Title:

Application of long-interval paired-pulse transcranial magnetic stimulation to motion-sensitive visual cortex does not lead to changes in motion discrimination

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HIGHLIGHTS

- Long-interval paired-pulse TMS was applied to visual cortex during a motion perception task
- The ppTMS was delivered according to scalp and meta-analytic coordinates, as well as sham
- No effects of active-versus-sham stimulation were observed on motion perception performance

ABSTRACT

The perception of visual motion is dependent on a set of occipitotemporal regions that are readily accessible to neuromodulation. The current study tested if paired-pulse Transcranial Magnetic Stimulation (ppTMS) could modulate motion perception by stimulating the occipital cortex as participants viewed near-threshold motion dot stimuli. In this sham-controlled study, fifteen subjects completed two sessions. On the first visit, resting motor threshold (RMT) was assessed, and participants performed an adaptive direction discrimination task to determine individual motion sensitivity. During the second visit, subjects performed the task with three difficulty levels as TMS pulses were delivered 150 and 50ms prior to motion stimulus onset at 120% RMT, under the logic that the cumulative inhibitory effect of these pulses would alter motion sensitivity. ppTMS was delivered at one of two locations: 3cm dorsal and 5cm lateral to inion (scalp-based coordinate), or at the site of peak activation for "motion" according to the NeuroSynth fMRI database (meta-analytic coordinate). Sham stimulation was delivered on one-third of trials by tilting the coil 90°. Analyses showed no significant active-versus-sham effects of ppTMS when stimulation was delivered to the meta-analytic ($p = 0.15$) or scalp-based coordinates ($p = 0.17$), which were separated by 29mm on average. Active-versus-sham stimulation differences did not interact with either stimulation location ($p=0.12$) or difficulty ($p = 0.33$). These findings fail to support the hypothesis that long-interval ppTMS recruits inhibitory processes in motion-sensitive cortex but must be considered within the limited parameters used in this design.

KEYWORDS

Transcranial Magnetic Stimulation; Visual Motion; Paired Pulse TMS**,** Motion Sensitive Cortex, hMT+

INTRODUCTION

The visual system provides an attractive target to investigate the capacity of non-invasive neuromodulation to affect cortical representations. Going beyond its more typical use in studying motor evoked potentials (MEPs) in hand muscles, transcranial magnetic stimulation (TMS) that targets visual perception takes advantage of the wide array of functional qualities of normal visual processing. One quality of the visual system which has been explored extensively is the capacity to perceive motion. In particular, area hMT+, the human homologue to macaque medial temporal cortex, is a relatively superficial cortical region that contains a robust representation of stimulus motion [1, 2].

While the neuromodulation of a number of visual functions have been extensively mapped, targeting motion-sensitive cortex remains challenging, with highly-variable rates of behavioral engagement as measured through the subjective -- subject-reported -- perception of brief flashes of lights "phosphenes" that are either stationary when TMS is applied over V1; or moving "mophenes" when applied over V5 [3-5]. It is unclear what approach is best to target motion perception in human subjects. Here, we investigated this question through application of paired-pulse transcranial magnetic stimulation (ppTMS) to motion-sensitive visual cortex using an objective task in which participants discriminated between the direction of moving dots. Using two different targeting approaches, we applied neurostimulation just before subjects had to make individually calibrated motion coherence judgments, in order to determine if ppTMS significantly disrupted those judgments.

Neuromodulatory effects of ppTMS have been extensively demonstrated in the motor cortex [6-12] and in non-motor cortical areas. For example, ppTMS to the parietal cortex has been reported to modulate excitability and behavior during tactile and visuospatial perception tasks [13, 14] while stimulation to the dorsolateral prefrontal cortex (DLPFC) during encoding modulates retrieval and working memory processes [15-17]. Within the domain of vision, ppTMS over primary visual cortex has

been reported to induce phosphene perception [18], modulate perceptual decision making [19], and disrupt motion perception [20-22] and prediction [23].

The characteristics of these observed effects are dependent on temporal and spatial parameters defining the ppTMS protocol. For example, prior studies used stimulus onset asynchronies (SOAs) between the ppTMS and the onset of visual motion that ranged from 42 ms before [21] to 100 ms after [24], typically attempting to modulate either baseline excitability when the visual stimulus appears or alter a specific process in the neuronal cascade. Similarly, the inter stimulus interval (ISI) between pulses plays an important role, with past literature in the motor cortex showing inhibitory effects with ISIs between 50 and 200 ms [25], maximal inhibition at 100 ms ISI [26], and previous ppTMS applications outside the motor cortex adopting ISIs within this range [26-28]. As reviewed in Vahabzadeh-Hagh (2014), provocation of a paired-pulse excitatory or inhibitory effect is predicated primarily on ISI and intensity of the condition (first) pulse, which varies considerably across studies, while the test (second) pulse intensity is more consistently held at suprathreshold values. Moreover, these studies relied on a variety of targeting techniques, including scalp landmarks (e.g., inion), functional mapping based on fMRI or EEG data (i.e., "functional localizers") [22, 29, 30], and identification of stationary or moving phosphenes.

Extending this literature, the current study applied long-interval (100 ms) suprathreshold ppTMS to area hMT+ immediately before participants were required to discriminate the direction of motion of visual stimuli in the contralateral visual field. It was hypothesized that ppTMS would cause behavioral impairment in motion perception, driven by accumulated inhibitory effects of the paired pulses in the contralateral visual cortex, similar to those reported by Laycock and colleagues [21]. We hypothesized that the discrimination task would be impacted by cortical inhibition effects, which occur 50–200 ms after suprathreshold TMS pulses [6, 31]. Greater modulatory effects were expected for meta-analytic

targeting relative to scalp-based targeting, as this approach scales with head size. To test this, 15 healthy young adults completed a motion discrimination protocol during which active or sham ppTMS, with an ISI of 100 ms, was applied to motion-sensitive cortex 50 ms before onset of the visual stimuli. Two different TMS targeting approaches were used:, scalp-based versus functional. As such, this study aimed to test ppTMS on an individually-calibrated motion sensitivity task to determine if modulatory effects could be observed.

MATERIAL AND METHODS

Participants:

Twenty-two healthy young adults were recruited and provided written informed consent for the present study, approved by the local University Institutional Review Board (Pro00082433). Of the 22 consented participants, four were excluded due to poor performance on the behavioral task (failure to reach 90% accuracy at 100% coherence), two for contra-indications to TMS, and one who voluntarily withdrew from the protocol. Therefore, data from 15 participants (8 females) who completed the protocol was used for these analyses. Participants had a mean age of 22.7 years (SD = 3.8) and had normal or corrected-to-normal vision. Participants were native English speakers and reported no neurological or psychological disorders. Participants were compensated $20 per hour for their time.

Protocol:

Participants enrolled in the two-visit protocol, with an average of 3.2 (SD = 2.9) days between visits. During the first visit, participants completed a TMS safety questionnaire and underwent urine drug and pregnancy screening to determine eligibility. After establishing a resting motor threshold (RMT), participants were trained on the motion discrimination task for which they completed between

660 and 1000 trials to reach asymptotic performance. No stimulation was administered during these practice blocks; however, the device was sending pulses in the air at a distance of several feet from the participant to acclimate them to the clicking sounds. On the second visit, after completing one block of practice without stimulation, participants performed the task at three difficulty levels determined based on their performance during the first session. Participants performed an average of 458 trials (SD = 47) which were pseudorandomized such that each participant viewed an equal number of trials at each difficulty level and an equal number across two active conditions (scalp coordinate and functional location; 2/3 of trials) and a sham condition (1/3 of trials). During these trials, participants received online ppTMS at two locations, randomly interleaved with a sham condition. For the sham condition, the coil was tilted from lying flat on the head to being positioned such that the edge of the coil was perpendicular to the head (i.e. rotated 90° around the axis of the handle). This alteration induced a significantly lower electric field in the brain while still producing a similar auditory sensation. These procedures are described in greater detail below.

Motion discrimination task:

Each trial of the motion discrimination task (**Figure 1**) began with presentation of a fixation cross on a computer monitor. Participants were required to fixate the cross and then, 750 to 1500 ms after fixation cross appearance, moving dots appeared in the right periphery. The center of the dot field was located 8° from the fixation cross and extended 12° in diameter. During the motion interval, dots moved at 15.5 °/s, either upwards to the right or upwards to the left at a 45˚ angle and remained on the screen for 150 ms. Following the motion, participants had 3 seconds to indicate with a button press if the direction of motion was to the left or right of vertical. After each answer, feedback was provided with a green fixation cross for correct responses and red for incorrect responses that was presented for 1

second. The viewing distance (eye-to-screen center) for each participant was approximately 56 cm, and they were instructed to perform the task as quickly and accurately as possible within the allotted time.

Difficulty on this task was manipulated by altering the coherence of the dot motion (i.e. the percentage of dots moving in the target direction). On the first visit, dot coherence was systematically altered according to a staircase schedule. At the beginning of each of nine blocks of 100 trials, coherence would start randomly at 0 or 100 percent coherence. After a correct decision, the coherence decreased by 0.2 times the difference between the coherence on that trial and 0%. After errors, the coherence increased by 0.1 times the difference between 100% and the coherence on that trial. The task was identical during the second visit, except that instead of an adaptive staircase procedure, three fixed coherence levels were presented that corresponded to 60% (hard), 75% (medium), and 90% (easy) accuracy according to individual performance during the first visit.

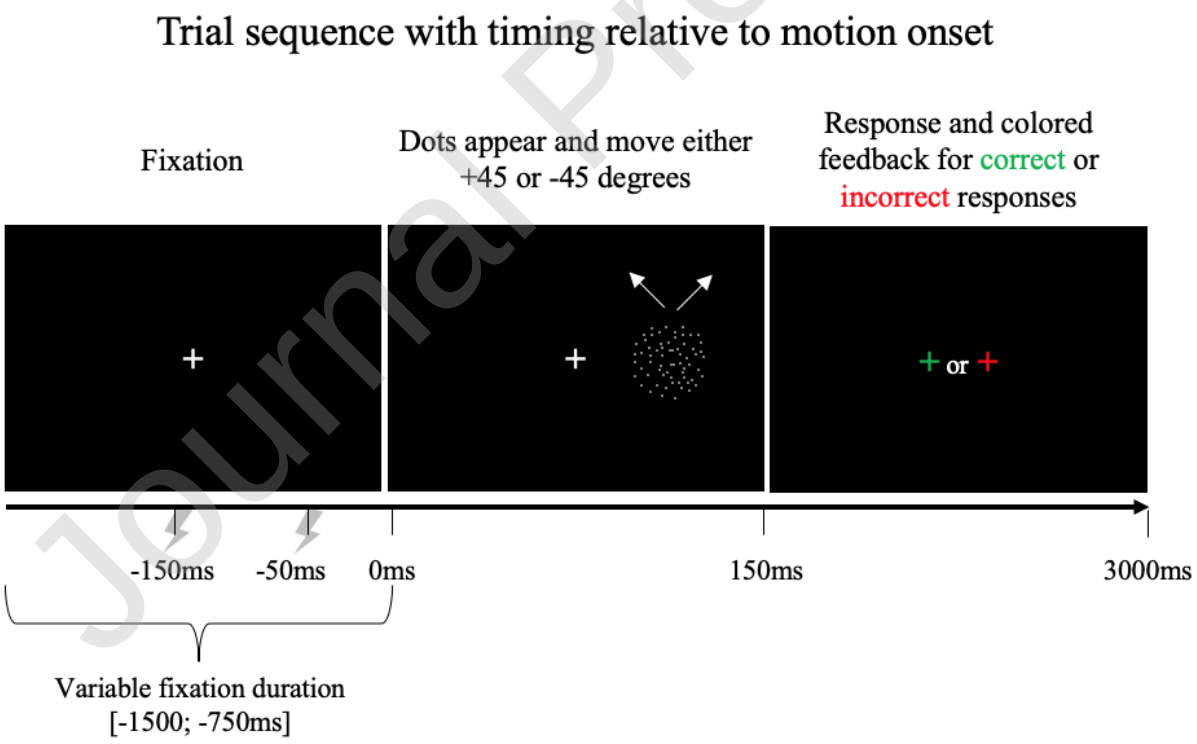

***Figure 1**: Schematic of trial sequence. On each trial a central fixation was presented, followed by dots in the right visual field that moved either diagonally to the upper left or upper right for 150 ms.*

Participants then had 3 seconds to respond and received feedback based on a change of the color of the fixation cross. During visit 1, no TMS was applied. During visit 2, ppTMS was applied with pulses occurring 150 ms and 50 ms prior to motion onset.

TMS Procedures:

All TMS procedures used a Cool-B65 butterfly (figure-of-eight) coil and a MagPro R30 stimulator (MagVenture, Denmark) guided by a BrainSight stereotactic neuronavigation system (Rogue Research, Canada).

Resting Motor Threshold (RMT): RMT was determined for each participant during the first visit. The hot spot was determined for left motor cortex that optimally elicited a MEP in the right first dorsal interosseous (FDI) muscle. RMT was then assessed as the lowest TMS pulse intensity that produced, on average, an MEP of 50 μV peak-to-peak amplitude according to a maximum likelihood estimator (TMS Motor Threshold Assessment Tool, MTAT 2.0, http://www.clinicalresearcher.org/software.html)

Paired-Pulse Stimulation: Online ppTMS was administered at 120% of RMT over motion-sensitive cortex. The first TMS pulse was delivered 150 ms prior to visual presentation of moving dots, followed by an inter-pulse interval of 100 ms. Therefore, the second TMS pulse occurred 50 ms before onset of the visual motion stimulus. The collective effects of the two pulses were thus expected to approximately span the interval before and during the motion discrimination task.

TMS Targeting: ppTMS was delivered to the left hemisphere of the motion-sensitive cortex, as this has been shown to produce visual-perceptual effects more consistently than the right hemisphere [22]. Two spatial targeting approaches were used. First, in line with numerous studies targeting visual motion cortex in humans, a scalp measurement (the ‘3-5 cm’) procedure was used [29, 30, 32]. After a manual

search for the inion, a marker was placed using neuronavigation three centimeters dorsal and five centimeters lateral to the inion. This measurement was marked in the same fashion for all participants and did not take into account individual differences in head size and shape.

A second method of targeting was derived from coactivation information derived from the meta-analytic platform Neurosynth (www.neurosynth.org). Neurosynth is a web-based, publicly accessible database of blood-oxygen-level dependent (BOLD) activations created from thousands of fMRI studies [33]. To derive a target from this database, a query was made to Neurosynth using the term "motion" which produced a meta-analysis synthesis of 383 studies, returning a forward probability map in standardized Montreal Neurological Institute (MNI) space. This map was subsequently scaled to each participant's head size by registering the left and right preauricular points and nasion in Brainsight and warping the Neurosynth map to the standard head model within the Brainsight software. This map was applied as an overlay on the standardized brain and the activation threshold increased to ascertain the peak activation, which was then defined as the second target. The different TMS conditions (scalp-based or meta-analytic TMS coordinates, and active/sham) were delivered in a randomized order.

Sham Stimulation: To control for nonspecific effects due to the clicking sound on task performance, sham stimulation was delivered on one-third of trials and evenly between the two targets. Sham stimulation was implemented by localizing the coil over the target locations, then tilting the coil 90° perpendicular to the surface of the head so that the outer edge of one of the figure-of-eight coil loops was touching the scalp. All other parameters described for the active conditions were held constant. To quantify the strength of brain stimulation in the sham versus active conditions, we measured the respective induced electric field. A triangular loop probe was placed at a distance of 15 mm under the coil surface touching the head to estimate the electric field induced in the superficial cortex [34, 35]. At

50% of maximum TMS machine output (coil current rate of change di/dt = 76 A/μs), we detected 74 V/m for active and 13 V/m for sham TMS. Thus, the sham TMS condition induced about 17.6 % of the electric field in the active condition in cortical areas. Therefore, the direct brain stimulation effects of sham are likely negligible compared to the active condition.

Data Analysis:

All statistical analyses were performed in MATLAB (MathWorks, Natick, MA, USA). We analyzed trial-by-trial accuracy (correct = 1, incorrect = 0) and reaction time using logistic mixed effects regression and linear mixed effects regression, respectively. Since motion coherences were selected to normalize accuracy across subjects, we treated Difficulty as a continuous fixed effect independent variable (hard = 1, medium = 2, easy = 3). TMS location was treated as a categorical fixed effect independent variable. In addition to main effects, both models featured Difficulty × TMS location interaction terms. Participant ID was used as a random effect in both models. We used a post-hoc Bonferroni correction to correct for the n = 2 statistical models used, leading to an alpha level at .025.

RESULTS

TMS Effects:

In general, ppTMS did not show an effect on behavior at either brain location during the motion discrimination task. Analyses performed using a logistic mixed effects regression demonstrated that pp-TMS did not affect motion discrimination accuracy at the Neurosynth location (main effect: $\beta = 0.189$, $p = 0.15$; interaction with difficulty: $\beta = -0.185$, $p = 0.12$) or at the 3-5 location (main effect: $\beta = -0.182$, $p = 0.17$; interaction with difficulty: $\beta = 0.121$, $p = 0.33$). ppTMS also did not affect reaction time at the Neurosynth location (main effect: $\beta = 0.020$, $p = 0.22$; interaction with difficulty: $\beta = -0.012$, $p = 0.28$)

or at the 3-5 location (main effect: $\beta = 0.013$, $p = 0.39$; interaction with difficulty: $\beta = 0.004$, $p = 0.73$). Significant main effects of difficulty were present for both accuracy ($\beta = 0.986$, $p < 0.0001$)

and reaction time ($\beta = -0.056$, $p < 0.01$) with means and standard errors shown in **Figure 2**.

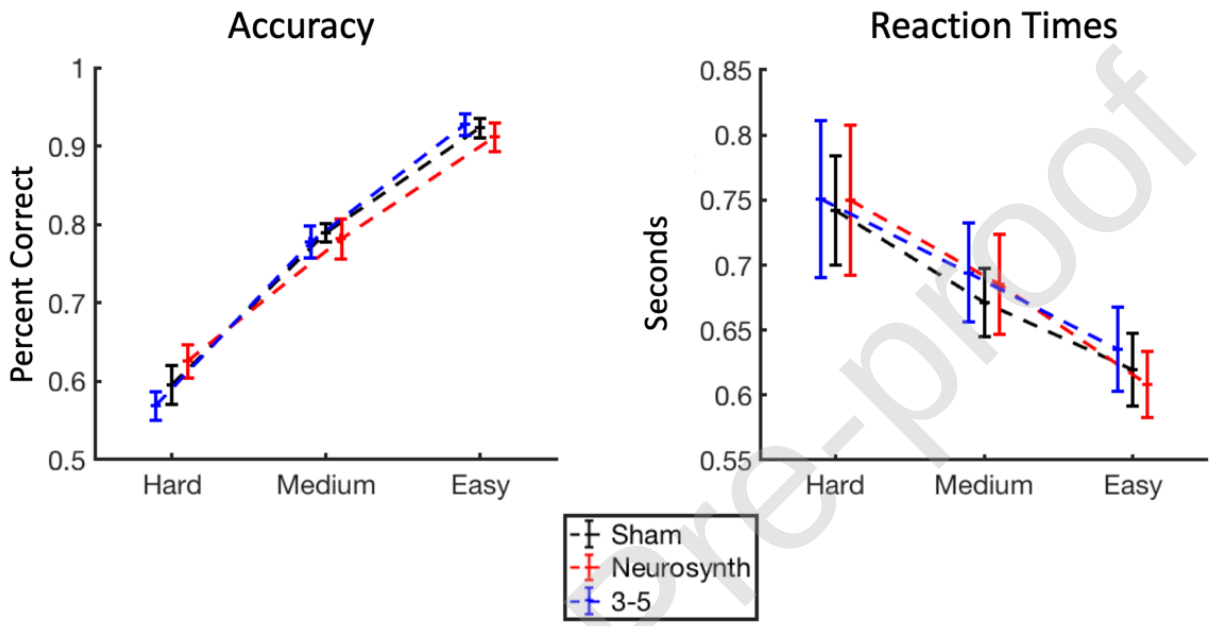

Figure 2. *Mean accuracy and reaction times, and bars indicating standard errors for sham stimulation (black), Neurosynth targeting (red) and 3-5 targeting (blue), shown across difficulty levels. Bars are staggered on the horizontal axis for ease of viewing.*

TMS Targeting:

Cortical targeting of TMS has improved greatly to create more accurate localization of desired neuromodulation. While neither of the approaches used in this study represent the state-of-the-art (e.g. fMRI-localized with electric-field modeling [36], they do offer a contrast between a common method that *does not* scale with head size (3-5 approach) and one that does (Neurosynth approach). As shown in **Figure 3**, variation between the methods was sizable, with a mean distance difference of 29 mm and a spread of several centimeters.

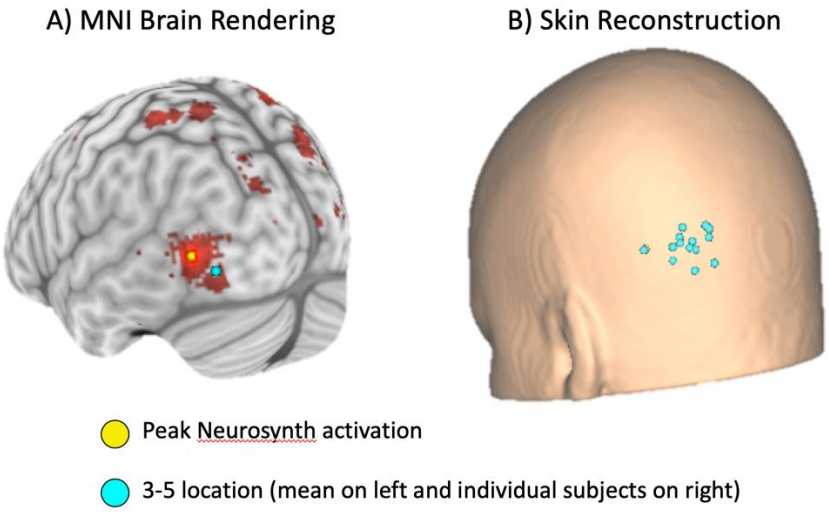

Figure 3*: A) Neurosynth target (yellow dot) on "motion" probabilistic map and mean 3-5 target (cyan) shown on an MNI brain rendering. B) Skin rendering with individual subject's 3-5 locations.*

DISCUSSION

This study assessed the effects of an online paired-pulse TMS protocol delivered over the left hMT+ at two distinct scalp targets as participants performed a motion direction discrimination task. This stimulation was expected to impair task performance, reducing accuracy and/or slowing down reaction times in motion direction discrimination. While this task showed reliable parametric behavioral effects with increasing accuracy and decreasing reaction time at higher coherence levels, there were no effects of ppTMS applied using either targeting method. We discuss possible explanations for this null finding below.

The results of the current study are in contrast with previous studies reporting modulation of motion perception after ppTMS over hMT+ with different parameters. Decreased accuracy in motion perception has been observed when ppTMS (ISI: 5 ms) in 15 participants was applied 42 and 10 ms prior to stimulus presentation [21] or in five subjects 60–80 ms after stimulus offset [22]. Fast and slow moving dots have been disrupted selectively by ppTMS (ISI: 26.7 ms) applied in 12 subjects

approximately 50 ms and 80 ms after stimulus onset respectively [20]. Furthermore, the capacity of predicting motion signal was impaired when ppTMS (ISI: 40 ms) was applied in 17 subjects, 13 ms before stimulus presentation [23]. Finally, ppTMS (ISI: 100 ms) to 36 subjects, applied 100 ms after stimulus onset, disrupted interception timing during a visual interception task [24]. Given that the current sample size of 15 is typical of these studies, and that the motion task was individually calibrated to maximize psychometric sensitivity, it is notable that the current study was not able to achieve similar active-versus-sham effects.[1]

Factors including task sensitivity to TMS [37] and/or TMS parameters could have contributed to the negative results. For instance, the duration of the visual stimulus presentation used in this experiment may have been suboptimal to support ppTMS aftereffects. In particular, at 150 ms, the total duration of the motion stimulus presentation is somewhat longer than for other designs that have used single pulse TMS to disrupt motion perception [22, 32, 38]. In many of those studies, durations shorter than 100 ms were used under the logic that longer durations of motion stimuli may outlast the effective duration of modulation induced by TMS. This logic is further accentuated by Beckers and Zeki (1995) who highlighted that there are two paths to process motion perception, a fast pathway with direct access hMT+ and a slow one that arrives first to the striate cortex (V1), delivering information to hMT+ around 50 ms later [32]. It is possible that if there was an effect due to the ppTMS in this study, it may have been compensated for by the delayed action of the slow pathway, such that no difference was seen between active and sham stimulation.

In a similar vein, the timing of delivery of the TMS pulses with respect to the stimulus onset may have influenced the results. According to the literature, the critical time window to disrupt motion

[1] To infer statistical power, we used a standard method [41] to calculate that future studies should aim to obtain at least 1600 observations per experimental condition. With the current experimental design a sample of 32 individuals would be ideal to obtain sufficient power.

perception with TMS applied over the hMT+ extends from −40 to 200 ms around the stimulus onset [21, 22, 32, 38]. While there is considerable heterogeneity in the experimental parameters used in these studies several have shown that disruption in motion perception can be achieved with single pulses in an early period ranging from −40 to 0 ms before stimulus onset [21, 38, 39]. In the current protocol, paired-pulse stimulation was delivered 150 or 50 ms before the onset of the motion stimulus under the logic that persistent inhibitory effects of this TMS intervention will last for several hundreds of milliseconds and therefore overlap with the task duration. However, late cortical disinhibition, which peaks approximately 200 ms after a suprathreshold pulse [40], may have interfered with the intended inhibitory effects of the pulses, yielding a mixture of inhibitory and facilitatory effects. Thus, this long-interval ppTMS paradigm may have been suboptimal for inducing robust modulatory effects in motion perception.

An important consideration in any TMS study is the spatial positioning of the coil relative to the desired cortical target. Methods for targeting motion-sensitive cortex in humans range from scalp measurement, to meta-analytic group coordinates (the ‘‘probabilistic approach”), to individualized targets based on anatomical or functional neuroimaging. The commonly used scalp coordinate-based approach was the first targeting method used in the current study. However, it is widely appreciated that such targeting does not scale with head size, and therefore a second approach was implemented in which targeting was based on the peak activation obtained from the NeuroSynth meta-analytic database and scaled to the head size of the participant. While neither of these targeting approaches led to active-versus-sham behavioral effects, it is interesting that they did produce markedly different coil placements across individuals. In particular, these two approaches were offset from each other by an average of 2.9 cm, with an overall spread of several centimeters. Nonetheless, future studies may wish to capture individual variability in the functional location of hMT+ using fMRI-based targeting.

Another final parameter choice that may have impacted the effects in this study was the decision to scale stimulation intensity at 120% of resting motor threshold. While such suprathreshold stimulation is common in TMS, it is based on sensitivity that is not derived specifically from the visual cortex and may have undermined potential behavioral results, suggesting that TMS motor thresholds cannot be assumed to be a reliable guide to the excitability of visual cortex. This suggests that more systematic investigations of the reliability of trial-wise TMS in eliciting consistent visual percepts with varying targeting approaches is necessary.

In conclusion, the present study highlights the challenges associated with neuromodulatory targeting using TMS to affect visual perception and underscores the need for further dose-response studies in TMS literature to better understand the underlying neural mechanisms. This study can therefore serve as a reference point for future studies that systematically vary stimulation parameters to explore how these parameters modulate TMS effects.

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