Theta-Burst Stimulation of Area MT+/V5 Does Not Affect Multiple Object Tracking Performance

by

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ABSTRACT

Behavioral, electrophysiological, and neuroimaging evidence has demonstrated that multiple object tracking (MOT) tasks draw upon visual perception, attention, and working memory cognitive processes. Functional neuroimaging studies identified the middle temporal visual area (MT+/V5) as one of several brain regions associated with MOT in humans. MT+/V5 is thought to be responsible for processing motion from visual information, regulating smooth pursuit eye movements, and encoding memory for motion. However, it is unclear how MT+/V5 interacts with attention and working memory performance processes during MOT. To investigate this question, the right MT+/V5 region was identified in 14 neurotypical subjects using structural magnetic resonance imaging (sMRI). The right MT+/V5 was stimulated using intermittent theta-burst stimulation (iTBS), continuous theta-burst stimulation (cTBS), and sham transcranial magnetic stimulation (TMS) using a within-subjects design. Average MOT performance was measured before and 5-min, 30-min, and 60-min after each stimulation protocol. There was no significant difference in average MOT performance across time, regardless of the stimulation condition.

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CHAPTER 1

INTRODUCTION

From naturalistic to specialized activities, many situations require human observers to attend to and track multiple moving targets in visual space to accomplish goal-directed tasks. For instance, driving requires attending to and tracking other vehicles in visual space to change lanes safely. This ability to attend to multiple objects has been extensively studied in the laboratory using multiple object tracking (MOT) experimental tasks (Cavanagh & Alvarez, 2005; Lochner & Trick, 2014; Ma & Flombaum, 2013; Meyerhoff et al., 2017; Pylyshyn & Storm, 1988; Pylyshyn et al., 2008; Scholl, 2009; Scimeca & Franconeri, 2015; Thomas & Seiffert, 2010). A typical MOT paradigm consists of several indistinguishable visual objects whereby a subset of objects are briefly designated as targets before an interval of motion occurs. After the motion interval, subjects distinguish the non-targets from the targets, whereby the proportion of correctly identified targets determines performance.

Functional neuroimaging evidence has identified several cortical regions, including the frontal eye fields (FEF), anterior intraparietal sulcus (AIPS), superior parietal lobule (SPL), posterior intraparietal sulcus (PIPS), and middle temporal complex (MT+/V5) that are involved in tracking and attending to objects in the visual field (Culham et al., 1998; Culham et al., 2001; Howe et al., 2009; Jovicich et al., 2001; Merkel et al., 2015). The FEF and SPL show more significant activity when attending to moving rather than stationary objects, which supports their role in suppressing (Burman & Bruce, 1997; Guitton et al., 1985; Priori et al., 1993) and generating (Doricchi et al., 1997) saccadic eye movements, respectively, during an MOT task. Activity in AIPS is

associated with attending to moving objects in the visual field rather than stationary objects (Donner et al., 2000; Wojciulik & Kanwisher, 1999), is sensitive to attentional load (Culham et al., 2001; Jovicich et al., 2001), and supports visually guided hand movements and grasping (Buelte et al., 2008). However, PIPS exhibited activity when attending to both stationary and moving objects (Howe et al., 2009). Interestingly, Xu and Chun (2006) found that activity in AIPS was modulated by the quantity and shape complexity of remembered objects, while activity in PIPS was modulated by the number of locations of remembering where objects were in visual space regardless of shape complexity. Given that MT+/V5 is responsible for processing motion direction and speed (Heutink et al., 2019; Kolster et al., 2010; Strong et al., 2017), is involved with memory for motion (Slotnick & Thakral, 2011), has retinotopic organization (Born & Bradley, 2005; Huk et al., 2002), and is modulated by attention (Berman & Colby, 2002), PIPS may function as a visual-spatial indexing mechanism to attended objects while working in tandem with MT+/V5 which projects visual information to PIPS. In other words, MT+/V5 may be responsible for processing object direction, speed, and location updating, while PIPS stores the remembered location of the object in visual space during MOT.

For example, Battelli et al. (2009) stimulated the left and right cerebral hemispheres of the intraparietal sulcus (IPS) and left and right MT+/V5 using transcranial magnetic stimulation (TMS). They found that behavioral MOT performance significantly decreased when IPS was stimulated, but no performance changes were observed when MT+/V5 was stimulated. On the other hand, Chakraborty et al. (2021) found that stimulating left MT+/V5 using TMS significantly decreased MOT performance over

time. Battelli et al. stimulated these regions using a low-frequency (1 Hz) repetitive TMS (rTMS). In contrast, Chakraborty et al. used a continuous theta-burst stimulation (cTBS) protocol. Using different TMS methodological procedures may explain the mixed findings when stimulating MT+/V5.

CHAPTER 2

LITERATURE REVIEW

MOT performance correlates highly with human attention control and working memory capacity (Harris et al., 2020; Huang et al., 2012; Tombu & Seiffert, 2008). For example, Kunar et al. (2008) used a dual-task paradigm where participants engaged in a telephone conversation, a shadowing task where they had to repeat a word spoken by the experimenter and a vocal generation task where the participants had to generate a new word that begins with the last letter that was spoken to them by the experimenter. The behavioral evidence showed that MOT performance was significantly reduced when engaging in the telephone conversation and the vocal generation task, but not the shadowing task. Both the telephone conversation and the vocal generation tasks required participants to store and update visual information from the MOT task; however, the telephone conversation also required participants to process and store relevant acoustic information to prepare for proper lexical retrieval resulting in slower response times and poorer MOT performance. The vocal generation task resulted in the slowest reaction time and even poorer MOT performance due to the increased cognitive demand for attention and working memory resources to retrieve and manipulate the appropriate lexical information that matches the established parameters after processing and storing the goal-relevant acoustic information. Since the shadowing task did not require the retrieval or manipulation of temporarily stored information to the degree of taxing attentional and working memory resources beyond availability, no significant changes in reaction time and MOT performance were observed. Similar results can be found in simulated driving scenarios and cellphone usage wherein participants show impaired reaction times to road

hazards, lane-keeping, and overall driving performance attributed to increased attention and cognitive demand to maintain a conversation (Horrey & Wickens, 2016). Demonstrating that increasing divided attention and cognitive load for working memory processing during tracking hinders MOT performance. In addition, these behavioral changes are also supported by electrophysiological evidence.

Drew and Vogel (2008) sought to establish distinct electrophysiological measures of target selection and sustained attention during a tracking task to determine which of these facets of attention is the principal limiting factor in tracking performance. The negative posterior contralateral (N2pc) event-related potential (ERP) component was selected because it is sensitive to the selection of targets in visual search tasks and occurs ~200 ms after the stimulus over posterior electrode sites (Eimer, 1996; Hopf et al., 2000, 2002, 2006; Luck et al., 1997; Luck & Hillyard, 1994). The contralateral delay activity (CDA) ERP component was also selected because it is sensitive to the number of objects maintained in visual working memory and possesses capacity limits (Jolicoeur et al., 2006; Mazza et al., 2007; McCollough et al., 2007; Vogel & Machizawa, 2004; Vogel et al., 2005; Woodman & Vogel, 2008). Results showed that tracking performance was strongly predicted by variability in the N2pc component during difficult target selection while tracking performance was strongly predicted by variability in the CDA component when tracking duration was prolonged with easier target selection. Meaning that the N2pc component's negative amplitude increases as a function of the increase in the number of targets needed to be selected. Similarly, the CDA component's negative amplitude increases as a function of tracking time and is modulated by the number of previously selected targets. Demonstrating that amplitude separation (i.e., the space

between amplitude measured across time) as the number of targets and tracking duration increases, was found to be a strong predictor of individual tracking ability. These findings demonstrate that the N2pc and CDA are strong neurophysiological predictors that underlie attention selection and sustained attention processes and are sensitive to capacity limits during MOT.

Prior research has also demonstrated that increasing the number of targets (Alvarez & Franconeri, 2007; Drew et al., 2011), the number of distractors (Bettencourt & Somers, 2009; Sears & Pylyshyn, 2000), the tracking duration (Oksama & Hyönä, 2004), object proximity (Bettencourt & Somers, 2009; Franconeri et al., 2010), and object speed (Franconeri et al., 2007; Holcombe et al., 2014; Meyerhoff et al., 2016; Tombu & Seiffert, 2011) tends to negatively influence MOT performance due to the greater cognitive demand on visual attention (Huang et al., 2012), attentional selection (Franconeri et al., 2007), working memory (Oksama & Hyönä, 2004; Wolfe et al., 2007), and visual information processing speed for consciously integrating perceptual stimuli (Parsons et al., 2014).

These differences may be best explained under Baddeley and Hitch's *working memory* system (Baddeley, 2000, 2012; Baddeley & Hitch, 1974; Conway & Engle, 1996; Engle, 2002; Kane et al., 2001), which consists of a multi-component process involving the manipulation and regulation of information held within temporary memory stores to perform higher-order cognitive processes. Selected sensory information (e.g., object targets and their spatial location) is moved into working memory for further processing and then encoded into long-term memory, if necessary, by the central executive component. The central executive component functions to allocate attentional

resources to complete goal-relevant tasks and acts as a gating mechanism, controlling what information requires further processing and how that information is processed. Meaning that additional attention resources are required as the amount of goal-relevant information (e.g., target objects) increases along with the need to suppress irrelevant information (e.g., non-targets and external distractors).

The central executive component contains three subsidiary temporary stores wherein acoustic and verbal information is held in the phonological loop, while visual and spatial information is held in the visuospatial sketchpad. Both the phonological loop and the visuospatial sketchpad possess a rehearsal system to mitigate information decay. Visual information about the target objects, such as their size, shape, color, and their spatial location, is stored in the visuospatial sketchpad. As the targets move amongst the non-targets, their spatial location is updated via the rehearsal system. A typical MOT task does not recruit the phonological loop, as there are no letters, words, or digits involved. However, the phonological loop can be recruited in a dual MOT task such as what was performed by Kunar et al. (2008). Lastly, the episodic buffer serves to interface the phonological store, the visuospatial sketchpad, and long-term memory and functions to bind information into accessible episodes through conscious awareness (see Adams et al., 2018 and Baddeley, 2012 for review).

While the visuospatial sketchpad serves to store visual and spatial information such as object size, shape, color, and location, the episodic buffer binds this information to the appropriate object allowing the viewer to consciously perceive objects and attribute an appropriate label to distinguish between target and non-target. In the MOT task, the target objects share a common characteristic, such as flashing a different color (or some

other indicator) instead of the non-targets. In addition, information can be bound creatively to form unique mental representations. For example, a common strategy that participants use is to imagine the targets are connected by imaginary lines to form a mental representation of shape (e.g., a square for four targets). Observers will fixate on a centroid at the center of the shape and utilize covert attention to track the targets as the mental representation of a shape held in working memory changes size and structure in accordance with the moving targets. This is known as the perceptual grouping model proposed by Yantis (1992). Baddeley (2012) also noted that the episodic buffer possesses capacity limits of about four pieces of episodes or 'chunks' of bindings containing features (e.g., remembering a blue circle instead of a circle shape and the color blue). Furthermore, the process of binding information is not attention-demanding, but maintaining the bound information against distraction is.

As stated previously, several brain regions are associated with actively tracking objects in MOT, but less is known about the role of MT+/V5 in contributing to tracking ability. This study aimed to contribute to the current literature on the role of MT+/V5 in MOT by temporarily manipulating neuron behavior using two theta-burst TMS protocols: intermittent theta-burst stimulation (iTBS) and cTBS (see Huang et al., 2005). iTBS is an approved TMS protocol by the U.S. Food and Drug Administration (FDA) to treat individuals with treatment-resistant depression and elicits prolonged cortical excitability (Cao & Harris, 2014; Cole et al., 2022; Cole et al., 2020; Gellersen & Kedzior, 2019; Konstantinou et al., 2021; Nettekoven et al., 2014; Tao et al., 2020; Tse et al., 2018; Yu et al., 2020). cTBS is an approved TMS protocol by the U.S. FDA to treat generalized anxiety disorder and obsessive-compulsive disorder and functions to decrease cortical

excitability (Chou et al., 2015; Huang et al., 2011; Isserles et al., 2013; Li et al., 2022; Littman & Datto, 2018; Vaithianathan et al., 2022). These TMS protocols can be safely used to investigate MT+/V5 because they allow MT+/V5 function to be modulated without affecting the perception of motion trajectories (Cai et al., 2014; Chakraborty et al., 2021; Chen et al., 2016; Kaderali et al., 2015; Silvanto et al., 2006). The right hemisphere MT+/V5 will be used as the target site based on evidence that MT+/V5 in the right hemisphere is sensitive to global motion perception and attention rather than the left hemisphere MT+/V5, which is more sensitive to motion perception and attention in the right visual field (Strong et al., 2017, 2019). Given the findings from Chakraborty et al., we predicted that MOT accuracy responses would significantly decrease from pre-test to post-test after administering cTBS due to the inhibitory effects of this protocol. On the other hand, MOT accuracy responses would significantly increase from pre-test to post-test after administering iTBS, hypothesizing that the excitatory effects from this protocol may result in an opposite effect and improve accuracy. Furthermore, MOT accuracy would not significantly differ in the post-test after sham TMS compared to the pre-test revealing an optimally calibrated task difficulty and any significant differences in the TMS treatment conditions are due to treatment effects and not practice effects.

CHAPTER 3

METHOD

All research conducted and reported herein complied with the Declaration of Helsinki ethical principles and was approved by the Institutional Review Board at Arizona State University.

Participants

An a priori power analysis using G*Power (Faul et al., 2007) with an Alpha level of .01, a Power level of .90, and a partial Eta squared effect size of 0.06 suggested a desired sample size of 42 to detect a medium effect size. To ensure maximum safety and prevention of adverse effects during TMS treatment, the Food and Drug Administration (FDA) recommends following the safety, ethical considerations, and guidelines outlined by Rossi et al. (2009, 2011), Keel et al. (2001), and Wassermann et al. (1996). Using the thirteen-item survey from Rossi et al. (2011), 34 right-handed participants with no neurological disorders and normal or corrected to normal visual acuity were determined to have minimal risk from TMS treatment and were eligible to participate. All participants gave written informed consent and were compensated $100 that was piecemealed across three separate sessions (i.e., $30 for participating in the first session, $30 for participating in the second session, and $40 for participating in the third session).

MOT Task

The task was programmed using Python ver. 2.7.3 (Van Rossum & Drake, 1995) and was generated using Spyder ver. 2.1.12 integrated development environment (Raybaut, 2009). The stimuli were shown on a Dell IN1930 (18.5 in., 1366 x 768 resolution) monitor. Participants observed the stimuli from a distance of 62 cm while in a

chinrest. The MOT stimuli comprise of eight blue circles on a black background wherein half of these circles flash red for three seconds, indicating that these circles are the targets the participant must attend to while ignoring the non-flashing circles. After the flashing ceases, the circles return to blue and move randomly around the screen for eight seconds before stopping. After the circles cease moving, the participant is prompted to make their responses by using the computer mouse to select the objects they know to be the targets and to guess any remaining targets. The number of allowable responses is equivalent to the number of targets during a trial (see Figure 1).

The MOT pre-test task consisted of four practice trials and 30 test trials, while the MOT post-test task consisted of only 30 test trials. The practice trials began with one target and one distractor and increased by increments of one target and one distractor until the fourth practice trial ended with four targets and four distractors. The test trials consistently had four targets and four distractors. In addition, the test trial velocity remained constant at four pixels per second, while the practice trial velocity was three pixels per second. Accuracy was measured across the 30 test trials and was calculated as the proportion of correct responses from the total allowable responses.

MRI Localization of MT+/V5

Several studies using positron emission tomography (PET), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and postmortem analysis methods, have identified a consistent anatomical location for MT+/V5 consisting of distinct cytoarchitecture and myelination relative to surrounding neuronal areas (Anderson et al., 1996; de Jong et al., 1994; Dupont et al., 1994; McCarthy et al., 1995; Shulman et al., 1998; Tootell et al., 1995; Uusitalo et al., 1997;

Walters et al., 2003; Watson et al., 1993; Zeki et al., 1991). Dumoulin et al. (2000) confirmed that MT+/V5 is typically buried within the sulci of the ventrolateral occipital cortex, posterior to the meeting point of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (i.e., Flechsig's Field 16). Thereby providing a consistent stereotaxic location of Talairach coordinates for the right hemisphere MT+/V5; $x = 44 \pm 3.3$, $y = -67 \pm 3.1$, $z = 0 \pm 5.1$; $n = 9$ (Dumoulin et al., 2000); $x = 41 \pm 3.7$, $y = -67 \pm 4.7$, $z = 2 \pm 3.2$, $n = 12$ (Watson et al., 1993); $x = 45 \pm 3.6$, $y = -76 \pm 7.5$, $z = 3 \pm 2.5$; $n = 6$ (Tootell et al., 1995); $x = 38$, $y = -62$, $z = 8$, $n = 3$ (Zeki et al., 1991) [Also see Anderson et al., 1998; de Jong., 1995; Dupont et al., 1994; McCarthy et al., 1995; Shulman et al., 1998; Uusitalo et al., 1997 for Talairach coordinates].

Structural T1 magnetic resonance imaging (sMRI) scans were obtained for each participant at no financial cost using a 3D MPRAGE sequence (TR = 2300 ms, TE = 4.5 ms, 1 x 1 x 1.1 mm^3 voxels, a field of view 240 x 256 mm^2, 180 sagittal slices) in a Philips Ingenia 3T scanner with a 32-channel head coil system at Barrow Neurological Institute in Phoenix, Arizona. T1 volumetric and surface-based parcellations and labels for each participant's sMRI scans were processed using BrainSuite21a (Shattuck & Leahy, 2002) and constructed using the USCBrain Atlas (Joshi et al., 2022). The Talairach coordinates from Dumoulin et al. were used in identifying the sulci of the ventrolateral occipital cortex in the right hemisphere.

Resting Motor Threshold Determination

Motor thresholds (MT) are defined as the minimum stimulator output to induce a visible motor response or "twitch" of the abductor pollicis brevis muscle (APB; Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2007). Each participant's MTs were

determined using the visual observation of muscle twitch (OM-MT) method consisting of 10-20 low-frequency (1Hz) single-pulse TMS administered to the left motor cortex (M1) to induce a 50% frequency (5-10) right APB muscle motor-evoked potential (MEP) criterion. Using an initial stimulator output of 20% with increasing increments of 5% for a maximum output of 90%, the figure-eight coil stimulator was oriented 45° over M1 from the scalp midline that divides the two hemispheres until a visible MEP. The maximum stimulator output of 90% when determining MTs was due to the limitations of the Magstim Rapid^2 stimulator having a maximum stimulator output of 45% when administering stimulation at 50 Hz. The optimal stimulation location or "hot spot" (Rossini et al., 1994) was identified by varying the location of the coil stimulator over M1 to facilitate the most visually pronounced MEP response. The stimulator output was either decreased or increased until the minimum stimulator output to elicit a 50% MEP frequency was found. The "hot spot" was marked using a non-toxic, washable marker while participants wore a white Caputron TMS head cap (Caputron Medical LLC., New Jersey, United States). The OM-MT method has been used by numerous researchers and clinicians in experimental (Denslow et al., 2005; Fierro et al., 2000; Göbel et al., 2006; Hoffman et al., 2010; Ishibashi et al., 2011; Oliveri & Valler, 2009; Pourtois et al., 2001; Seifert et al., 2010; Van der Werf et al., 2007) and clinical environments (Barth et al., 2011; Borckardt et al., 2008; Cohen et al., 2004; Epstein et al., 2007; Fitzgerald et al., 2008; Goyal et al., 2007; Mogg et al., 2007; Vercammen et al., 2009) with supporting evidence of its reliability (Varnava et al., 2011).

Theta-Burst Stimulation Parameters

iTBS and cTBS were delivered at 50% of participants' calibrated MTs (see above) using a Magstim D70 Alpha 70 mm figure-eight coil connected to a Magstim Rapid^2 stimulator (The Magstim Company Ltd., Whitland, United Kingdom) guided by Brainsight TMS neuronavigation system (Rogue Research Inc., Montreal, Canada). iTBS is a burst of three high-frequency (50 Hz) pulses, 20 ms apart (or 5 Hz), delivered for 200 ms intervals for two seconds before an eight-second interval of no stimulation. This pattern repeats every 10 seconds totaling 190 seconds (600 pulses). cTBS is a burst of three high-frequency (50 Hz) pulses, 20 ms apart (or 5 Hz), delivered for 40 seconds (600 pulses) without interruption (see Huang et al., 2005).

Procedure

Eligible and willing participants underwent structural magnetic resonance imaging (MRI) at Barrow Neurological Institute in Phoenix, Arizona, on a separate day before the experiment to localize the right MT+/V5. Using a within-subjects design, participants were randomly assigned a de-identified subject number and completed three TMS sessions (iTBS, cTBS, and sham TMS) on separate days. The order in which the participants completed the TMS sessions was counterbalanced to reduce extraneous variables such as order effects.

Beginning each session, participants completed the MOT pre-test before calibrating MTs using the OM-MT method. The session's respective TMS treatment was administered to the participant's MT+/V5 using 50% stimulation output of their calibrated MT (mean = 38.42, range = 24-45, SD = 4.68). Stimulation trajectory was identified by each participant's Talairach coordinates of MT+/V5 and guided by the

Brainsight TMS neuronavigation system. Participants then completed three MOT post-test tasks 5-min, 30-min, and 60-min after stimulation was delivered.

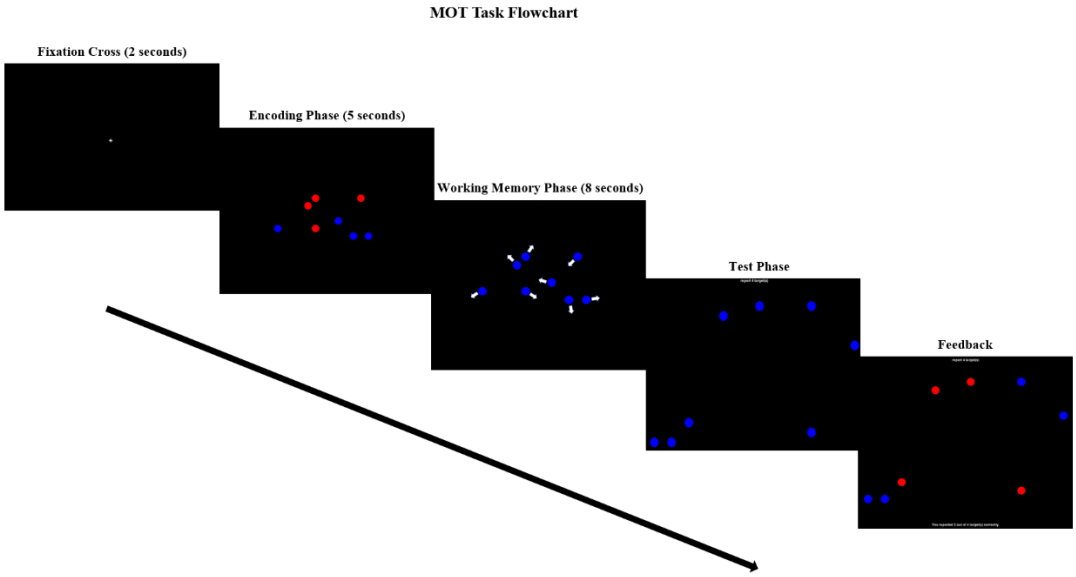

Figure 1. A schematic representation of a single trial from the MOT task. Participants were presented with a fixation cross for two seconds before eight blue circles on a black background appeared. Four of the eight circles would flash red for five seconds representing the targets the participant needed to remember and track. The red flashing targets returned to their original color before moving around the screen for eight seconds. Participants reported the targets during the test phase by hovering over the indented circle with the mouse cursor and making their selection with the left mouse button. Participants were given feedback on their accuracy at the end of each trial for two seconds.

CHAPTER 4

RESULTS

A total of 14 participants (age M = 23.71, range = 18-30, SD = 4.01, five females, nine males) were used in the final analysis of the 34 recruited subjects. 17 participants voluntarily withdrew from the experiment, one participant was withdrawn from the study upon experiencing mild adverse physical effects from the TMS system, and two participants were removed from the final analysis for not following task instructions. The mean average Talairach coordinates and standard deviations for targeting the right hemisphere MT+/V5 were x = 41.29 ± 4.37, y = -64.25 ± 3.07, z = 0.93 ± 2.86 (n = 14). The mean average and standard deviation using 50% stimulation output of participants' calibrated MTs were 38.42 and 4.68, respectively.

A repeated measures analysis of variance (ANOVA) general linear model was conducted using IBM SPSS Statistics (version 28) to test the effect of TMS stimulation (iTBS, cTBS, and sham TMS) on MOT accuracy between pre-test and post-tests (5-minutes, 30-minutes, and 60-minutes). The objective of this analysis, as it relates to the established hypotheses, is to determine whether MOT accuracy significantly differs as a function of time from pre-test (before TMS treatment) to post-test (after TMS treatment) by separate MOT accuracy by TMS conditions. Results from Mauchly's test indicate that the assumption of sphericity was not violated, $\chi^2(5) = 6.93$, $p > .05$. With sphericity assumed, results from the repeated measures ANOVA indicate that there was no significant two-way interaction between TMS condition and the time of testing on MOT accuracy, $F(6, 32) = 0.234$, $p = 964$, $\eta_p^2 = .013$, and no significant main effect of time of testing on MOT accuracy, $F(3, 35) = 1.60$, $p = .195$, $\eta_p^2 = .04$. Furthermore, Bonferroni

corrected post hoc results showed no significant difference in MOT accuracy for the sham TMS condition.

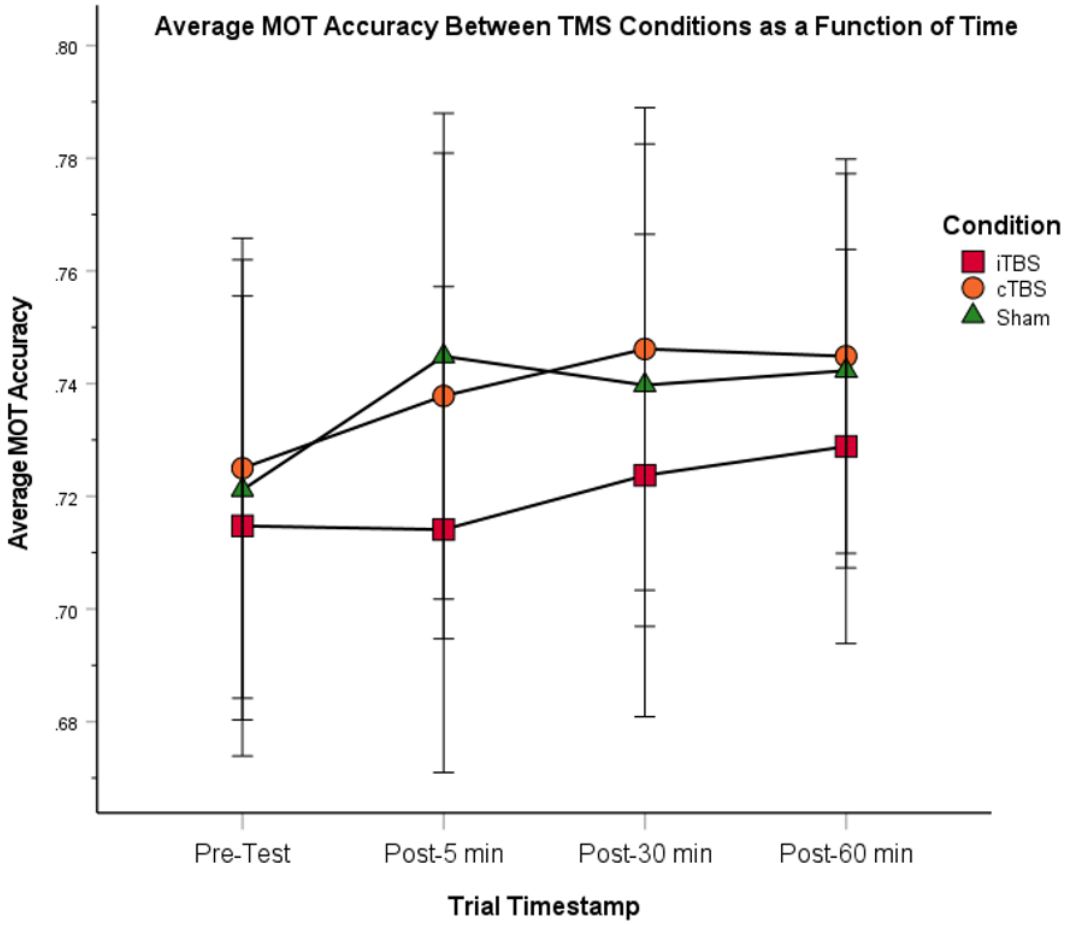

Figure 2. MOT accuracy was measured before, 5-min, 30-min, and 60-min after a stimulation protocol was administered across three counterbalanced separate days. Subjects' average MOT accuracy scores were determined by calculating the mean from thirty trials for each pre-test and post-test task attempt. The three TMS conditions are denoted by the red square (iTBS), orange circle (cTBS), and green triangle (sham), which are connected by their respective black lines. Icon location denotes the average MOT accuracy per pre-test and post-test attempt and is separated by condition. 95% confidence intervals are denoted by the T-shape error bars for each pre-test and post-test attempt and are separated by condition. Error bars are shown as 95% confidence intervals.

CHAPTER 5

DISCUSSION

The purpose of this study was to generate new knowledge and assess the function of MT+/V5 in MOT by temporarily manipulating neuron behavior using iTBS and cTBS TMS protocols that have been shown to induce prolonged neuron excitatory and inhibitory activation, respectively. No other known study involving MOT has used iTBS, and only one has used cTBS on MT+/V5 (see Chakraborty et al., 2021). Furthermore, no other known study has used these stimulation protocols on the right MT+/V5 while involving MOT. These findings do not support our predictions that iTBS and cTBS to the right MT+/V5 causally change MOT performance. However, our prediction that sham TMS would result in no significant differences was supported. Confirming an optimally calibrated task difficulty to mitigate effects found from practice effects (Bartels et al., 2010).

Contrary to the findings reported by Chakraborty et al. (2021), who found that cTBS to the left MT+/V5 significantly reduced MOT performance in the left hemifield compared to the right hemifield, our findings are not consistent with prior literature despite their speculation that stimulating the right MT+/V5 would yield similar results as stimulating the left MT+/V5. Instead, these findings are consistent with Batelli et al. (2009), who found that 1Hz rTMS over IPS affects behavioral performance when tracking objects, but 1Hz rTMS over MT+/V5 does not. This is consistent with previous evidence of IPS being selectively activated during attentive tracking and MT+/V5 showing activation regardless of active or passive viewing of motion (Culham et al., 1998). The role of MT+/V5 in MOT may serve a function beyond just motion perception,

but more research on using theta-burst stimulation and MT+/V5 when investigating MOT must be done before conclusions can be made due to the limited literature available.

A potential explanation for the role of MT+/V5 may lie in the distinction between attentive tracking and maintaining motion information in memory within the context of MOT. Silvanto et al. (2010) found that when TMS was administered to MT+/V5 during the maintenance period of a visual short-term memory task, phosphene motion was enhanced when the direction of the memory item was congruent compared to a baseline phosphene measure where no motion stimuli were present, while phosphene motion was weakened when the direction of the memory item was incongruent. Concluding that MT+/V5 activity that is retinotopically organized is associated with motion information held in visual working memory. It is plausible that MT+/V5 may aid in the maintenance of motion information of goal-directed moving stimuli instead of the tracking of currently attended moving stimuli. In their investigation of motion processing areas associated with the detection of direction changes in a random dot pattern task, Martinez-Trujillo et al. (2007) found that MT+/V5 activation preceded inferior parietal lobe (IPL) activation, which suggests that IPL activation may be dependent on sensory processing in MT+/V5 given the evidence that IPL is involved in orienting attention and patients with lesions to the IPL experience visuospatial neglect (Mort et al., 2003). The findings from Martinez-Trujillo et al. still suggest that MT+/V5 may act as a feedforwarding mechanism that updates the direction and spatial location of moving goal-oriented stimuli held in the PIPS, but also may be a key component for the rehearsal system within the visuospatial sketchpad. However, this theory requires further testing to determine the distinction between tracking and motion information maintenance.

Limitations

This study contained a few limitations. First, the desired sample size of 42, as determined by the a priori power analysis was not achieved, thereby increasing the probability of a type II error (Cohen, 1992). In contrast, the sample size (n = 14) is comparable to other TMS studies of a similar design and nature (Ackerley et al., 2010; Batelli et al., 2009; Bosco et al., 2008; Cai et al., 2014; Chakraborty et al., 2021; Huang et al., 2005; Kanai et al., 2011; Maus et al., 2013; Murd et al., 2012; Nurki et al., 2013; Painter et al., 2015; Slotnick & Thakral, 2011; Silvanto et al., 2006; Strong et al., 2017; Strong et al., 2019; Tadin et al., 2011; Talelli et al., 2007; Thakral & Slotnick, 2011; Yousif et al., 2016) which brings into question whether TMS studies in general possess sufficient statistical power or are the findings a result of idiosyncratic tendencies (i.e., type I errors). Second, the stimulation site was localized using averaged Talairach coordinates from structural MRI scans mapped onto a brain atlas rather than localized using functional MRI scans specific to the subject. However, given the consistency of MT+/V5's structural location (see Dumoulin et al., 2000) and size (LH = 202 ± 55 mm^2, RH = 265 ± 71 mm^2; see Kolster et al., 2010), our procedure in targeting MT+/V5 using the Brainsight TMS neuronavigation system and stimulating with the Magstim D70 Alpha 70 mm figure-8 coil that has a focality of 15 cm^2 (150 mm^2; Deng et al., 2014) should have been sufficient. Lastly, a competing method for determining motor threshold in research is measuring motor evoked potentials (MEP) using electromyography (EMG-MT). This process involves identifying a reliable frequency and scalp location over M1 that elicits an MEP response of around 100 μV. Then, an MEP response of at least 50 μV is determined using a descending frequency procedure in 50% of 10-20 consecutive low-

frequency (1 Hz) TMS using single pulse stimulation (Rothwell et al., 1999). However, there are mixed findings on the effectiveness and safety when comparing the OM-MT and MEG-MT methods for determining motor threshold (Balslev et al., 2007; Conforto et al., 2004; Hanajima et al., 2007; Pridmore et al., 1998; Westin et al., 2014) and the consensus on which method to use is unclear (Anderson & George, 2009). The OM-MT method was used because this method is often utilized in clinical treatment environments with supporting validity (Varnava et al., 2011), but more testing is needed to determine which method for determining the motor threshold is effective and safe for administering TMS.

CHAPTER 6

CONCLUSION

In summary, these findings demonstrate that iTBS and cTBS to the right MT+/V5 do not significantly change tracking performance in a MOT task across time despite recent claims. This may be due to MT+/V5 playing a more critical role in the maintenance for motion information in memory for goal-oriented moving stimuli instead of tracking already attended moving stimuli which a typical MOT task is unable to capture. These findings indicate that more research is needed to determine the role of MT+/V5 when selective and divided attention is used to track multiple moving objects.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

This research was approved by the Institutional Review Board at Arizona State University under STUDY00006050

APPROVAL:CONTINUATION

Marco Santello
IAFSE-BHSE: Bioengineering, Harrington Department of
480/965-8279
Marco.Santello@asu.edu

Dear Marco Santello:

On 2/22/2023 the ASU IRB reviewed the following protocol:

Type of Review:	Modification and Continuing Review
Title:	Neural and behavioral basis of sensorimotor control and learning
Investigator:	Marco Santello
IRB ID:	STUDY00006050
Category of review:	
Funding:	Name: NSF-SBE: Division of Behavioral & Cognitive Sciences (BCS), Grant Office ID: FP00032336; Name: NSF: Directorate for Social, Behavioral & Economic Science (SBE), Grant Office ID: 00014638, Funding Source ID: 1827752
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Attention, Memory & Stimulation Research Study_flyer.pdf, Category: Recruitment Materials; • Consent Form_mod4.pdf, Category: Consent Form; • Eligibility form for Brain stimulation experiments.pdf, Category: Recruitment Materials; • Study Recruitment Form_mod4.pdf, Category: Recruitment Materials;

The IRB approved the protocol from 2/22/2023 to 8/21/2023 inclusive. Three weeks before 8/21/2023 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 8/21/2023 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc: Archana Shashidhar Mysore
Gene Brewer
Aishwarya Haradanahalli Krishna Murthy
Gabriel De La Rocha
William Noll
Lohita Mallavarapu
Myles Alucard
Simone TOMA
Marco Santello
Emmanuella Tagoe
Archana Shashidhar Mysore
Maya Eleff
Christopher Blais
Yen-Hsun Wu
Michael Ruta