, noise, or both. If TMS suppresses neural signals (lowers sensitivity) then we should expect double-pass data to be similar to the prediction in panel C. On the other hand, if TMS increases neural noise the data should resemble panel D. If both suppression and neural noise are increased we would expect data to be similar to panel E.



Supplementary figure 2. The TMS coil was positioned (red dot) approximately 2cm above and 1cm to the right of the inion (blue line intersection) to induce phosphenes (A). Before phosphene localization participants were trained to indicate the location and shape of a simulated phosphene on the screen (B; see section 2.3). During spTMS and rTMS protocols either one or three pulses (50ms apart) were delivered 50ms after stimulus onset (C). Pulses during offline cTBS and iTBS were delivered as shown in D.