UNIVERSITY OF CALIFORNIA, MERCED

Perturbations to cognitive systems and downstream effects on behavior

A dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Cognitive & Information Sciences

by

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2021

This dissertation is dedicated to my love, Cory.
Thanks for hanging in there with me.
Let's go live our life now!

To Sasha and Epona,
Y'all deserve co-authorship at this point.
To my family,
For being supportive even if you don't have a clue what I'm doing.
To my Nana,
I am thankful for you always.

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the Arduino sent a command to begin the sequence of flashes with the 10mm LED at different interval durations. The photoreceptor and laser were placed at the same height as the trigger for the motion capture system to begin recording data, ensuring that the beginning of the visual sequence and the flashing lights were time-locked.

1.3. Time spent in the extension, flexion, and holding phases across auditory and visual tapping conditions with error bars depicting standard error of the mean. Extension time and holding time were found to significantly differ across interval duration, demonstrating that both the upward phase of movement and the holding phase are used for error correction despite changes in tapping style or stimulus modality. Flexion time was found to significantly differ across both stimulus modality and tapping style but not interval duration, serving as a co-contributor to error correction.

1.4. A) Extension velocity for the interval durations (500, 750, 1000ms) for each tapping style (synchronization and syncopation) with error bars reflecting standard error of the mean. Extension velocity significantly differed across all three interval durations, decreasing as the interval duration increased. Extension velocity did not differ across tapping style or stimulus modality (auditory and visual stimuli). The variance of extension velocity significantly increased during visual timing and syncopation to stimuli. B) The absolute value of flexion velocity for each interval duration (500, 750, and 1000ms) and each tapping style with error bars reflecting standard error of the mean. Flexion velocity differed as a function of tapping style, observing a decrease in velocity during syncopation compared to synchronization. The variance of flexion velocity significantly increased during visuomotor timing compared to auditory-motor timing, and also significantly increased during syncopation compared to synchronization. Both figures depict the marked asymmetry between flexion and extension velocity, with much more emphasis placed on flexion than on extension.

1.5. Distribution of asynchronies for each condition with error bars depicting standard error of the mean. In general, asynchrony across all conditions grew larger as the interval durations increased, as predicted by Weber's law. The variance of asynchrony significantly increased during visuomotor timing compared to auditory timing, increased during syncopation compared to synchronization, and also increased as interval duration increased.

2.1.The top panel depicts the subject's view of the experiment, and the bottom screen depicts the left (green) and right (purple) hand speed of all trials for equidistant conditions.

2.2. Response time of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

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Pabst, A., & Balasubramaniam, R. (2018). Trajectory formation during sensorimotor synchronization and syncopation to auditory and visual metronomes. *Experimental brain research*, 1-10.

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Wang, E., Pabst, A., & Balasubramaniam, R. (2019). Motor Sequence Learning: Using Arm-Reaching Task for Learning. Poster presented at the *2019 UROC Undergraduate Research Symposium,* Merced, CA.

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Abstract

Human action and perception are dependent upon continuous interactions between the brain, the body, and the environment. Our expectations of how to function in the world around us are largely determined by affordances within our environment and our bodies, and when our predictions are disturbed or perturbed, we need to determine how to behave in a novel and adaptive way given a new set of affordances. In this dissertation, I examine different ways in which the brain and body respond to perturbations from the environment by studying these perturbations effects on behavior. In the first chapter, I conducted a study to determine how humans respond to sequences of auditory and visual stimuli, and how errors in their timing to stimuli are corrected by one's own movement. In the second chapter, I investigate how the human body, specifically the arms, responds to drastic changes in haptic sensation using elastic and viscous forces on the hands during reaching movements. The third chapter extends the definition of perturbation to include exogenous perturbations to the brain using transcranial magnetic stimulation. The motor cortex and posterior parietal cortex were modulated to be less responsive during consolidation of motor and declarative skills, and I examined how participants used different strategies to adapt to this perturbation. In the fourth chapter, I used meta-analytic methods to determine what, if any, commonalities exist among participants who received perturbations using facilitatory transcranial magnetic stimulation to the brain to determine if this method enhances cognition. This work is intended to add further insight into the connections between the human brain and body, and how we respond behaviorally when perturbations are introduced to our systems, which include the environment we operate in. This dissertation, Perturbations to cognitive systems and downstream effects on behavior, is submitted by Alexandria Pabst in the summer of 2021 in partial fulfillment of the degree Doctor of Philosophy in Cognitive and Information Sciences at the University of California, Merced, under the guidance of Ramesh Balasubramaniam.

Prologue

Imagine you are an actor in a stage performance. It is opening night of your show, and you have practiced your lines and body movements to the point of memorization. You could even close your eyes and simulate different rehearsals, both from past experience and in newly imagined scenarios. You have practiced different line deliveries, different dance techniques, and know where each and every prop of yours is available to access backstage. Your brain has essentially created a mental model to predict how you will perform. Our brains continuously update this information based on inferences that we make from what we perceive in the environment. For instance, if you hear a loud crowd before the curtain is pulled up, you use that information to update your anticipated state – you might prepare to engage your diaphragm more so that you can project your voice further into the crowd. You also might use this information to lay humor on thicker during delivery of your lines, or even use your body to exaggerate behaviors to draw out more laughs from the audience.

In this example, your brain is using information from the environment to predict how you should behave to achieve your goal state. What is unique about the human brain is that it adapts incredibly quickly when predictions do not match up with what is being experienced in the real world. As an actor, it is often the case where someone could forget their lines, an emergency could happen in the theater, or an audience member's phone could go off and interrupt the flow of the performance. Actors and performers are great examples of how to overcome unexpected situations and quickly adapt because the show must go on. Some adaptations are inherent to the human brain and body, while other cases of adaptation are grounded in context and experience.

The human brain receives external information through the sensory receptors, including pain- and touch-receptors in the skin, through photoreceptors in the retina, cilia in the cochlea, and taste receptors on the tongue. This sensory information from our body and the environment is transduced into neural signals called action potentials that stimulate neurons and carry information about the current environmental state. These action potentials are processed by many areas in the brain so quickly and efficiently that humans can respond behaviorally in millisecond ranges. This is especially important in many scenarios, including but not limited to: threat response, postural and motor commands, and making critical evaluations. Areas of the brain that are integral to updating our predictions for future action include the motor system, where the cerebellum exchanges afferent sensory information with the motor system's efferent sensory outputs via the inferior olivary nucleus (Von Helmholtz, 1867; von Holst & Mittelstaedt, 1950; Sperry 1950; Wolpert et al., 1998; Wolpert & Flanagan, 2001). Even in the smallest deviances, which may even be produced by one's own behavior, are recognized and accounted for.

In the context of this dissertation, I envelop these mismatches in predictions between the produced behavior and expected behavior as perturbations. Perturbations don't necessarily need to come from the

environment – they can be directly applied to the brain or body, or even produced by the system controlling it. This dissertation aims to understand how perturbations, when applied to a cognitive system, affect the system's resulting behavior. A cognitive system in this context is defined as a dynamical system whose behavior is influenced by past experience and is shaped by the context surrounding it. This encompasses the brain, the body, and the environment together working as a single unit.

To understand how our brains and our bodies both operate within an environment, we can investigate how humans correct their own prediction errors. Sensorimotor timing is a thoroughly investigated field in which many studies have been conducted to determine the neural correlates of timekeeping processes and to understand how our movements adapt in response to perturbations in the stimulus or violations in expectancy. Chapter 1 directly compares visual and auditory sensorimotor synchronization and syncopation with the finger. Whether we are consciously aware of timekeeping errors being made while entraining to a rhythm, our current movements are heavily influenced by prior movements. I investigated the different phases of finger movement, specifically flexion, extension, and holding phase, that act as error correction processing during timekeeping behaviors.

Finger tapping and timekeeping behaviors are just one paradigm that allows us to understand how humans respond to perturbations. These perturbations are caused directly by the system that created the movement, so what happens when perturbations from external forces are introduced to a cognitive system? Chapter 2 scales up the investigation into how the body responds to environmental perturbations – specifically the impact of forces on the arms. I simulated elastic and viscous environments in which participants were instructed to perform bimanual reaching behaviors. These environments are not commonly encountered in everyday human experience. As such, it is important to determine how a system would respond in a novel scenario with naturalistic movement behaviors.

Applying perturbations to the body is one avenue for determining how humans respond when environmental conditions are manipulated. In Chapter 3 and 4, I investigate the impact of perturbations applied directly to the brain by way of transcranial magnetic stimulation (TMS). I focus on TMS applications that facilitate and inhibit neural populations to determine how modulation of different cortical areas influences downstream behavior in a variety of contexts. TMS has been promising in the case of altering behavior that has been impacted by disease, specifically in the cases of psychiatric disorders like depression (O'Reardon et al., 2007). However, it is relatively unclear how TMS can alter behavior in healthy populations, as individuals variably respond to TMS and its various patterns of stimulation. Chapter 4 aims to address this issue by employing meta-analytic methods to determine if facilitatory theta-burst stimulation, one pattern of stimulation notorious for its variability in effects across subjects, can enhance healthy human behavior.

Finally, in the Epilogue of this dissertation, I position the findings of this work in relation to several theories that can account for human adaptation to prediction error and how this can be followed up with future experimentation. This dissertation employs a wide variety of methodologies to determine how humans adapt to errors in prediction, to novel environments, and to chemical changes in the brain. I propose the use of mixed-methods to examine changes in an entire cognitive system when perturbations are applied to better determine the pathways of adaptive behavior.

Chapter 1
Trajectory formation during sensorimotor synchronization and syncopation to auditory and visual metronomes

Previous work on sensorimotor synchronization has investigated the dynamics of finger tapping and how individual movement trajectories contribute to timing accuracy via asymmetry in movement velocities. The present study investigated sensorimotor synchronization (in-phase) and syncopation (anti-phase) to both an auditory metronome and a visual flashing light at multiple frequencies to understand how individual movement phases contribute to the variability of timekeeping and error correction in different sensory modalities and with different task constraints. Results demonstrate that the proportional time spent in both the upward phase of movement and the holding phase of movement (time spent on the surface of the table) remain relatively invariant across both stimulus modalities and across tapping styles (syncopation and synchronization), but changes with interval duration, increasing as interval duration increases. The time spent in the downward phase of movement did significantly differ across stimulus modality and tapping style, increasing during both visuomotor timing and syncopation, accompanied by a significant decrease in flexion velocity during syncopation. Extension velocity and flexion time were found to be the main contributors to differences between visual and auditory timing, while flexion velocity and flexion time were found to be the main contributors to differences between synchronization and syncopation. No correlations were found between asynchrony and the upward, downward, or holding phases of movement, suggesting the existence of multiple error correction strategies.

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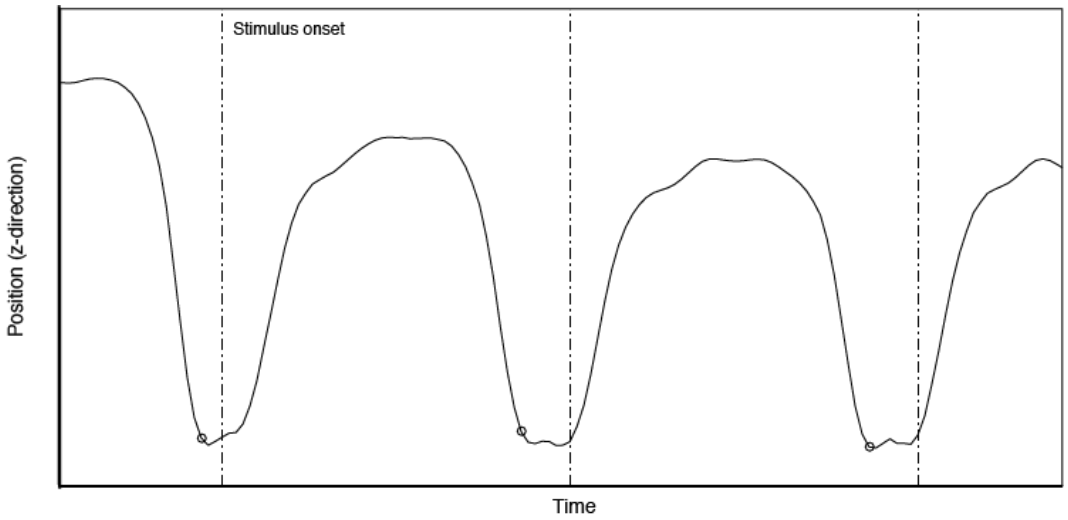
Introduction

Sensorimotor synchronization is the process by which humans coordinate their movements to a repetitive stimulus in the environment, most commonly investigated using a simple finger tapping paradigm (for an extensive review on sensorimotor synchronization, see Balasubramaniam 2005; Repp 2005; Repp and Su 2013; Ross and Balasubramaniam 2014; Comstock et al. 2018). Previous studies have focused on understanding the theoretical implications for neuro-entrainment and sensorimotor synchronization to various stimuli, diverging in opinion between the traditional information processing approach (Vorberg and Hambuch 1984; Vorberg and Wing 1996; Schulze and Vorberg 2002; Doumas and Wing 2007; Delignières et al. 2009) and more recent theory from the dynamical systems approach (Ross and Balasubramaniam 2014;

Balasubramaniam 2005; Riley and Turvey 2002). Very few studies, however, have investigated the contribution of movement trajectories in the flexion, extension, and holding phases to error correction processes, or have compared these trajectories across visual and auditory modalities (Krause et al. 2010; Hove and Keller 2010 for visuomotor synchronization; Balasubramaniam et al. 2004 for auditory synchronization; Repp 2003; Kurgansky 2008; Hove et al. 2013; Lorås et al. 2012; Sugano et al. 2012). A visual depiction of the three phases of movement comprising a trajectory (flexion, extension, holding) in response to a stimulus is found in Fig. 1.1. Even fewer studies have clearly addressed differences between synchronization and syncopation, the action of tapping between beats in an isochronous metronome sequence, irrespective of stimulus modality (Balasubramaniam 2005; Mayville et al. 2001).



1.1 A typical movement trajectory in response to a metronome, with the upward movement representing extension, the downward movement toward the beat (in synchronization) representing flexion, and the non-movement stabilization referring to the holding phase (the onset of which is marked with an open circle). A custom MATLAB program was built to identify the different trajectory phases of each trial and calculate the time spent in each trajectory. Holding phase is calculated as the time spent in a non-movement phase when velocity reaches 9.5% of the maximum velocity achieved over the course of an individual trial. Extension is calculated as the time spent when the velocity is greater than the 9.5% minimum and the acceleration of the trajectory is positive. Flexion is calculated as the time spent when velocity is greater than 9.5% of the maximum velocity for that trial and the acceleration of the trajectory is negative.

Torre and Balasubramaniam (2009) investigated the extent to which both information processing theory and dynamical systems theory represent timekeeping in the context of auditory sensorimotor synchronization, and if the two theories account for different aspects of timing and synchronization. One way to test this is to control the type of additional incoming sensory stimulation in the

presence of an auditory metronome; Torre and Balasubramaniam (2009) compared kinematics between auditory–motor synchronization trials with intermittent haptic feedback (tapping) and auditory–motor trials with continuous haptic feedback (oscillations, i.e., circular finger movements with continuous finger-to-table contact). They showed significantly higher timing variability in synchronized oscillations than synchronized tapping, and suggested that this could be due to peripheral sensory feedback during finger tapping perpetuating consistent error correction processes. Asynchrony is defined as the arrival of the effector in response to a stimulus during timing tasks relative to the onset of the stimulus, and can be either negative or positive (see Repp 2005 for discussion on negative mean asynchrony). The three phases of the finger tap movement are disproportionately adjusted to optimize the trajectory of the finger in order to ensure that the tap occurs on time with the target stimulus. These three tap phases, therefore, are adjusted continuously in order to minimize timing asynchronies. Torre and Balasubramaniam (2009) observed a strong negative correlation between asynchrony and the duration of the immediately following extension cycle for synchronized finger tapping, which suggests that the late arrival of the finger is compensated by a shorter return phase and conversely for early arrival. Thus, the duration of time spent in extension phase in repetitive timing tasks may help with requirements of precision and accuracy relative to a target event, but it is unknown how the holding phase of movement contributes to consistent error correction. Torre and Balasubramaniam (2009) and Balasubramaniam et al. (2004) both compared the extension and flexion phases of repetitive finger tapping and repetitive finger oscillations, whereas the current study aims to examine the error correction mechanisms involved in tapping synchronization and syncopation in both auditory and visual modalities. Our specific interest is in how the holding phase (i.e., period of non-movement between extension and flexion) contributes to reducing timing errors.

No studies have directly compared the kinematics of synchronization and syncopation across auditory and visual domains. The present study aimed to both replicate and test hypotheses. The first hypothesis was that we would replicate Hove et al. (2013) in the visual modality, supporting that an increase in positive mean asynchrony would be accompanied by a decrease in interval duration. Along with this replication, we expected a marked asymmetry in movement velocity between the flexion and extension phases in both modalities: greater flexion velocity than extension velocity (Balasubramaniam et al. 2004), and a Weber-like increase in variability with increased interval duration (Gibbon 1977). The second hypothesis was that we would find three novel effects: (1) the kinematics of movement would differ between auditory and visual timing because they likely reflect separate underlying neural processes (Comstock and Balasubramaniam 2018); (2) that kinematics of synchronization and syncopation for visual and auditory metronomes would differ, reflecting separate neural pathways for synchronized and syncopated movements (Mayville et al. 2001); (3) auditory and visual metronome modality would affect correlations between relative asynchrony (the average asynchrony per trial subtracted from the raw

asynchrony of each interval) and the three phases of movement. Negative correlations were expected to occur between relative asynchrony and the extension and holding phases with an auditory metronome. Weaker correlations were expected between relative asynchrony and all three phases of movement for visuomotor timing because of proposed weaker temporal coupling for the visuomotor system (Comstock and Balasubramaniam 2018).

Methods

Participants

Seventeen undergraduate participants (15 female, 2 male; aged 18–32 years) at the University of California, Merced, were recruited from the undergraduate subject pool and completed this experiment for course credit. The protocol was approved by the UC Merced Institutional Review Board (IRB) and informed consent was given prior to participation. None of the participants reported having any neurological or motor issues that would prevent them from completing the study. All participants reported normal or corrected vision and no auditory atypicalities. All participants reported being right-handed. Seven participants reported having some musical experience with a range of 2–4 years of experience (additive) with a wide range of instruments, including guitar (2 years), violin (1–2 years), clarinet (2–3 years), and piano (2 years). Musical experience was not found to have main effects on any of the dependent variables analyzed, and thus was not used for further analysis. Dance experience was collected on a pre-experiment questionnaire, but was also not used for further analysis due to large variability of experience across participants.

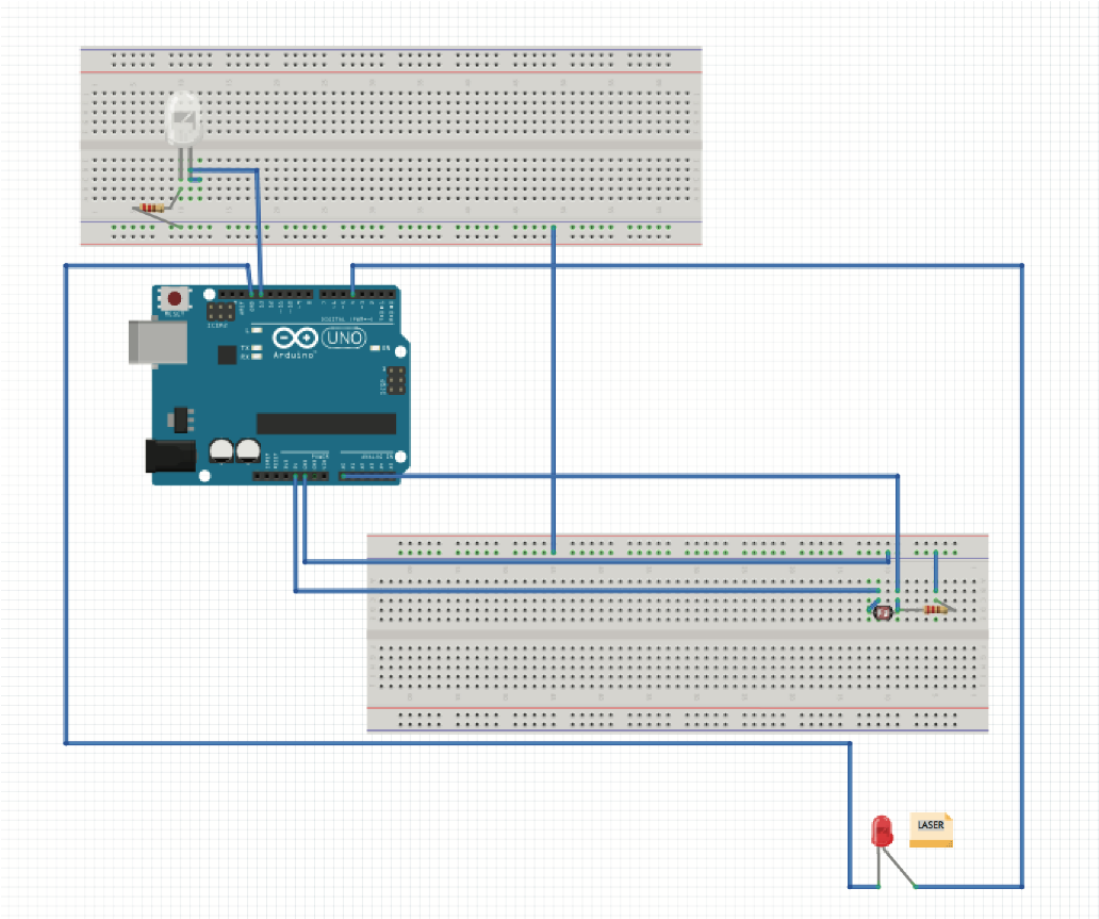
Procedure

A VICON™ motion capture system with eight Bonita B10 cameras was used for data collection. Data were collected at a sampling rate of 100 Hz. Participants were instructed to sit down at a (740 mm) high table in the center of the recording space. After obtaining informed consent, participants were briefed on the experimental procedures, and were asked to place their right hand on the table in a comfortable position. Participants were outfitted with four Vicon 14 mm reflective markers on their right hand. Markers were placed on the left ulnar projection of the wrist, the right radial projection of the wrist, and the medial metacarpal for stabilization, and another marker was placed on the distal phalanx of the index finger. Participants were told that they would hear a series of beats, and they would be instructed to either tap along to the beat or tap in between every beat. Participants were also instructed to tap along to the beat of a flashing light or in between flashes. Tapping movements in these visual and auditory conditions were captured in two separate counterbalanced blocks, and the trials within these blocks were randomized by tapping style (i.e., synchronization or syncopation with the stimulus) and interval duration (500, 750, 1000 ms). There were five trials per condition (12 conditions total) with 30 cycles per trial (60 trials total). Participants practiced syncopating and synchronizing with each interval duration for both auditory and visual condition types until they were comfortable

with performing the task in all conditions. Our factors for statistical analyses were stimulus modality (auditory vs. visual), musical experience (having two or more years of musical experience vs. having no musical experience), tapping style (synchronization and syncopation), and interval duration (500, 750, and 1000 ms intervals). The experimenter prompted the participant on the correct tapping style before the start of every trial. After the experiment, participants were asked to complete a brief survey collecting demographic information, including musical experience, dance experience, and languages spoken.

Stimuli

Participants were instructed to perform repetitive tapping movements with the right index finger that either synchronized or syncopated with the following stimuli: an auditory metronome or flashing light, delivered at inter-onset intervals of 1000 ms (1 Hz), 750 ms (1.33 Hz) or 500 ms (2 Hz). A 20-ms sine wave metronome with no ramp was created using Sound Studio 4.5.4.7z software and transformed into .wav files (16 bit 44,000 Hz). A period of silence equivalent to the stimulus IOI preceded presentation of the first tone of each auditory stimulus, and then used to space the subsequent tones for a total of 30 tones per trial. Participants listened to the metronome sequences through Sennheiser HD 280pro headphones. The volume of the headphones was set to 70 dB. One participant complained about the volume of the auditory stimuli, and their headphone volume was lowered to a comfortable level (65 dB). They were not excluded from the analysis. Visual stimuli were produced through Arduino 1.8.4 software and delivered to a circuit containing a 10-mm white LED, flashing for 20 ms at intervals of 500, 750, and 1000 ms. Participants completed the visual tapping block in semi-darkness with the light from the LED and the computer screen being the only light sources. 5 V were delivered to the LED and had a luminance of 18–20 cd, which was visible enough for participants to verbally confirm that they could focus and see the stimulus. No subjects indicated that they could not see the visual stimulus. The flash of light was delivered 30 times per trial. A custom laser tripwire was created so that the LED began flashing when the laser beam was crossed at the z-threshold. A diagram of this visual metronome generator is depicted in Fig. 1.2. Both auditory and visual stimuli were delivered through the Vicon Nexus software and time-locked with the motion capture recording using a z-threshold trigger matching the LED stimulus tripwire.



1.2 A circuit diagram of the custom laser tripwire created to begin start the sequence of flashing lights in the visual conditions. An Arduino Uno R3 was supplied power via USB and was connected to a breadboard hosting a photoreceptor and additionally was connected to a laser-pointer. When the beam of light emitting from the laser that was pointed at the photoreceptor was broken, the Arduino sent a command to begin the sequence of flashes with the 10mm LED at different interval durations. The photoreceptor and laser were placed at the same height as the trigger for the motion capture system to begin recording data, ensuring that the beginning of the visual sequence and the flashing lights were time-locked.

Analysis

Vertical movement trajectories were extracted and analyzed using a custom MATLAB R2015b (Mathworks, Natick, Mass., USA) script. Data was filtered using a fifth-order Savitzky–Golay filter (frame size 13 samples), and then velocity and acceleration were calculated. The movement phases of each tap were extension (up), followed by flexion (down), and the subsequent holding phase (dwell, on the surface of the table), shown in Fig. 1.1. Each finger tap movement cycle time was calculated by combining the time spent in flexion, extension, and holding phases for each respective tap. Holding phase was

calculated by measuring the time spent when the finger trajectory velocity was less than or equal to 9.5% of the maximum velocity per trial, using the procedure outlined in Balasubramaniam et al. (2004). Flexion and extension were calculated by using negative and positive velocity as identifiers, because we decelerate during flexion and accelerate during extension. Trials were visually inspected individually; any trial missing 5 taps was excluded from further analysis, and extra taps. It is important to underscore that these three-movement phases are defined in a functional manner using kinematic data, and do not necessarily correspond to muscular activation or biomechanical properties of finger flexion and extension. Asynchrony was calculated as the time from the beginning of the holding cycle to the onset of the stimulus, identified by the holding time that was closest to a metronome event. In the synchronization conditions, negative asynchrony indicates that the tap preceded the metronome event (beep/flash), while positive asynchrony indicates that the tap occurred after the metronome event. Measuring asynchrony in syncopation conditions was done in the same way, but instead of in reference to the metronome events was in reference to the halfway point between metronome events. Cross-correlations were calculated between relative asynchrony and the immediate subsequent extension time, flexion time, and holding time. Relative asynchrony was calculated as the mean asynchrony subtracted from each individual asynchrony per trial. A grand average correlation per condition was calculated by averaging the Fisher-transformed correlation scores of each individual trial and back-transforming the averages using the inverse of the Fisher function.

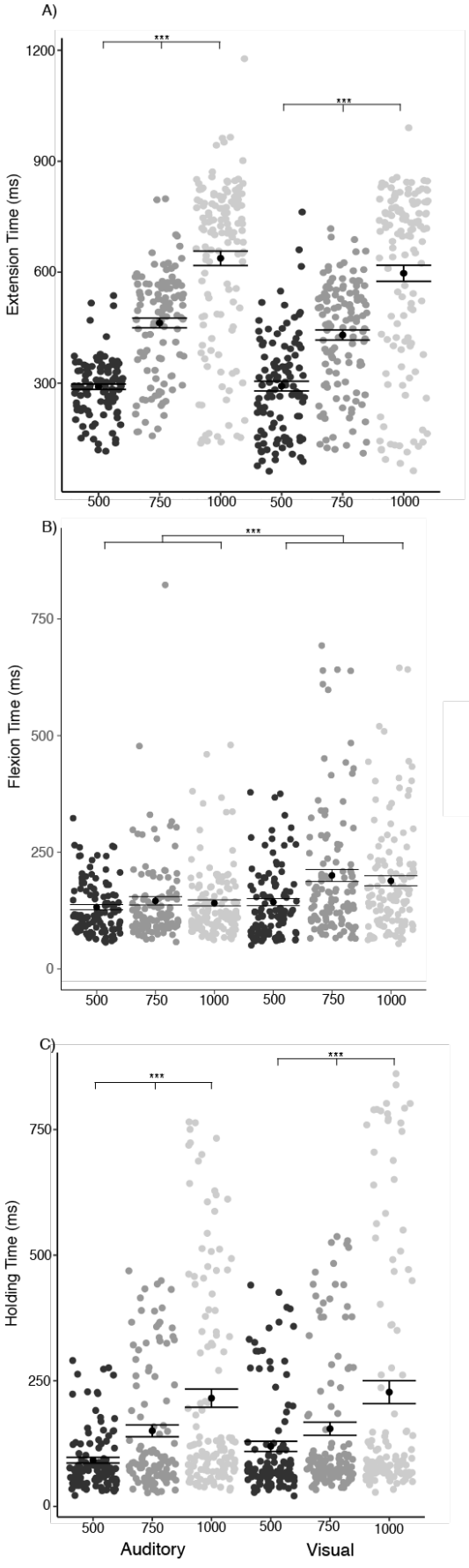
Results

We analyzed the effects of stimulus modality (auditory vs. visual), tapping style (synchronization and syncopation), and interval duration (500, 750, and 1000 ms intervals) on extension time, flexion velocity and asynchrony with linear-mixed effects models. These same effects were also analyzed on flexion time, holding time, and extension velocity using linear-mixed effects models using the log-normal distribution of the data. In addition, the same analyses were calculated on the variance of each dependent variable, with linear-mixed effects models run on the variance of extension time and holding time, and linear-mixed effects models using the log-normal distribution of the data on the variance of flexion time, extension and flexion velocity, and asynchrony, a total of 12 linear models run. Results reported from linear-mixed effects models report the estimate and 95% confidence intervals. Values reported using the log-normal distribution of the data are using the back-transformed estimates and confidence intervals of the transformed data. Estimates and confidence intervals for significant effects on variance are reported as standard deviation. Both analyses used the lmer4 package (Bates et al. 2015) in the R environment (R development core team 2015). In all models, participants and trial order were specified as random intercepts. Visual inspection of the residual plots did not reveal any obvious violations of homoscedasticity or normality. p values were obtained for

the linear-mixed effects models through the lmerTest package in R (Kuznetsova et al. 2017). The significance threshold was set to 0.05.

Timing of movement trajectories

Linear-mixed effects modeling revealed that extension time did not differ across stimulus modality or tapping style, but did differ significantly across interval durations (see Fig. 1.3). Time spent in extension phase during 750-ms interval durations compared to the time spent in extension phase during 500-ms interval durations significantly increased by 150.61 ms [95% CI (104.03, 197.20), $p<.001$]. Additionally, time spent in extension phase during 1000-ms interval durations compared to the time spent in extension phase during 500-ms interval durations significantly increased by 339.37 ms [95% CI (293.50, 385.24), $p<.001$). No significant interaction effects were found for extension time. No significant main effects or interactions occurred for the variance of extension time.


A)
Extension Time (ms)
1200
900
600
300
***
***
500
750
1000
500
750
1000
B)
Flexion Time (ms)
750
500
250
0
***
500
750
1000
500
750
1000
C)
Holding Time (ms)
750
500
250
0
***
***
500
750
1000
500
750
1000
Auditory
Visual

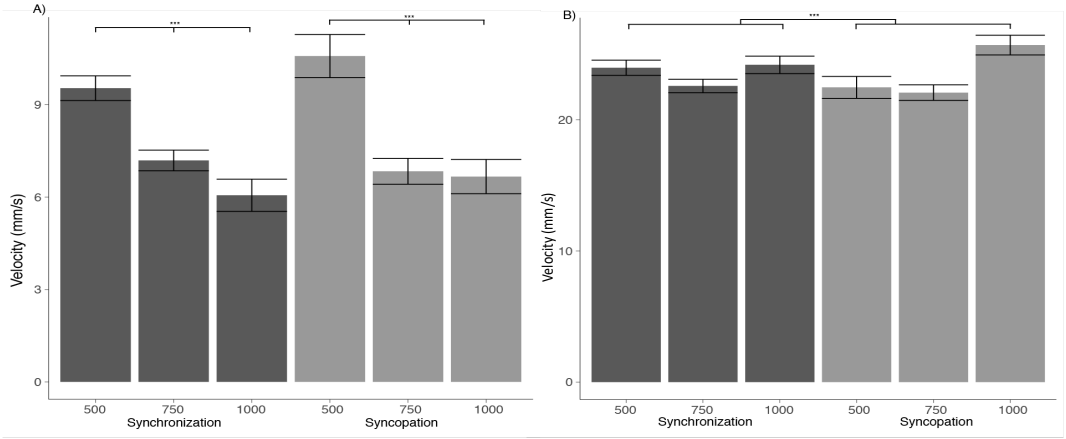
1.3 Time spent in the extension, flexion, and holding phases across auditory and visual tapping conditions with error bars depicting standard error of the mean. Extension time and holding time were found to significantly differ across interval duration, demonstrating that both the upward phase of movement and the holding phase are used for error correction despite changes in tapping style or stimulus modality. Flexion time was found to significantly differ across both stimulus modality and tapping style but not interval duration, serving as a co-contributor to error correction.

Linear–mixed effects models revealed that flexion time differed across both stimulus modality and tapping style, and only the 1000-ms interval duration (see Fig. 1.3). Time spent in flexion phase while tapping to a visual stimulus compared to tapping to an auditory stimulus increased by 1.18 ms [95% CI (1.02, 1.36), p=.02]. Additionally, tapping in syncopation with a stimulus compared to tapping in synchronization with a stimulus increased time spent in the flexion phase by 1.39 ms [95% CI (1.18, 1.62), p<.001]. Compared to 500-ms interval durations, tapping at 1000ms interval durations increased flexion time significantly by 1.15 ms [95% CI (1.01, 1.32), p=.04), and no main effect of interval duration was found 750 ms intervals. A significant interaction between tapping style and stimulus modality was found on flexion time, with flexion time significantly decreasing by 2.34 ms [95% CI (−1.67, −1.08), p=.009] during syncopation with visual flashes compared to synchronization with auditory tones. Main effects of stimulus modality, tapping style, and interval duration were found on the variance of flexion time. Flexion time variance increased during visuomotor timing compared to auditory timing by 1.99 ms [95% CI (1.40, 2.83), p<.001]. Compared to synchronization, syncopation increased flexion time variance by 2.80 ms [95% CI (1.92, 4.10), p<.001]. Tapping at 750-ms interval durations compared to 500-ms interval durations increased flexion time variance by 1.45 ms [95% CI (1.03, 2.03), p=.03], and tapping at 1000-ms interval durations compared to 500-ms interval durations increased flexion time variance by 1.63 ms [95% CI (1.17, 2.28), p=.004]. A significant interaction was observed for flexion time variance between tapping style and stimulus modality: flexion time variance significantly decreased during visuomotor syncopation compared to audiomotor synchronization by 2.97 ms [95% CI (−5.07, −1.73), p<.001].

For holding time, a main effect of interval duration was observed. Tapping at 750-ms interval durations compared to 500-ms interval durations increased time spent in the holding phase by 1.62 ms [95% CI (1.33, 1.97), p<.001]. Tapping at 1000-ms interval durations compared to 500-ms interval durations also increased holding time by 1.89 ms [95% CI (1.55, 2.30), p<.001]. No significant interactions were observed with holding time. Interval duration had a main effect on the variance of holding time, with variance increasing when tapping to a 1000-ms metronome by 80.50 ms [95% CI (50.73, 101.92), p=.001].

Analysis of velocity profiles

For extension velocity, main effects were observed across interval duration, shown in Fig. 1.4. Compared to tapping at a frequency of 500 ms, tapping at an interval duration of 750 ms significantly decreased velocity by 1.42 mm/s [95% CI (−1.63, −1.24), p<.001), while tapping at a frequency of 1000 ms decreased extension velocity by 1.99 mm/s [95% CI (−2.27, −1.74), p<.001]. No significant interactions were observed for extension velocity. Main effects of tapping style, stimulus modality, and interval duration were found on the variance of extension velocity. During syncopation, the variance of extension velocity increased by 1.57 mm/s [95% CI (1.25, 1.98), p<.001] compared to tapping in synchronization with stimuli. Visuomotor timing compared to audiomotor timing increased the variance of extension velocity by 1.48 mm/s [95% CI (1.20, 1.82), p<.001]. Compared to tapping at an interval duration of 500 ms, tapping at 1000-ms interval durations decreased extension velocity variance by 1.48 mm/s [95% CI (−1.80, −1.21), p<.001], however this same decrease in variance was not observed for 750-ms interval durations. A significant interaction was found between stimulus modality and tapping style: tapping in syncopation with a visual stimulus compared to synchronizing with auditory tones decreased the variance of extension velocity decreased by 1.41 mm/s [95% CI (−1.94, − 1.02), p = .04]. No other interaction effects were observed for the variance of extension velocity.



1.4 A) Extension velocity for the interval durations (500, 750, 1000ms) for each tapping style (synchronization and syncopation) with error bars reflecting standard error of the mean. Extension velocity significantly differed across all three interval durations, decreasing as the interval duration increased. Extension velocity did not differ across tapping style or stimulus modality (auditory and visual stimuli). The variance of extension velocity significantly increased during visual timing and syncopation to stimuli. B) The absolute value of flexion velocity for each interval duration (500, 750, and 1000ms) and each tapping style with error bars reflecting standard error of the mean. Flexion velocity differed as a function of tapping style, observing a decrease in velocity during syncopation

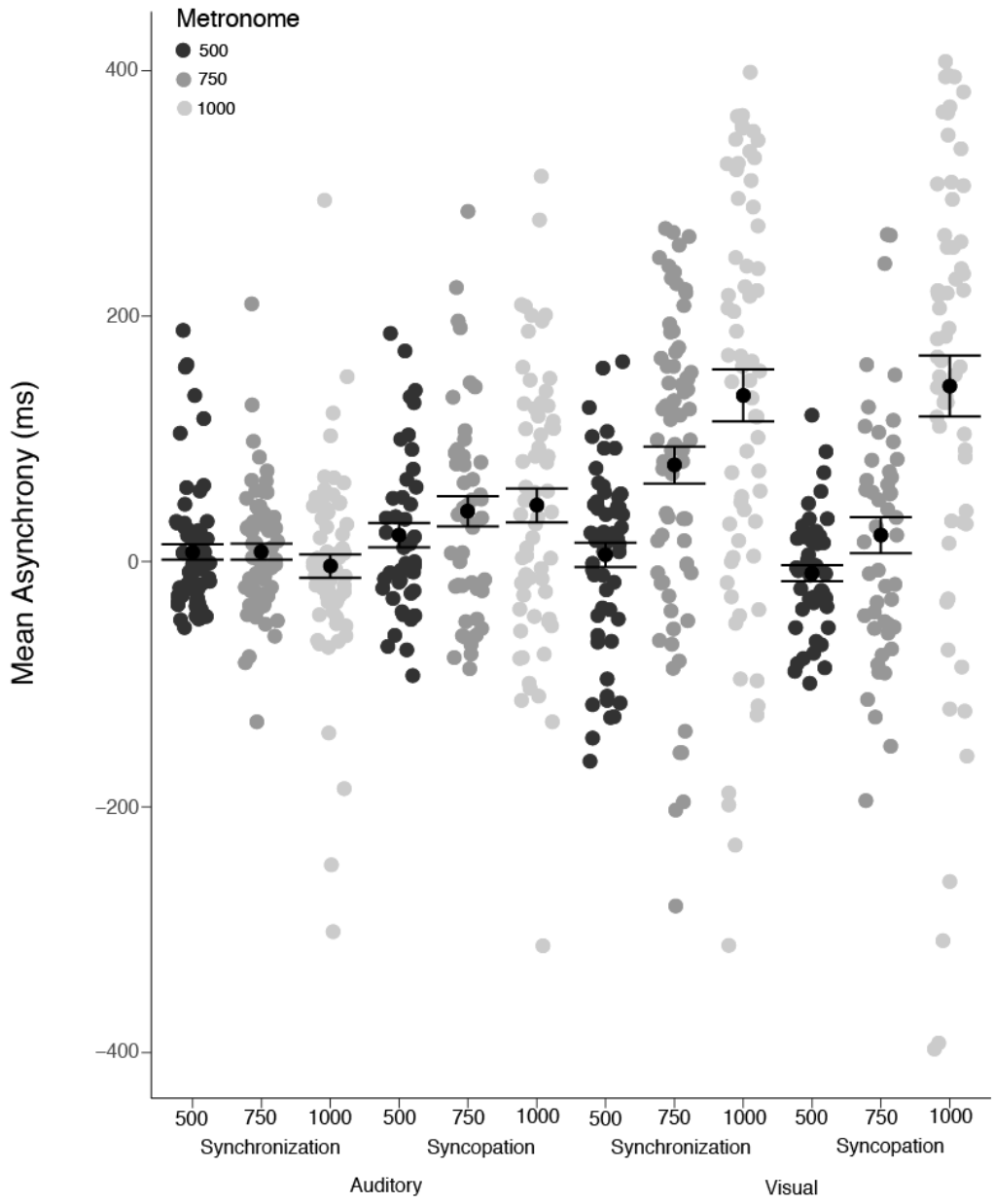
compared to synchronization. The variance of flexion velocity significantly increased during visuomotor timing compared to auditory-motor timing, and also significantly increased during syncopation compared to synchronization. Both figures depict the marked asymmetry between flexion and extension velocity, with much more emphasis placed on flexion than on extension.

For flexion velocity, a main effect of tapping style was found. Tapping in syncopation with a stimulus compared to tapping in synchronization with a stimulus significantly decreased flexion velocity by −3.80 mm/s [95% CI (−5.99, −1.60), p=.001]. Significant interactions were observed between stimulus modality and tapping style, and additionally between tapping style and the 1000-ms interval duration. Compared to synchronization with an auditory metronome, syncopating to visual flashes significantly increased flexion velocity by 4.08 mm/s [95% CI (0.98, 7.18), p=.01]. When tapping in syncopation with a rhythm at 1000-ms interval duration, comparative to tapping in synchronization with a rhythm at 500-ms interval durations, flexion velocity significantly increased by 3.66 mm/s [95% CI (0.72, 6.61), p=.02]. No other significant interactions were observed for flexion velocity. Main effects of both stimulus modality and tapping style were observed on the variance of flexion velocity. Tapping to a visual flash as opposed to tapping to an auditory tone increased flexion velocity variance by 1.45 mm/s [95% CI (1.27, 1.66), p<.001]. Tapping in syncopation to a stimulus compared to tapping in synchronization with a stimulus also increased flexion velocity variance by 1.47 mm/s [95% CI (1.27, 1.70), p<.001]. An interaction effect between tapping style and stimulus modality was observed on the variance of flexion velocity; the variance decreased by 1.43 mm/s [95% CI (−1.76, −1.17), p=.001].

Analysis of asynchrony measurements

No main effects on asynchrony were observed across conditions, however significant two-way interactions were observed between modality and interval duration (see Fig. 5). When tapping to a visual metronome at 750 ms, compared to tapping to an auditory metronome at 500 ms, asynchrony significantly increased by 75.94 ms [95% CI (24.99, 126.88), p=.004). Tapping to a visual metronome at 1000 ms, also compared to tapping to an auditory metronome at 500 ms, significantly increased asynchrony by 143.02 ms [95% CI (92, 194.03), p<.001). Error correction becomes much more variable in the visual modality as the frequency of the metronome decreases. No other significant interactions were observed on asynchrony. Main effects of stimulus modality, tapping style, and interval duration were all found on the variance of asynchrony. Visuomotor timing, compared to audiomotor timing, increased the variance of asynchrony by 2.78 ms [95% CI (2.38, 3.45), p < .001]. Syncopation, compared to synchronization, also increased asynchrony variance by 3.42 ms [95% CI (2.80, 4.18), p < .001]. Interval duration also increased asynchrony variance: compared to tapping at 500-ms interval durations, tapping at 750 ms intervals increased variance by 1.55 ms [95% CI (1.30, 1.86), p < .001], and tapping during 1000 ms intervals increased asynchrony variance by 1.90 ms [95% CI (1.59, 2.27),

p<.001]. Several interaction effects were observed across asynchrony variance. Visuomotor timing during syncopation as opposed to audiomotor timing during synchronization significantly decreased asynchrony variance by 2.88 ms [95% CI (−3.82, −2.17), p<.001]. Additionally, visuomotor timing during 1000-ms interval durations compared to audiomotor timing during 500-ms interval durations significantly decreased variance of asynchrony by 1.76 ms [95% CI (−2.28, −1.36), p<.001]. Tap style and interval duration also interacted: compared to synchronization at 500 ms intervals, syncopation during 750 ms intervals reduced the variance of asynchrony by 2.02 ms [95% CI (− 2.68, − 1.53), p < .001], and syncopation during 1000 ms intervals reduced the variance of asynchrony by 2.29 ms [95% CI (−2.99, −1.75), p<.001].



1.5. Distribution of asynchronies for each condition with error bars depicting standard error of the mean. In general, asynchrony across all conditions grew larger as the interval durations increased, as predicted by Weber's law. The variance of asynchrony significantly increased during visuomotor timing compared to auditory timing, increased during syncopation compared to synchronization, and also increased as interval duration increased.

No significant correlations between relative asynchrony and the immediate subsequent extension time, flexion time, or holding time were found in any conditions, indicating that variability surrounding asynchrony cannot be

attributable to individual movement phases, but rather is spread across the entire tapping interval itself.

Discussion

The purpose of this study was to explore the contribution of kinematics to timing processes by investigating the differences between synchronization and syncopation to visual and auditory stimuli. We were specifically interested in how the holding phase involving haptic feedback (finger contact with the table surface) contributes to the error correction process in timing. We successfully replicated Balasubramaniam et al. (2004) in their finding of a marked asymmetry between extension and flexion velocity, with faster flexion than extension. This asymmetry between flexion and extension velocities is demonstrated in Fig. 1.4. We did not find an increase in positive mean asynchronies as the interval duration of visual stimuli decreased, as shown by Hove et al. (2013). Our results instead support the opposite with an interaction between stimulus modality and interval duration: an increase in asynchrony as interval duration increased during visual timing compared to tapping to an auditory stimulus at a shorter interval duration. This could occur because of internally generated uncertainty surrounding the onset of visual stimuli at slower intervals, and participants have a more variable distribution of asynchronies during slower interval durations when tapping to visual stimuli (Kurgansky 2008). Increasing task constraints on a simple tapping paradigm would likely increase variability in performance, and our finding of increased asynchrony variance during visuomotor timing compared to audiomotor timing, during syncopation compared to synchronization, and during increased duration of the interval supports this. Furthermore, our predicted increase in Weber-like variance as interval duration increased was observed for the variance of both the holding time and flexion time of movement, demonstrating that the holding and flexion phases contributed the largest source of variance to the timing interval. These results are consistent with several other studies demonstrating this same increase in variability across inter-tap intervals (ITIs) as the frequency of the metronome decreases (Gibbon 1977; Hove et al. 2014), whereas our study found that this increase of variance in ITIs is attributable to the holding phase of movement during tapping.

Nagasaki (1991) demonstrated that asymmetry of cyclic extension and flexion velocities decrease as interval duration decreases during synchronized movements, and Nagasaki (1989) reported asymmetry of extension and flexion velocity was present in a wide range of interval durations with an exception of an intermediate interval duration of 433 ms where the observed velocity and acceleration of flexion and extension was symmetrical. The present study successfully replicated similar findings in Balasubramaniam et al. (2004). Extension velocity significantly decreased as interval duration increased (see Fig. 1.4) and flexion velocity remained stable across interval durations. As for novel effects, we observed significant differences in both extension and flexion velocity variance between visual and auditory tapping, with velocity during visuomotor timing increase in variability compared to audiomotor timing. We also observed

significant differences in flexion velocity and its variance across synchronization and syncopation, with the velocity of the downward movement decreasing when tapping between events rather than tapping at the onset of the event, and an increase in variability. Main effects of stimulus modality and tapping style on asynchrony were not observed, meaning participants were accurate relative to their own performance for both visual and auditory timing during both synchronization and syncopation, so the modulation of velocity must be a successful error correction strategy. The time spent in extension phase and holding phase were the movement phases shown to differ the most as a function of interval duration while the time spent in flexion phase was modulated by stimulus modality and tapping style. Unlike Torre and Balasubramaniam (2009), the present study did not find that the immediate subsequent movement cycles following asynchrony were negatively correlated with relative asynchrony. This suggests that the mechanisms of trajectory formation and error correction might be quite different in finger tapping with haptic contact compared to rhythmic finger oscillations at equivalent movement speeds (Doumas and Wing 2007). However, because the time spent in both extension and holding phases of movement varied as a function of metronome frequency but did not significantly differ across stimulus modality or tapping style but flexion time was modulated by stimulus modality and tapping style, we can determine that there are multiple error correction strategies utilized, like timing strategies of legato and staccato tapping described in Hove et al. (2014), that may wash out correlations if they exist between relative asynchrony and the subsequent movement phases. The timing strategy that contributes to the differences found between visual and auditory timing appears to be a function of extension and flexion velocity variance and a modulation of flexion time, and the timing strategy that contributes to the differences found between synchronization and syncopation appears to be a function of the velocity of the downward movement and the time spent in flexion. Flexion time increases during syncopation and becomes increasingly variable, and this is accompanied by a significant decrease in flexion velocity and an increase in variance of extension and flexion velocity. Syncopation seems to be characterized by slower movement and increased variability while approaching the onset of a stimulus, which in turn could increase variability of asynchrony during syncopation.

Both flexion time and flexion velocity significantly differed when participants syncopated to the event compared to participants synchronizing to the event. Synchronization and syncopation are not functionally equivalent, refuting Balasubramaniam et al.'s (2004) finding that these two styles of tapping could be functionally equivalent because they found no significant differences, and our results suggest that this difference is reflected by the downward movement trajectory. One explanation for this could be the way the movement trajectories were defined: Balasubramaniam et al. (2004) only investigated extension and flexion, whereas we subdivided movement trajectories into extension, flexion, and holding phases. Dividing the holding movement between extension and flexion time could have prevented differences from existing

between the movement phases in previous work. Semjen et al. (1992) found that at interval durations greater than 500 ms, the variability of ITIs during anti-phase tapping decreases as interval duration increases. Our results suggest the opposite: variance increased during flexion in anti-phase and additionally increased with interval duration, and both flexion and extension velocity variance increased during syncopation. Semjen (2000) suggests that this could be because participants were unprepared to syncopate, however participants in the present study were informed before the presentation of each trial to either synchronize or syncopate with the stimuli, and were explicitly told to tap between the stimuli for syncopation. This increase in variability for flexion velocity could be reflecting the underlying neural processes that differentiate synchronization and syncopation. Mayville et al. (2001) found results indicating that syncopation movements were updated on a cycle by cycle basis, recruiting more neural resources for prediction and attentional demands than synchronization required. Syncopation recruits an extensive neural network, including the basal ganglia, dorsolateral premotor cortex, areas of supplementary motor cortex (SMA), and prefrontal and temporal association cortices (Mayville et al. 2001). The present study supports those results through behavioral data, however further investigation is still needed to investigate the underlying neural processes for auditory and visual syncopation. One future direction is the application of transcranial magnetic stimulation (TMS) to areas involved in sensorimotor timing, and how down-regulation using continuous theta-burst stimulation (cTBS) or up-regulation using intermittent theta-burst stimulation (iTBS) of these areas influence both our perception of time and how it affects timing accuracy (Huang et al. 2005).

The results of the present study also indicate through an interaction that asynchrony significantly increased when participants tapped to a visual stimulus at larger interval durations than when they tapped to an auditory stimulus at shorter interval durations (shown in Fig. 5). This could demonstrate a weaker temporal coupling for visual system compared to the auditory system, supporting previous work (Repp 2003; Patel and Iversen 2014; Comstock and Balasubramaniam 2018). The reactive mode of timing, indicated by positive asynchronies which could reflect reacting to an event rather than predicting its location in a temporal sequence, could occur because the neural networks underlying visual timekeeping processes are better adapted to reacting to stimuli rather than predicting the upcoming beat (Repp and Penel 2002; Repp 2003; Patel 2014). Jäncke et al. (2000) and Penhune et al. (1998) both suggest that in tapping synchronization tasks, different areas of the cerebellum are active depending on the sensory modality of the stimulus, and that only audiomotor synchronization utilizes the SMA. In addition, Hove et al. (2013) demonstrated in an fMRI study that the putamen is significantly more active in audiomotor synchronization than in visuomotor synchronization to isochronous stimuli. The tight perception–action coupling between the audiomotor cortices likely aids audiomotor synchronization and syncopation (Patel and Iversen 2014), while visuomotor integration takes much more processing time. A spatial component

like motion added to visual synchronization can improve accuracy (Hove and Keller 2010; Hove et al. 2010, 2013). Future work should investigate the contribution of movement phases in response to stimuli that are altered spatially and temporally. The investigation of how brain networks underlying these different kinds of error correction are modulated by the type of stimulus presented is likely to be a fruitful area for further research (see for, e.g., Comstock and Balasubramaniam 2018).

In summary, these results demonstrate that timing is modulated through extension, flexion, and holding phases continuously as interval duration increases. However, the flexion phase seems to serve as the period of adjustment for visual timing and anti-phase tapping. Additionally, velocity becomes much more variable during syncopation. This, accompanied by increased variance of asynchrony for longer interval durations, for visuomotor timing, and for syncopation, supports previous literature arguing that not only do audiomotor and visuomotor timing networks utilize different pathways, but synchronization and syncopation timing may also utilize different neural networks. A lack of correlations occurring between relative asynchrony and its subsequent movement phases across all conditions likely indicates that there are multiple kinds of timing strategies utilized that require deeper investigation.

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Chapter 2
Manipulation of haptic sensation during bimanual coordination

Bimanual movements require efficient coordination between two limbs to achieve goals like reaching and grasping objects. Usually, human bimanual coordination is characterized by the synchronization of parameters of movement, including response time, movement time, and peak velocity. The current experiment aimed to investigate bimanual coordination and synchronicity of the arms when haptic sensations are manipulated using elastic and viscous forces. Using a KINARM robotic exoskeleton, manipulations of force, the strength of the force, and distance were applied to the hands during reaching movements. Results demonstrated that distance manipulations significantly desynchronized the limbs across all dependent measures, and for some dependent measures, force manipulations significantly desynchronized the limbs. These findings contribute to our understanding of how reaching movements in an ecologically valid setting are impacted by the application of viscous and elastic forces to the hands.

Introduction

Humans utilize their limbs and bodies in many ways, including coordinating to achieve important goals. Prior research has concentrated on bimanual coordination of the fingers (Kelso et al., 1979a,b), and models of coordination dynamics were first constructed to account for simple finger movements (Fitts, 1954; Buchanan et al., 1996; Buchanan et al., 1997; DeGuzman et al., 1997; Haken et al., 1985). Notably, these findings indicated that speed-accuracy tradeoffs were made as conditions increased in difficulty: specifically, participants took longer amounts of time to reach the target when difficulty was increased, usually by varying the size of the target destination. Additionally, these relationships remained constant despite differences in reach distance to the target for each hand. The fingers became temporally coupled regardless of manipulations to spatial locations of the targets.

One criticism of prior work is that these relationships have been investigated in laboratory environments, asking participants to reproduce movements that are not normally made in familiar environments. Recently, this work has been extended to include wrist movements and elbow movements (Bozzacchi et al., 2017), but rarely does this work include ecologically valid movements made by the entire arm (Ronsse et al., 2008). While these studies have investigated manipulations to difficulty via changing the size of visual targets, it is less common to find studies that investigate manipulations of other sensory domains, particularly haptic sensations (Casadio et al., 2010; Descoins et al., 2006).

In the current study, we aimed to investigate the role of haptic sensation in bimanual coupling. Specifically, we manipulated haptic sensation through the addition of forces to each hand. Viscous forces and elastic forces were used to perturb participants proprioception during reaching movements. Additionally,

distance and strength of the forces were manipulated. We hypothesized that forces would decrease measurements of movement parameters, as these forces would likely make movement more difficult compared to no force conditions. An additional hypothesis related to coupling between limbs was that elastic and viscous loads applied to each limb would decouple, as the participant would have to construct a strategy to move their limbs when forces were different, which would increase time-based parameters and likely interfere with synchronization. However, if the forces were the same across each hand, then the hands should be synchronized. Further, these relationships should remain constant despite differences in distance, and any increase in forces would likely see an increase in time-based parameters of movement.

This study is novel in that bimanual coordination has not directly compared reaching movements under haptic manipulation using elastic and viscous forces. Additionally, this is the first known use of the KINARM robotic exoskeleton to create an ecologically valid environment for participants to move around in specifically for investigation of bimanual coupling under these conditions.

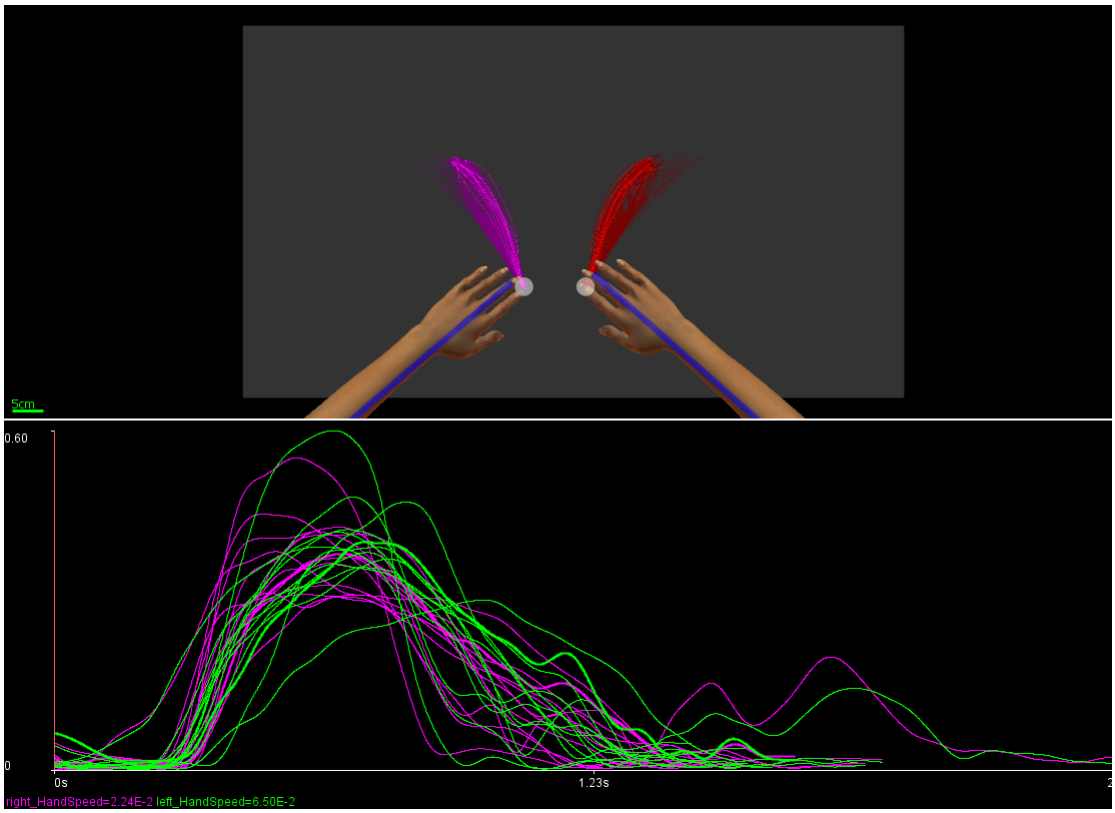
Methods

Participants

Thirty-five healthy volunteers (mean age 20.51 ± 2.31 years, 21 female, 1 non-binary) participated in the study. Thirty-two participants self-reported being right-handed (3 left-handed). All participants provided written informed consent prior to participating. The experiment was approved by the Internal Review Board of the University of California, Merced, and was conducted in accordance with the Declaration of Helsinki.

KINARM robotic exoskeleton

The experiment was performed using a KINARM upper-limb robotic exoskeleton (BKIN Technologies Ltd, Ontario, Canada). The KINARM exoskeleton has widely been used in clinical assessment for the diagnosis of stroke and other motor deficits (Dukelow et al., 2010; Semrau et al., 2015) and is frequently used to investigate motor control in healthy human and non-human primate subjects. The participants are seated in a chair, place their arms in bins, and are pushed into a structured environment that contains a horizontal glass screen, and an LED television reflects the image onto the glass screen (see Figure 2.1). Participants observe and interact with stimuli using their arms in both X and Y dimensions and can move seamlessly in this environment. As participants interact with stimuli, forces or perturbations can be applied to their shoulders, forearms, or fingertips, interfering with the subject's planned course of action. This device is calibrated to each individual subject to adjust for height and arm-length differences. The data are recorded at a sampling rate of 4000Hz and are automatically down sampled by the KINARM's robot computer to 1000Hz when calculating and storing the position, velocity, and acceleration of each limb and the hand, elbow, and shoulder joints.



2.1. The top panel depicts the subject's view of the experiment, and the bottom screen depicts the left (green) and right (purple) hand speed of all trials for equidistant conditions.

Procedure

After providing informed consent, participants were instructed to fill out a pre-experiment questionnaire which probed demographic information, including gender and age. Data involving musical and language experience were also collected but were not considered for this study. Participants were then seated in the robotic chair and the device was calibrated so each subject could move their limbs comfortably. No pinching sensations between the upper and lower arm were reported, and the seat height was adjusted so each participant could view their limbs and the stimuli without any discomfort. As a result of the calibration procedure, an opaque white circle appeared on the tips of the participants' index fingers which followed hand movements in real time. After the calibration procedure, participants were further instructed to place these circles that are representative of their hands into two white targets (1.5cm radius) to initiate each trial. After each hand was placed in these starting positions, two red targets (1.5cm radius each) would appear, and participants were instructed to reach toward these red targets with both hands as quickly and accurately as possible. Accuracy was defined as the distance between the center of the red target and the representative circles of the participant's hands. After successfully reaching

these targets, the stimuli would disappear to signal the current trial's end, and participants would place their hands in the starting positions again to initiate the next trial.

Three variables were manipulated each trial: the distance of the targets, the application of forces, and the strength of the applied forces. The manipulation of the distance had three levels: higher amplitude for the left target, higher amplitude for the right target, or equal amplitude for both targets. Forces had four levels: no forces applied to either hand (control), elastic forces applied to both hands, viscous forces applied to both hands, and elastic forces applied to one hand with viscous forces applied to the other. The elastic force was always resistant from the starting target position and grew stronger with increased distance, eliciting the feeling of a rubber band sensation on the upper limb. The viscous force applied a dampener on the limb so that an increase in velocity was accompanied by an increase in resistance. These forces were applied to the fingertips of each limb. The strength of the forces had four levels: no forces (control), low force output (elastic: F = 30N; viscous: F = -15N), medium force output (elastic: F = 36.25N; viscous: F = -20N), and high force output (elastic: F = 42.5N; viscous: F = -25N).

Participants completed 5 trials per manipulation, resulting in 195 trials total, and the full run-time of the experiment (including the calibration procedure) lasted approximately half an hour. All trials, including control conditions, were randomly assigned. Movements were made in the X and Y direction away from the midline and extended the elbow joint.

Data Analysis

Data from each trial were stored in .c3d files for each subject and imported into MATLAB. Proprietary MATLAB functions supplied from BKIN Technologies added hand kinematics (velocity and acceleration) and to apply a 3^{rd} order double-pass filter with a 3db cutoff of the 6^{th} order final filter at 10Hz. A custom MATLAB script was used to extract the response time, movement time, reaction time, and peak velocity and acceleration (including their respective indices) of each limb for each trial. These data for each subject were imported into an Excel spreadsheet for statistical analysis in R (R version 4.0.4). Reaction times that were greater than 5000ms were removed, as these trials likely indicate divergence in attention away from the task at hand (Lachaud & Renaud, 2011).

Reaction time was calculated as the difference between stimulus onset and movement onset. Movement onset was defined as the timepoint where the velocity of the limb has reached 5% of each trial's peak velocity. Movement time for each limb was calculated as the difference between movement onset and when the hand reached the target. Total response time was calculated for each limb as the time from stimulus onset to the hand reaching the target.

Linear mixed-effects models were used to analyze the effects dependent measures of reaction time, movement time, total response time, peak velocity, and peak acceleration, and the timepoints of peak velocity and peak acceleration using the "lme4" R package (Bates et al., 2014). Fixed effects were defined as

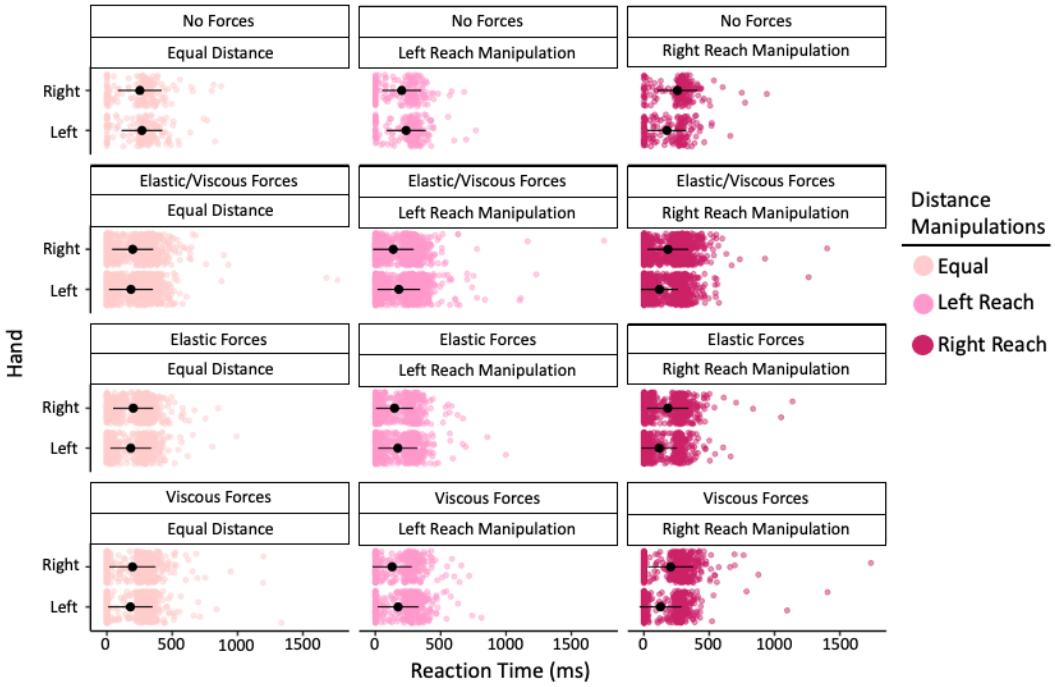
follows: hand (2 levels), distance (3 levels), and forces (4 levels) with interaction effects specified between each factor. Strength of applied forces were not included after model investigation revealed no significant impact on the dependent measurements. Random effects were specified for participants and trials. For reaction time and response time, the log of the values was modeled as the data were heavily skewed. The estimates and their respective standard errors were back transformed for interpretability, and the reported results are the estimates of each coefficient (with respect to the intercept). Treatment coding was used for mixed-effects modeling, with the intercept defined as: Left hand + Equal Distance + No Loads. P-values were obtained from the “lmerTest” R package (Kunzetsova et al., 2017).

Results

Reaction Time

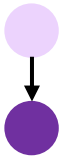
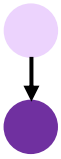
For reaction time, no significant differences were found between hands, indicating that at baseline the limbs were synchronized (see Figure 2.2 and Table 2.1 for visuals and descriptive statistics). Significant differences were found across reaction time for all load conditions compared to no load conditions, specifically all loads significantly decreased reaction time (Elastic/Elastic: 50.40 ± 1.23ms, $t = -4.58$, $p < .0001$; Viscous/Viscous: 30.88 ± 1.23ms, $t = -6.96$, $p < .0001$; Elastic/Viscous: 43.38 ± 1.22ms, $t = -5.68$, $p < .0001$).

Significant interaction effects were found between hand and Elastic loads applied to both hands, significantly increasing reaction time (244.69±1.35ms, $t = 2.06$, $p = 0.04$), indicating increased desynchronization between the hands in this condition compared to the intercept. A significant interaction effect was found between hand and right-reach distance manipulation, significantly increasing reaction time compared to hand during an equidistant reach condition (492.75ms ± 1.43ms, $t = 3.61$, $p < .001$), indicating desynchronization between the limbs. No significant interactions were observed between hand and left-reach distance manipulation, or between the hand and other load conditions.



2.2. Reaction time of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

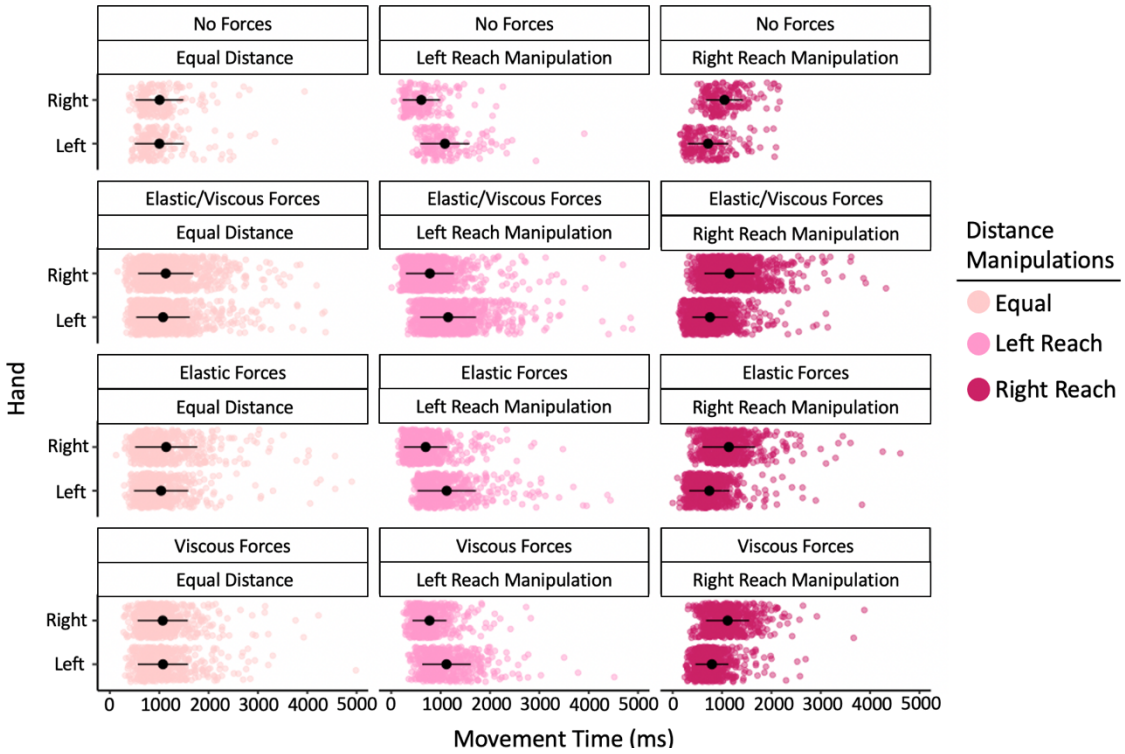
2.1. Mean reaction time in milliseconds (±SD) across conditions for the left and right hand, along with the absolute difference in time between the left and right hands.

Forces	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand
Start / End									
None	235 (149)	Δ34	202 (150)	268 (156)	Δ81	253 (167)	176 (151)	Δ81	257 (153)
Elastic	172 (150)	Δ25	147 (141)	184 (157)	Δ19	202 (153)	117 (137)	Δ65	182 (158)
Viscous	174 (157)	Δ46	128 (150)	181 (170)	Δ15	196 (176)	127 (162)	Δ77	204 (174)
Elastic/ Viscous	179 (164)	Δ42	137 (156)	185 (169)	Δ13	198 (157)	119 (143)	Δ64	183 (157)

Movement Time

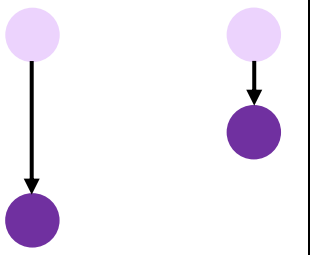
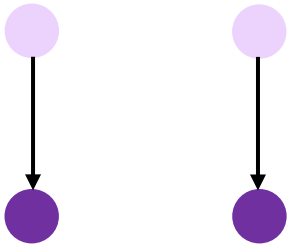
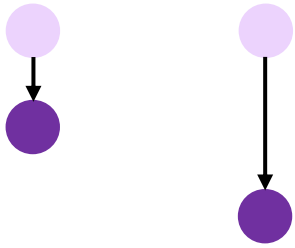
For movement time, no significant differences were found between hands, indicating during this period of movement that the limbs were synchronized at baseline (see Figure 2.3 and Table 2.2 for visuals and descriptive statistics). Significant increases in movement time were found for both different loads and viscous loads applied to both hands compared to no loads condition (Elastic/Viscous: 1092.17±33.83ms, t = 2.66, p = 0.008; Viscous/Viscous: 1076.99±36.14ms, t = 1.07, p = 0.04), and no significant differences in movement time were found for elastic loads compared to no loads.

Significant interaction effects were observed between distance manipulations and the hand. Compared to the left hand during equidistant reaches, the right hand during a left-reach manipulation had significantly decreased movement time (520.69±62.57ms, t = -7.69, p < .0001), and the right hand during a right-reach manipulation had significantly increased movement time (1330.42±62.57ms, t = 5.25, p < .0001). These interaction effects indicate significant desynchronization between the limbs during distance manipulations. No significant interaction effects were found between hand and load types.



2.3. Movement time of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

2.2. Mean movement time in milliseconds (±SD) across conditions for the left and right hand, along with the absolute difference in time between the left and right hands.

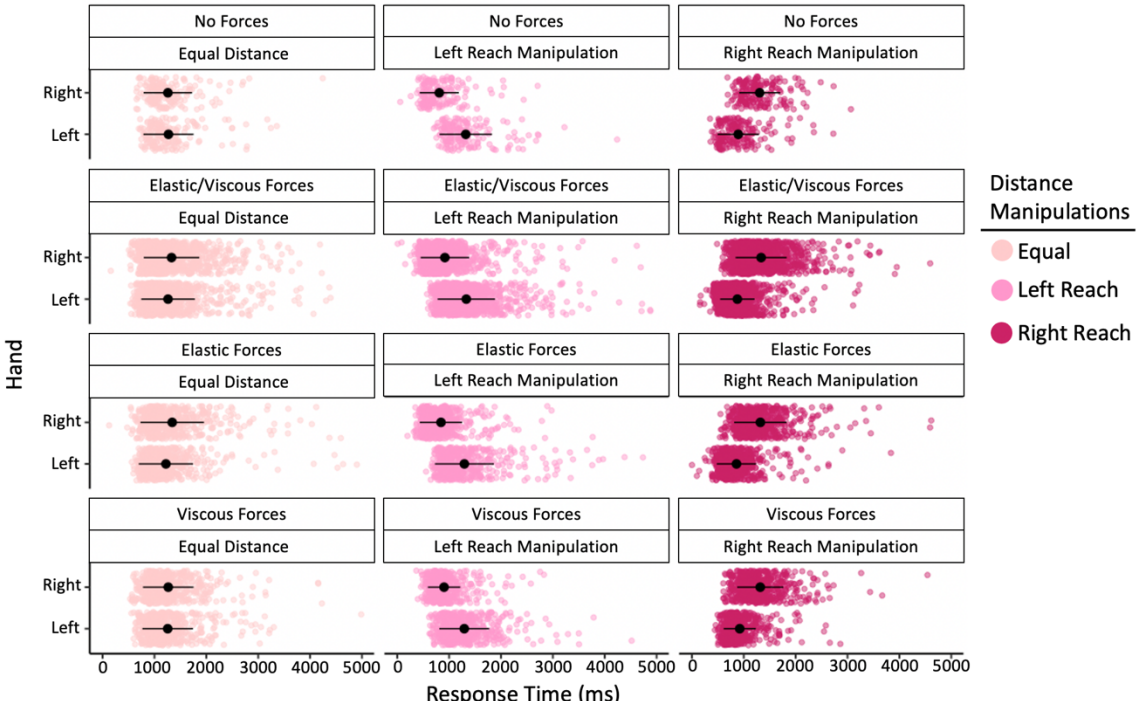
Forces	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand
Start / End									
None	1086 (497)	Δ477	609 (381)	1002 (498)	Δ4	1006 (484)	718 (411)	Δ332	1050 (375)
Elastic	1122 (592)	Δ425	697 (439)	1037 (550)	Δ103	1140 (630)	742 (407)	Δ396	1138 (532)
Viscous	1118 (491)	Δ344	774 (345)	1075 (510)	Δ5	1070 (511)	795 (335)	Δ319	1114 (437)
Elastic/ Viscous	1152 (566)	Δ56	781 (487)	1076 (544)	Δ56	1132 (561)	756 (359)	Δ395	1152 (511)

Total Response Time

For total response time, no significant differences were observed either for the hand or any of the force manipulations compared to baseline (see Figure 2.4 and Table 2.3 for visuals and descriptive statistics).

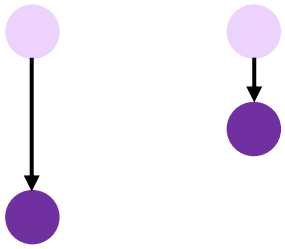
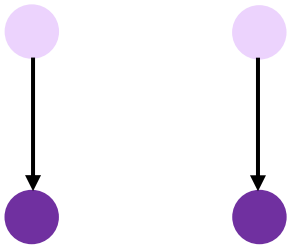
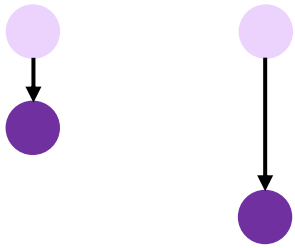
Significant interactions were observed between the hand and load type. Compared to the left hand with no loads, the right hand with elastic loads saw a significant increase in total response time (1299.85±1.04ms, t =. 2.30, p = 0.02), indicating desynchronization between the limbs when elastic loads were applied to both hands. Additionally, significant interactions were observed between hand and both manipulations of distance (compared to equidistant conditions), specifically, during left-reach manipulations, a significant decrease in total response time was observed for the right hand compared to the left hand (713.37±1.04ms, t = -11.92, p < .0001). During right-reach manipulations, a significant increase in total response time was observed for the right hand compared to the left hand (1844.57±1.54ms, t = 9.95, p < .0001). This indicates that distance manipulations significantly increased desynchronization between the hands for total response time measurements. Further, a significant interaction was observed between viscous force type and the right-reach distance manipulation, specifically these conditions compared to baseline significantly increased total response time (2807.36±1.42ms, t = 2.42, p = 0.02). These differences in timing are further illustrated in Table 2.3, which displays the left

and right total response times, along with the difference in response time between the limbs.



2.4. Total response time of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

Table 2.3. Mean total response time in milliseconds (±SD) across conditions for the left and right hand, along with the absolute difference in time between the left and right hands.

Forces	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand	Left Hand	Δt	Right Hand
Start / End									
None	1321 (484)	Δ511	810 (377)	1271 (484)	Δ12	1259 (469)	894 (400)	Δ414	1307 (396)
Elastic	1294 (569)	Δ451	843 (409)	1221 (523)	Δ121	1342 (613)	859 (380)	Δ461	1320 (506)
Viscous	1292 (482)	Δ390	902 (314)	1255 (489)	Δ11	1266 (488)	922 (311)	Δ396	1318 (45)
Elastic/ Viscous	1331 (554)	Δ413	918 (468)	1261 (517)	Δ68	1330 (536)	876 (331)	Δ459	1335 (494)

Velocity

Two measurements of velocity were investigated: peak velocity and the timepoint of peak velocity occurring. Both measurements are important indicators of desynchronization or decoupling between the limbs: if the limbs are synchronized, they should not only be synchronized in their respective peak velocities, but also in when peak velocity is occurring for each limb.

Peak Velocity

The intercept for peak velocity, with fixed effects defined as equidistant distance + no loads + left hand was 218.49±6.47cm/s. Significant differences were found for all fixed effects. For the hand, the right hand compared to the left hand had significantly decreased peak velocity by 21.30±3.43cm/s ($t = -6.21$, $p < .0001$). All force conditions significantly decreased peak velocity compared to no load conditions (Elastic/Viscous: 130.46±2.62ms, $t = -33.57$, $p < .001$; Elastic/Elastic: 154.27±2.82cm/s, $t = -22.77$, $p < .0001$; Viscous/Viscous: 105.71±2.80cm/s, $t = -40.26$, $p < .0001$.

Both distance manipulations significantly decreased peak velocity compared to equidistant reach conditions (Left-reach manipulation: 210.36±3.43cm/s, $t = -2.37$, $p = 0.02$; Right-reach manipulation: 140.68±3.43cm/s, $t = -22.69$, $p < .0001$).

Significant interactions were observed between hand and load types. Compared to the left hand during no load conditions, the right hand and different

load types significantly increased peak velocity (227.77±3.71cm/s, $t = 2.50$, $p = 0.01$). Compared to the left hand during no load conditions, the right hand with viscous forces applied to both hands also significantly increased peak velocity (229.19±3.96cm/s, $t = 2.70$, $p = .007$). This suggests that velocities diverged across hands when viscous forces and different force types were applied to the hands. No significant interactions were observed between the hand and elastic forces for peak velocity.

Significant interaction effects were observed between the hand and distance manipulations. Compared to the left hand during equidistant reaches, the right hand with a left-reach distance manipulation significantly decreased peak velocity by 54.85±4.85cm/s ($t = -11.31$, $p < .0001$), whereas the right hand with a right-reach distance manipulation significantly increased peak velocity by 70.66±4.85cm/s ($t = 14.57$, $p < .0001$). This suggests desynchronization between the hands with respect to peak velocity when distance was manipulated.

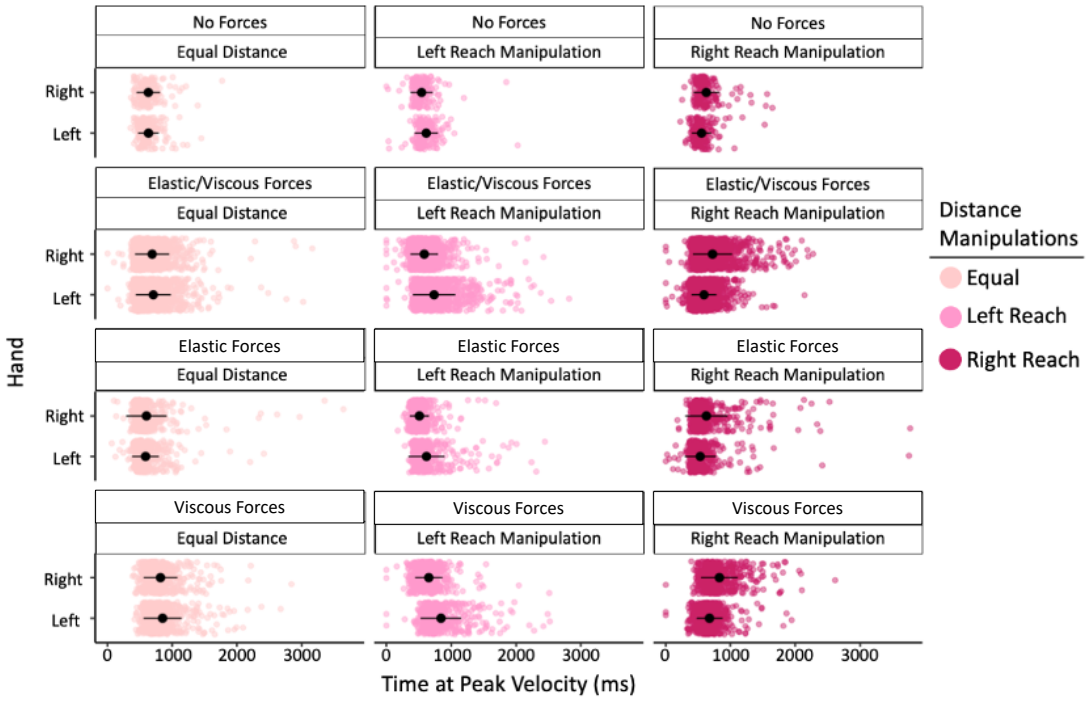
Timepoint of Peak Velocity

The intercept for the index of peak velocity, with fixed effects defined as equidistant distance + no loads + left hand occurred at 633.37±31.96ms.

No significant differences were found between hands compared to the intercept, indicating that for control conditions, the limbs were synchronized. Different forces applied to each arm significantly increased the timepoint of peak velocity by 81.68±17.43ms ($t = 4.69$, $p < .0001$). Additionally, viscous forces applied to each arm significantly increased the timepoint of peak velocity by 220.68±18.62ms ($t = 11.85$, $p < .0001$).

No significant interaction effects were observed between the hand and any force conditions, indicating that force conditions alone did not have an impact on desynchronization between the limbs with respect to the timepoint of peak velocity, despite peak velocity significantly differing, this did not significantly alter the timepoint at which it occurred.

Significant interactions were observed between the hand and distance manipulations for the timepoint of peak velocity. Specifically, compared to the left hand during equidistant reaches, the right hand during left-reach manipulations significantly decreased the timepoint of peak velocity by 68.57±32.23ms ($t = -2.13$, $p = 0.03$), and the right hand during right-reach manipulations saw a significant increase in the timepoint at peak velocity (709.99±32.23ms, $t = 2.38$, $p = .02$). This, paired with results from peak velocity measurements, indicate that velocities were indeed desynchronized between the hands when distance was manipulated (see Figure 2.5).



2.5. Time at peak velocity of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

Acceleration

Two measurements of acceleration were investigated: peak acceleration and the timepoint of peak acceleration occurring for each hand.

Peak Acceleration

The intercept for peak acceleration, with fixed effects defined as equidistant distance + left hand + no forces was 1606.94±79.48cm/s^2. Significant differences were observed between the hands, with the right hand having a significant decrease in peak acceleration (1402.32±43.40cm/s^2, $t = -4.71$, $p < .0001$), indicating that desynchronization at peak acceleration was already occurring between the limbs during control conditions.

Significant decreases in peak acceleration were observed for all force conditions compared to no force conditions. Different loads applied to the limbs decreased acceleration by 752.73±33.18cm/s^2 ($t = -22.68$, $p < .0001$) compared to no force conditions. Elastic forces applied to both hands significantly decreased peak acceleration by 443.93±35.70cm/s^2 ($t = -12.44$, $p < .0001$), and viscous forces applied to both hands significantly decreased peak acceleration by 1055.25±35.45cm/s^2 ($t = -29.76$, $p < .0001$).

Significant interactions were observed between hand and force type: for right hand and different forces applied to both limbs, an increase in peak acceleration was observed (1739.16±46.93cm/s^2, $t = 2.82$, $p = .005$). Compared

to no force conditions and the left hand, the right hand with elastic loads saw an increase in peak acceleration by 117.41±50.48cm/s^2 (t = 2.33, p = .02), and the right hand with viscous loads saw an increase in peak acceleration by 157.21±50.14cm/s^2 (t = 3.14, p = .002). These interaction effects indicate that forces decoupled the limbs via peak acceleration.

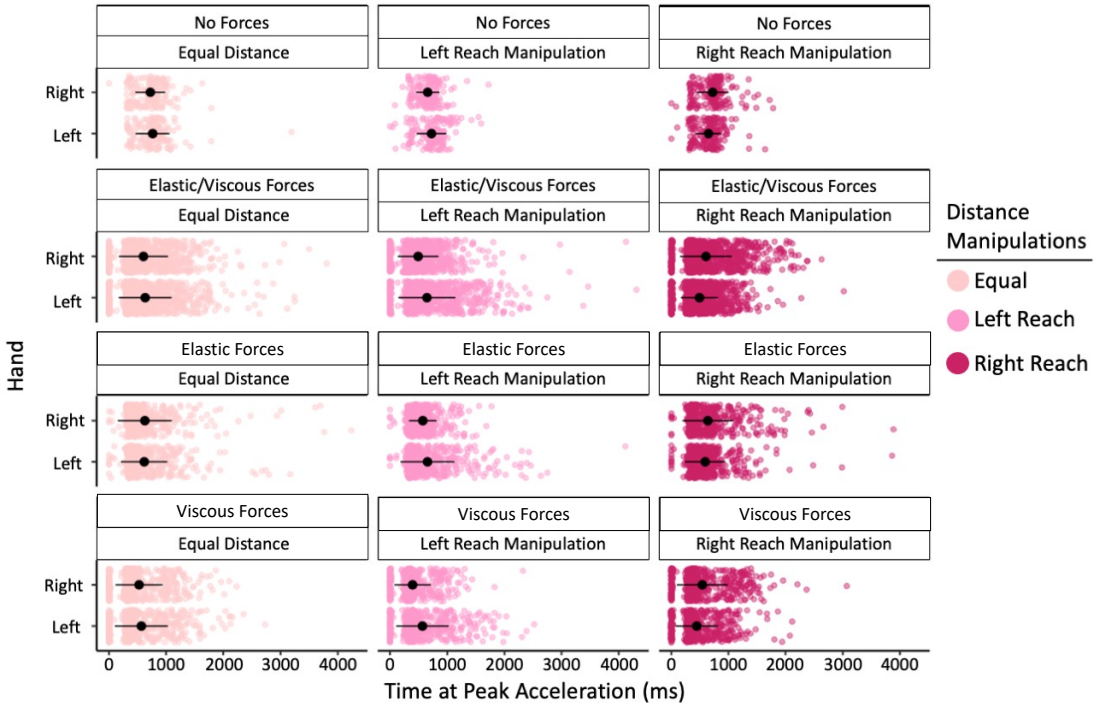
Additionally, significant interaction effects were observed between hand and distance manipulations. Compared to the left hand during equidistant reaches, the right hand during left-reach manipulations decreased in peak acceleration by 231.07±61.38cm/s^2 (t = -3.77, p = .0002). Compared to the left hand during equidistant reaches, the right hand during right-reach manipulations saw an increase in peak acceleration by 432.96±61.38cm/s^2 (t = 7.05, p < .0001). These interactions also suggest decoupling during the limbs with respect to peak acceleration during distance manipulations.

Timepoint of Peak Acceleration

The intercept for timepoint of peak acceleration, with fixed effects defined as equidistant distance + left hand + no forces was at 763.09±39.47ms.

No significant differences were observed between the hands for timepoint at peak acceleration. Compared to no forces, all force types had a significant decrease in timepoint at peak acceleration (Elastic/Viscous: 638.45±31.31ms, t = -3.98, p < .0001; Elastic/Elastic: 628.81±33.69ms, t = -3.99, p < .0001; Viscous/Viscous: 566.88±33.46ms, t = -5.87, p < .0001).

Only one significant interaction effect was observed between hand and distance: for the right hand during a right-reach manipulation, a significant increase in timepoint of peak acceleration occurred (877.94±57.92ms, t = 1.98, p = 0.05). No other significant interactions between the hand and any other condition (see Figure 2.6).



2.6. Time at peak acceleration of the hands for all conditions across force and distance manipulations. The black dot signifies the mean, and the bars represent standard deviation.

Discussion

The major gap this current study is attempting to fill is our understanding of how variants of haptic sensation can influence bimanual reaching movements, specifically in terms of how coupling between the limbs is affected. As of yet, this has not been investigated in terms of directly comparing viscous and elastic forces to each other directly, and how variations in these kinds of forces may influence coupling between the limbs. The overarching hypothesis of this study was that forces will influence coupling between the limbs, specifically that application of difference forces to the arms (Elastic/Viscous) would significantly desynchronize the limbs, and the same kind of forces applied to both arms would not decouple the limbs. Additionally, we extended this hypothesis to include manipulations of distance: even when distance differed, the limbs should be synchronized when the same forces were applied to both arms but would decouple when different forces were applied to each arm. This gap is important to fill because we can later apply this work to making systems that operate in unusual environments like underwater or with elastic bands more efficient for users. This work has indirect application to Fitts' Law (Fitts, 1954) in terms of approving accessibility sciences for operations where bimanual movements of the arms are necessary to perform tasks in environments where viscosity and elasticity affects the limbs. Directly, this aids our understanding in how different

aspects of sensation, particularly haptic sensation, influences the coordination of bimanual movements.

To study this gap, we employed innovative technology using the KINARM exoskeleton to apply forces to the hand and investigate these movement parameters in an ecologically valid context. Importantly, we found that in equidistant conditions when no forces were applied, no desynchronization was observed between the limbs, apart from peak velocity and peak acceleration. This is consistent with prior research indicating that bimanual movements tend to synchronize, especially in conditions where distance is equal (Swinnen et al., 1991; Riek et al., 2003). However, we did find decoupling between the limbs via interaction effects between hand and distance manipulations for every dependent variable, indicating that distance significantly decoupled the limbs during bimanual reaches. Additionally, all forces significantly decoupled the limbs with respect to reaction time, peak velocity, peak acceleration, and the timepoint of peak acceleration, signifying that many aspects of movement are modulated due to addition of haptic sensation, whether that's different forces applied to both hands, elastic forces applied to both hands, and viscous forces applied to both hands.

Distance has not previously been shown to be a significant factor in some studies for decoupling of the limbs. Many studies, including Kelso et al., (1979) and Jackson and colleagues (1999) have shown that even with distance manipulated, the limbs still tend to synchronize which is shown through no significant differences between the hands for any movement parameters investigated, including response time and velocity. One hypothesis for how distance modulates movement parameters between the limbs, even in control conditions, is that all trials were randomly distributed, including the control trials. Thus, participants may have had exposure to trials where forces were implemented before they had exposure to control trials and had constructed top-down strategies to counteract trials that contain forces regardless of distance, evidenced by virtually all movement parameters being affected by force conditions.

An alternative explanation for distance modulating the coupling relationship between the limbs could be that the experiment is conducted in a much more ecologically valid setting compared to prior literature. Specifically, participants are pivoting from the elbow joint and have freedom to move their entire arms in any direction they want without barriers in specific directional planes, which increases the degrees of freedom to account for and may contribute to distance modulations in movement parameters. Previously conducted studies required participants to move in specific planes of movement with just their fingers or wrist flexion (Kelso et al., 1979a,b), where movement is much more restricted and isn't reflective of movements that are made in the real world to complete tasks.

Desynchronization between the hands was also observed for peak velocity and peak acceleration for both differing force applications and viscous force applications, whereas desynchronization occurred between the hands

during elastic force applications for reaction time, total response time, and peak acceleration. This divergence in how variant force applications are impacting time-based aspects of movement (reaction time and response time) versus components of the movement themselves (velocity and acceleration) may reflect components of the force equations, where elastic forces are affected by distance, and viscous forces are affected by rate of movement. Realistically, reaction time being affected by elastic forces wouldn't differ in perception compared to null forces, as the hand at 5% of peak velocity should not be very far from the start target, however the greater the distance increases, the harder the force resists, and may impact the time to reach the end targets. Furthermore, the strength of the elastic force may not be high enough to significantly impact movement parameters like velocity and acceleration significantly since the distance does not require use of the full body to successfully reach the end targets.

A limitation to the current study is that these movement parameters were only investigated for the hands, where the forces were directly applied. Further investigation of the elbow and shoulder joint movement parameters and how they respond to these manipulations would be necessary to understand how the entire arm responds and to account for several degrees of freedom. An additional limitation is that the strength of the forces did not seem to be a significant factor for our dependent measurements – adding this parameter introduced more variance in the linear mixed effects models and was highly correlated with several other factors. A more rigorous investigation into the strength of forces, perhaps by allowing for adaptive forces for each individual participant so proprioception of the haptic force is somewhat consistent across participants despite differences in athletic ability may elucidate our understanding of how this factor influences bimanual coordination.

Based on the results of the current study, a follow-up investigation where control trials are placed at the beginning and end of the experiment could inform our findings regarding distance manipulations and whether participants did enact top-down strategies and adapted to force trials over time, which may have carried over into control trials.

This study filled a gap in the literature pertaining to the different kinds of haptic perception and sensation that influence human's ability to move bimanually in environments. Generally, forces impacted all components of movement studied, and differences between the hands were observed when distance was manipulated for peak velocity and peak acceleration. Distance was found to significantly desynchronize the limbs across all movement parameters, whereas elastic forces and viscous forces differentially desynchronized the limbs for purely time-based parameters and movement-throughout-time parameters. Overall, this research provides insight regarding bimanual coordination in particular haptic environments, and that in some cases, the limbs become decoupled from each other because of the haptic manipulations.

Acknowledgments
We would like to thank Tim Schwartz and Nicholas Walters for their contributions to the coding of the experiment.

Chapter 3
Possible involvement of the left posterior-parietal cortex in declarative and procedural memory systems

When learning two skills in immediate succession that are traditionally thought to utilize differential processes for encoding and consolidation of the learned skill, the memory of the second learned skill interferes with the memory of the first, causing a reduction in performance of the first skill (Brown & Robertson, 2007). This is a phenomenon known as retroactive memory interference and has been investigated with declarative and procedural memory systems. Prevention of retroactive interference between two competing memories has been successful via use of transcranial magnetic stimulation (TMS) when applied immediately after encoding both skills (Cohen & Robertson, 2011). Importantly, the area stimulated needs to be directly involved in the consolidation of the first skill learned to prevent interference between competing declarative and procedural memories. The present study aimed to understand the role of the left posterior parietal cortex (lPPC) and left primary motor cortex (lM1) in memory consolidation by downregulating these areas directly after encoding declarative and procedural skills. Results showed that for both the declarative skill and the procedural skill, the task order and the site of stimulation had no significant differences and no interaction effects when compared to sham stimulation. While this study does not indicate that lPPC or lM1 are involved in consolidation of either declarative or procedural memories during an interference task, these results provide insight into how variation in task parameters, stimulation parameters, and participant characteristics may inform future replications of previous studies.

Introduction

Imagine a scenario in which an agent is acquiring information from multiple sources in quick succession. A common example of this would be a child navigating a normal weekday during the academic school year – taking multiple courses, learning both history and a foreign language, math and critical thinking skills, and perhaps participating in organized sports and learning new physical proficiencies all within the span of a single day. Assume that most of the information acquired throughout the day will stay relevant, and will need to be accessed at a future time point (both in the short and long-term) in order for that child be successful in that particular environment. In this example and in many other similar scenarios, the brain encodes the sensory neural activations and relevant associative processes during acquisition, one of the first stages of learning, and depending on current processes and the information received, will undergo a process called pattern separation for consolidation. Within the first few seconds of acquiring information, that information can be quickly retrieved if needed using short term memory stores, which are dependent upon the sensory system that is being utilized to acquire that information. Accessing these

representations within a temporal scale of milliseconds to seconds is utilizing an agent's short-term working memory capacity (Hebb, 1949). Long-term consolidation is the memory process by which encoded information will become ingrained in the brain by way of physiological processes like long-term potentiation (LTP) of an ensemble of neurons, which rely on neurotransmitter molecules called N-methyl-D-aspartate (NMDA; Hebb, 1949, Collingridge & Bliss, 1987) and occurs on a temporal order of hours to days (or possibly even longer). On the cellular and molecular level, NMDA is emitted in the neural synapse during learning between a pre- and post-synaptic neuron, and when the post-synaptic neuron uptakes NMDA, it sends a retrograde messenger in the form of nitric oxide back to the pre-synaptic neuron to encourage the strength of connection between those two neurons to increase. Stronger connections between neurons and populations of neurons result in stronger memories according to Hebbian learning, from which the classic phrase "neurons that fire together, wire together" stems (Hebb, 1949; O'Reilly & Norman, 2002).

Memory interference is thought to occur when overlap exists between multiple representations in memory that need to be maintained, and because of this overlap only the strongest representation will be able take hold and become encoded for future retrieval. Memory 'representations' in the context of this review are defined as the neural population codes that are a result of the encoding stage of learning, and are a culmination of dynamical processes. They are dependent on the environmental conditions and underlying dynamics of the system that produced them, and as such, are subject to change across both space and time as they become accessed or activated upon retrieval of the said representation (Friston & Price, 2001). Much of the data obtained from experiments on patient populations has provided evidence that implicit and explicit memory representations are encoded and consolidated in modular neural systems, as Alzheimer's patients are unable to learn new declarative information, but can acquire new motor skills with practice (Grossman et al. 1998; Nebes 1997; Beatty et al. 1994). Parkinson's and Huntington's patients experience the opposite: the ability to acquire new semantic and declarative information and the inability to learn new procedural skills (Knopman & Nissen, 1991; Pascual-Leone et al. 1993).

Consolidation takes place in areas of the brain that are differentially dependent on the nature of information encoded. For example, procedural memories are thought to utilize the basal ganglia, thalamo-cortical, and cerebellar feedback loops in combination with activation in motor and pre-motor cortices while declarative memories are encoded in the medial temporal lobe and hippocampus (Doyon et al. 2003; Buckner et al. 1999; Burgess et al. 2002). However, recent evidence purports that these memory systems are not as separable as once thought. Cohen and Robertson (2011) used repetitive transcranial magnetic stimulation (TMS) to down-regulate right dorsolateral-prefrontal cortex (rDLPFC) after participants completed two behavioral tasks: participants first learned a word list, followed by implicitly learning a motor sequence task. TMS was applied immediately after learning those skills to

effectively disrupt the active consolidation of the memories, and they found that the memory of the word list was preserved after a time span of 12 hours. The same study also demonstrated that when the order of the tasks was reversed, and participants learned the implicit motor sequence followed by the explicit word list, followed by downregulation of primary motor cortex (M1) with rTMS, the memory of the implicit sequence was preserved across a time span of 12 hours. Sham conditions demonstrated a significant amount of interference occurring between initial learning of the skills and retesting after a 12-hour period for both the explicit and implicitly learned skills. Interference can be prevented through online measures (TMS) or through off-line measures (sleep; Sonni & Spencer, 2015), but not much is understood about the functional role of interference between different kinds of memory. Memory interference could arise because of an overlap between the encoding stages of procedural and declarative memories.

Competition from these two memories would otherwise have impaired behavioral performance. If these memory systems were completely separable as older and more established theories propose (Squire & Wixted, 2011), then interference, demonstrated as decreased behavioral performance in this task, must too, be separable and dissociable from other neural systems. Declarative information acquired should have no impact on information acquired through procedural learning because of the utilization of separate memory systems, and vice versa. This is not what is observed in many behavioral and neurological experiments using human subjects.

Edwin Robertson (2012) proposes that memory interference may allow for memories that utilize different neural processing pathways be combined together during the consolidation process, also referred to as binding. It is not entirely clear what a functional role of interference would be in the current state of the literature, but we do know that we can reduce memory interference by using transcranial magnetic stimulation to disrupt areas involved in a first task during the consolidation period immediately following encoding (Brown & Robertson, 2007; Cohen & Robertson, 2011) without observing deficits in behavioral performance. If interference can be prevented without observable behavioral cost, this raises the question if interference only arises due to a lack of neural resources for encoding both memories, and if there is another functional purpose.

The current study aimed to investigate the extent to which lPPC was involved in declarative and procedural memory systems and partially replicate previous work (Cohen & Robertson, 2011). The posterior parietal cortex is a proposed site of multisensory integration (Andersen & Buneo, 2002) and is implicated in visuo-spatial working memory retrieval (Olson & Berryhill, 2009; Buchsbaum & D'Esposito, 2008) and in episodic memory recollection (Simons et al., 2010). The posterior parietal region has many subdivisions, including the intraparietal sulcus, superior marginal gyrus, and superior parietal lobule, each of which have different functional roles, and is anatomically distinct across individuals (Grefkes and Fink, 2005; Reichenbach et al., 2011). Due to its

involvement in both motor-based and declarative-based tasks, we aimed to understand the role of the PPC in declarative and procedural long-term memory consolidation.

Methods

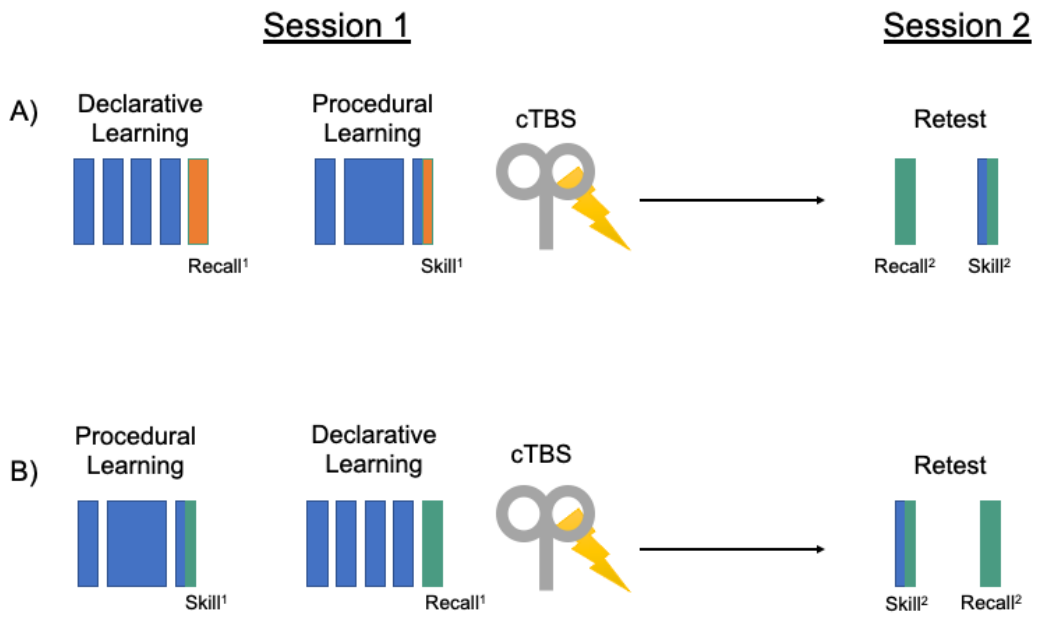
Participants

One hundred sixty-six participants were recruited for this study (104 female) ages 18-35 years (mean age = 19.66, SD = 2.12 years), recruited from the University of California, Merced undergraduate student subject pool and volunteers from the community of Merced, CA. All participants self-reported being right-hand dominant and were screened for contraindications for TMS, including increased risk for seizure, neurological and psychiatric illness, metal in or on the body other than dental fillings, history of syncope, head injury, and spinal abnormalities (Huang et al. 2005). Participants were asked to remove all metal jewelry and eyeglasses containing metal screws prior to TMS. Five participants did not show up for the retesting portion of the study, and as a result their data was not used in the final analysis. Nine participants had an error rate during the serial reaction time task that exceeded 20% of total responses, and 1 participant experienced technical issues with the stimulus software during experimentation, and thus were not included in the analyzed dataset. This resulted in 151 participants completing the entire study, and 46 of those participants explicitly memorized 5 or more components of the motor sequence, which has been shown to interfere with declarative memory consolidation (Robertson et al., 2004; Press et al., 2005). Due to this, learning style of the motor sequence during the procedural task was included as a factor in analyses. Student participants were granted course credit for volunteering, and the experimental protocol was carried out in accordance with the Declaration of Helsinki and reviewed by the University of California, Merced Institutional Review Board. Participants were given informed consent before the experiment. After providing consent, participants were asked to complete a pre-experiment questionnaire, collecting basic demographic information including age and gender.

Procedure

Participants were pseudo-randomly assigned to one of two task orders: the first, Procedural then Declarative (PD), and the second, Declarative then Procedural (DP)). Participants were then pseudo-randomly assigned to the site of stimulation (3 levels: sham stimulation, left M1, and left PPC). Participants were asked to complete a word list learning task (declarative) and a serial reaction time task (procedural), respective of the experiment order they were assigned to. TMS was applied immediately after completion of the second task to ensure disruption of memory consolidation, as shown in previous research (Cohen and Robertson, 2011). Participants returned 4 hours later for additional retesting, measured by free verbal recall of the word list and a retest of the learned motor skill. The experimental procedure is demonstrated in Figure 3.1. The time

window between testing and retesting was 12 hours in previous work (Brown & Robertson, 2007; Cohen & Robertson, 2011), but was reduced to 4 hours due to laboratory testing constraints and that motor consolidation has been shown to occur between 4-6 hours (Brashers-Krug, et al., 1996; Krakauer & Shadmehr, 2006).



3.1 Experimental design. A) Order DP begins with the declarative skill test followed by the procedural skill test. This is then followed by application of cTBS to the stimulation site. Four hours later participants partake in the second session, which are retests of the previously learned skills. B) Order PD begins with the procedural skill test and is followed by the declarative skill test. cTBS is then applied to the stimulation site, and participants come back for retesting of both skills four hours later.

Word-list task

Participants were instructed to sit in front of a computer screen and attempt to memorize a list of words. All words were nouns chosen from the MRC Psycholinguistic database (Coltheart, 1981) ranging from 1-3 syllables, 4-11 letter word length, a KF frequency between 40 and 50, familiarity rating between 500 and 600, and a concreteness rating between 500 and 600. Sixteen words were presented via Paradigm presentation software (Perception Research Systems, 2007) on the computer screen for two seconds each, with a 500ms pause between each word. The list was presented to each participant 5 times during the first session of testing, and after each presentation of the list, participants were asked to verbally free recall as many words as they could remember to the experimenter. The word list was randomized before the initial

testing session and was presented to participants in the same order for each of the five presentations. The number of words remembered during the fifth recall was used as a score for the pre-TMS measure. When participants arrived for the second session, they were asked to verbally free recall as many words as they could possibly remember without the list being presented, and this was used as a measure of declarative recall post-TMS. Errors in recall were transcribed by the experimenter, and after the second session of behavioral testing, participants were asked about memory strategies used to memorize the list of words. The strategies reported included no strategies (8 participants), auditory rehearsal (41 participants), association (75 participants), internally spatializing each of the words, like a memory palace (20 participants), or other strategies (5 participants). If participants reported more than one strategy, the second strategy reported was the strategy used for further analysis, as this was described by many participants as the main strategy they utilized during the testing session.

Serial Reaction Time Test (SRTT)

The SRTT is a motor sequence-learning task that is commonly used as a measure of implicit procedural memory throughout motor-learning research (Robertson, 2007). The version of the SRTT that was used for the current study was adapted from Brown & Robertson (2007). Stimuli were presented through Paradigm software (Perception Research Systems, 2007). Participants were instructed to respond to a (2.5cm radius) green circle that could appear at four different locations on a screen as quickly as they possibly could. The circle would appear on the screen and stay there until participants responded. The four locations were separated into quadrants on the computer screen, and participants could respond by pressing the numbers 1-4 for that number's respective location (1 was a response for the circle in the top left quadrant, 2 for the top right quadrant, 3 for the bottom left quadrant, and 4 for the bottom right quadrant). The 12-item sequence (2-3-1-4-3-2-4-1-3-4-2-1) was presented to participants 15 times per testing block (180 trials per block) for 5 blocks during initial testing. Each testing block was separated by a randomized number block consisting of 48 trials (before and after the presentation of each sequence block). Testing sequence learning post-TMS consisted of a single block of the sequence (180 trials) between 48 randomized number trials. The reaction times of the last 48 trials of randomized numbers and the last 48 trials of the learned sequence for both pre- and post-TMS were used for further analysis. Incorrect responses were removed, and responses greater than 2.7 SD of those 96 trials analyzed (pre and post) were discarded. After the second session of behavioral testing, participants were asked if they noticed a pattern of numbers emerge from the serial reaction-time task, and if they did report noticing a pattern, they were asked if they could explicitly recall that pattern of numbers. Participants who recalled five or more numbers from the 12-item sequence were categorized as having an explicit learning style for the sequence task, consistent with Brown & Robertson (2007). Participants who were unable to recall 5 or more items from the 12-item sequence were categorized as having an implicit learning style for the sequence task.

Transcranial Magnetic Stimulation (TMS)

A c-TBS (continuous Theta-Burst Stimulation) paradigm was used, described by Huang et al. (2005), which downregulates targeted regions of cortex for approximately 20-40 minutes after stimulation. The protocol used a 40-sec train of three pulses at 50Hz repeated at 200ms intervals, for a total of 600 pulses. The c-TBS protocol was applied to targeted brain regions at 80% of the participant's active motor threshold (AMT) as has been shown in prior research to effectively down-regulate motor cortex (Huang et al., 2005) and other areas of cortex, including the posterior parietal cortex (Krause et al., 2012). AMT was determined for each participant to be the lowest percentage of stimulator output that produced a visible muscle twitch in 5 out of 10 trials in the first dorsal interosseous (FDI) muscle of the right hand during isometric contraction. If a participant's AMT was higher than 56% of the maximum stimulator output, due to IRB protocol and equipment limitations, those participants were stimulated at 45% of the maximum stimulator output. 44 participants received less than 80% of AMT, and visual inspection of the data does not indicate that their performance significantly differed. The best location for FDI in left motor cortex was determined by comparing the size and consistency of motor evoked potentials (MEPs) for each participant. Ag/AgCl sintered electrodes were placed over the belly of the right-FDI muscle to record MEPs during rest, and a ground electrode was placed over the posterior side of the right ulna close to the elbow where little to no muscle was directly underneath the ground electrode. For single-pulse stimulation provided to left motor cortex to find the FDI motor hotspot, a 70mm figure-of-eight coil (Magstim, D70^2 double 70mm coil, Carmarthenshire, United Kingdom) was placed tangential to the scalp at an angle of ~45° from the anterior-posterior midline.

After AMT was determined for each participant, c-TBS was applied to lPPC, lM1, or in a sham control condition where the coil was flipped and placed on top of lM1, oriented so that pulses were delivered away from the participant. Magstim Visor 2 3-D motion-capture guided-neuronavigation was used to scale each individual participant's brain model to the Talairach brain using head size and shape to locate coordinates for lPPC for individual participants. 3-D Talairach coordinates for lPPC at (-40, -50, 51) were determined from previous literature (Krause et al. 2012), and the coil faced the anterior direction at ~45° from the anterior-posterior midline. These coordinates have consistently produced measurable behavioral effects across many studies when stimulated with TMS (Krause et al. 2012, Ross et al. 2018). For c-TBS to lM1, the center of the coil was placed on the area that was previously determined to be the motor-hotspot facing the anterior direction at ~45° from the anterior-posterior midline, which has been consistently shown to produce reliable behavioral effects when stimulated (Huang et al., 2005; Cohen & Robertson, 2011).

Statistical Analyses

All statistical analyses were conducted using R (Version 3.6.1). Verbal recall scores were calculated by subtracting the initial recall score (normalized for each participant) from the recall score 4 hours after testing (R_2).
Learning scores for the implicit serial reaction time task were calculated by averaging the last 48 trials of the learned sequence (S1) and the last 48 trials of a randomized series (R1) of trials separately, and subtracting the average sequenced reaction times from the averaged randomized reaction times for both pre and post-TMS sessions (Pre-TMS learning score (L1) = R1 – S1; Post-TMS learning score (L2) = R2 – S2). A final learning score was generated by subtracting pre-TMS scores from post-TMS scores (Overall Learning Score (LS) = L2 – L1), with a negative value indicating that the sequence was not consolidated, and a positive score indicating that the sequence was consolidated and the procedural memory preserved. ANOVAs were used to assess significance of both the recall scores and procedural skill scores with stimulation site and learning style of the procedural skill included as factors specified with interaction effects.

A generalized linear mixed-effects model was run on sequenced reaction times from the sequence-learning task in individuals who implicitly learned the sequence in the SRTT, with task order, the site stimulated (sham, lPPC, lM1), and pre- and post-TMS identifiers as interaction terms in the model, and participants and items were included as a random effect in the model to account for individual variability. Participants who did not explicitly memorize the sequence were solely included in this model to understand the true effect of TMS on memory consolidation without residual variance from explicitly memorizing the sequence. Effects from all models reported include the estimate and standard error, t-value, and p-value. The significance threshold was set to 0.05.

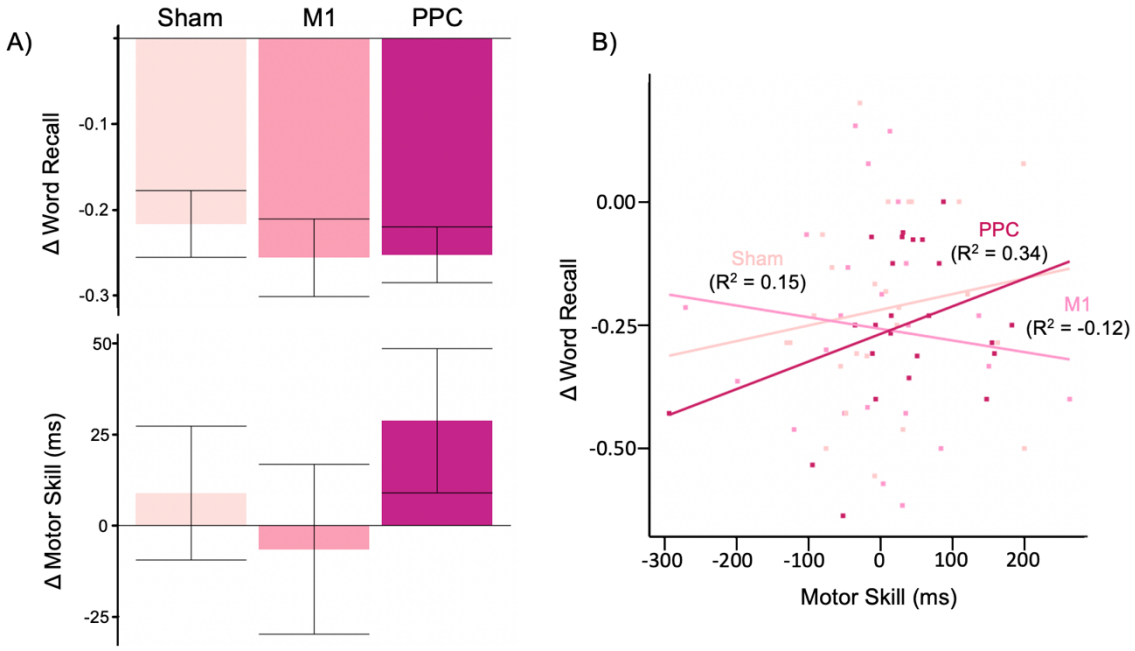
Results

Task Order DP

For recall change, no differences were found across site of stimulation, and no significant interaction effect was observed between memorization of the procedural sequence and site of stimulation for pooled data. This lack of an interaction effect indicates that explicit memorization of the sequence during procedural skill learning did not significantly impact participants' overall performance on the declarative task.

For the learning score, no differences were observed across the site of stimulation. Additionally, no interaction effects were observed between memorization of the procedural sequence and site of stimulation (see Figure 3.2).

The correlations between change in motor skill and word recall for the sham condition was not significant ($R = 0.15$, $df = 25$, $p = 0.47$). The correlation between change in motor skill and word recall for the PPC stimulation condition was not significant ($R = 0.34$, $df = 24$, $p = 0.10$). The correlation between change in motor skill and word recall for the M1 stimulation condition was not significant ($R = -0.12$, $df = 23$, $p = 0.59$).



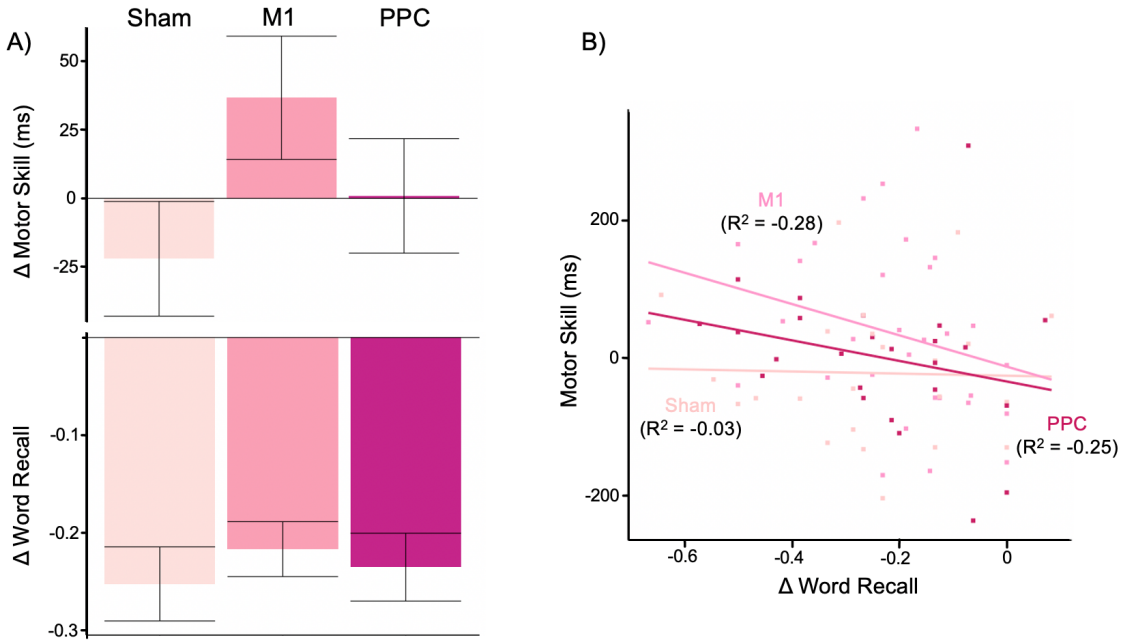
3.2. A) For task order DP, the differences in recall performance and change in motor skill across stimulation groups. B) The correlations between change in motor skill and recall performance across stimulation groups.

Task Order PD

No significant differences were found across stimulation site for learning score. Furthermore, including learning style of the motor sequence during the serial-reaction time task as an interaction term in the model produced no significant differences or interactions. This finding was inconsistent with our initial hypotheses and indicated a failure to replicate Brown & Robertson (2007), which prompted further investigation using non-aggregated trial data and could provide a more nuanced explanation for these inconsistencies.

For recall change, site of stimulation and memorization of the motor sequence did not impact change in recall performance. Additionally, no significant interaction was observed between memorization of the motor sequence and sites of stimulation (see Figure 3.3).

No correlations were observed between change in motor skill and change in word recall for the sham condition ($R = -0.03$, $df = 23$, $p = 0.89$), for stimulation at M1 ($R = -0.28$, $df = 31$, $p = 0.13$), or for stimulation at PPC ($R = -0.25$, $df = 25$, $p = 0.23$).



3.3. A) For task order PD, the differences in change of motor skill and word recall performance across stimulation groups. B) The correlations between change in motor skill and word recall performance across stimulation groups.

Reaction-time

A linear mixed effects model was used to determine how experimental factors influenced raw reaction times before and after stimulation conditions. Only correct responses from the sequenced reaction times that were less than or equal to 3000ms were included. Additionally, only participants who completed the task correctly, and who did not memorize the implicit sequence, were included in the reaction time analysis. Factors were set for task order, stimulation site, and pre-TMS versus post-TMS distinction, and were specified with interaction effects. Random effects were designated for participants and for trial number.

A main effect of task order was observed. When compared to DP task order, PD task order saw a reduction of 91.16 ± 41.50ms (t = -2.20, p = 0.03), indicating that participants were generally faster across all trials, pre- and post-TMS, when learning the procedural skill first. Additionally, marginal effects of site of stimulation were observed with M1 stimulation and PPC stimulation both showing a decrease in overall reaction time compared to sham (-78.54 ± 39.81ms, t = -1.97, p = 0.05 for M1; -68.01 ± 40.31ms, t = 1.69, p = 0.09 for PPC). This indicates that brain stimulation to these areas may potentially reduce reaction time, however these effects should be interpreted with caution. A main effect of time was observed, with post-TMS trials observing a significant decrease in reaction time (-66.40 ± 10.10, t = -6.57, p < .0001).

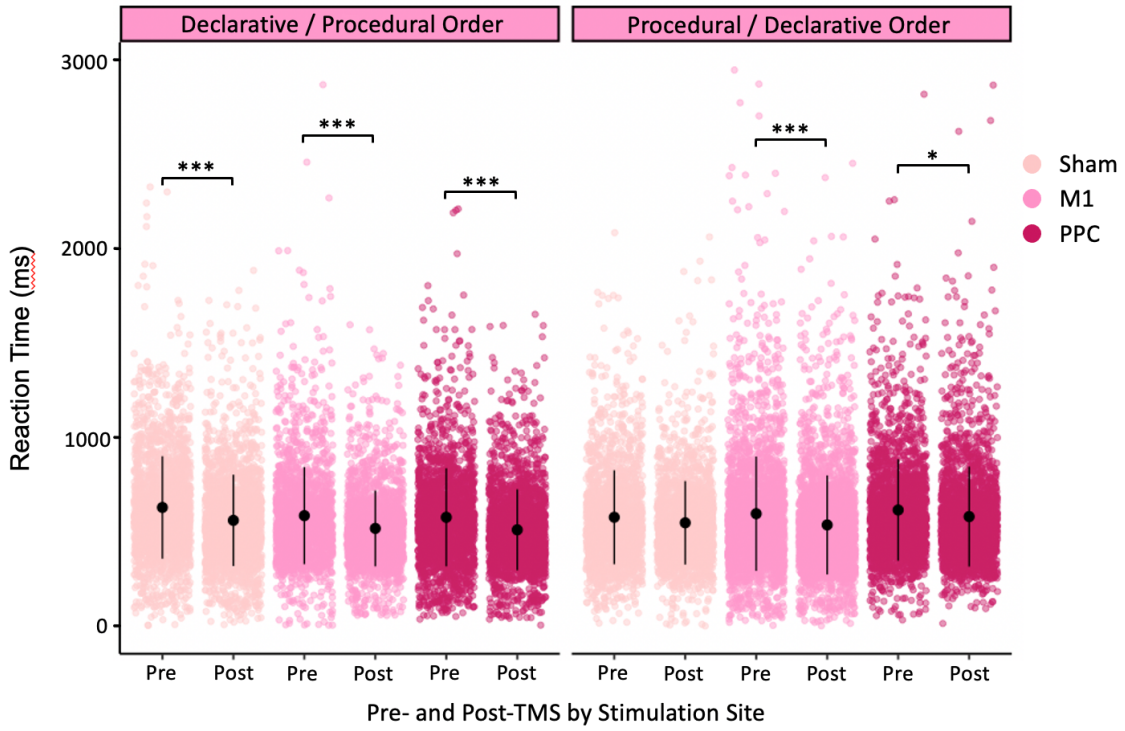
Significant interaction effects were observed between task order and stimulation site. Surprisingly, both M1 and PPC sites in the PD task order, when compared to the DP task order with sham stimulation, had significantly higher

reaction times (158.18 ± 56.39ms, t = 2.81, p = .006 for M1; 144.44 ± 58.30ms, t = 2.48, p = .01 for PPC). While these interaction effects may point to increased reaction times in stimulated groups compared to sham, specifically in the PD order, this doesn't account for pre-post differences. When accounting for these differences with three-way interaction effects, only when stimulation was provided to M1 in the PD group, post-TMS reaction times were significantly lower compared to the DP task order for sham stimulation in pre-TMS reaction times (-58.94 ±19.69ms, t = -2.99, p = .003). There were no significant differences when investigating this same interaction effect with the PPC stimulation group (11.96 ± 20.33ms, t = 0.59, p – 0.56).

Planned contrasts between each group further elucidated differences within each group with respect to three-way interactions (shown in Figure 3.4). In the DP task order with sham stimulation, reaction time significantly differed across time, with the post-TMS reaction times being reduced by 66.40ms ± 10.10ms (t = 6.57, p < .0001). This was a surprising finding, given that we did not expect participants who received no stimulation to perform faster on the second round of testing. No differences in reaction times were observed across time for the PD task order with sham stimulation (estimate = 23.84 ± 10.34ms, t = 2.31, p = 0.47).

For the group receiving M1 stimulation, significant differences were observed across time for both the DP and PD task ordered groups. In the DP task order, post-TMS reaction times were 58.98 ± 9.66ms faster than pre-TMS reaction times (t = 6.11, p < .0001), indicating that the procedural sequence was consolidated in this group. In the PD task order, reaction times in the post-TMS condition were 75.36 ± 9.25ms faster than pre-TMS reaction times (t = 8.15, p < .0001), also indicating that the procedural sequence may have been consolidated in this group.

For the group receiving PPC stimulation, significant differences were also observed between pre- and post-TMS reaction times. The DP task order group saw a decrease in reaction times by 92.19 ± 9.79ms from pre- to post-task (t = 9.41, p < .0001), whereas the PD task order group saw a decrease in reaction times by 37.76 ± 10.41ms from pre- to post- task (t = 3.62, p = 0.02), demonstrating that after stimulation to PPC, the motor sequence may have been consolidated.



3.4. Reaction times across task order and stimulation site, differentiated by pre-TMS and post-TMS testing. Significant differences were observed between pre- and post-TMS reaction times in all groups except for sham stimulation in the PD task order.

Discussion

This study attempted to replicate in part the Brown & Robertson (2007) and the Cohen and Robertson (2011) works by comparing sham stimulation to M1 and left posterior parietal cortex stimulation using the same dual-task interference paradigm. We hypothesized that posterior parietal cortex is involved in the procedural consolidation of information, given that it is a site of sensorimotor integration and visual-spatial integration (Andersen, 1995; Iacoboni et al., 1998), and the serial reaction time task used to test motor memory binds together visual, spatial, and motor information together. Due to the PPC's involvement in episodic recollection, we also hypothesized that interference could be reduced for the declarative task via stimulation of the PPC before consolidation. When using ANOVAs to determine differences across groups, neither task order nor site of stimulation (including interactions) were found to be significant for either recall performance or skill performance. However, when investigating at a more granular level using mixed-effects modeling on reaction times, differences from pre- to post-TMS were found in all stimulation groups and across task orders with the exception of the sham group in the PD task order.

Based on these results, we failed to reject the null hypotheses, and it is uncertain whether the posterior parietal cortex is involved in the consolidation of either declarative or procedural memories, when the consolidation time for each

memory is 4 hours. While the PPC has been implicated in multisensory integration and episodic recollection and visual working memory, due to the size and anatomical variability across subjects, we may not have targeted the correct area involved in the processing of either declarative or procedural memories. Additionally, it is uncertain whether initial estimations of the time course of consolidation for procedural memories are accurate for serial reaction time testing. With more time between testing and retesting, (between 6-12 hours), we may have seen stronger effects of interference reduction between declarative and procedural memories.

One reason why the results are mixed could be because of individual variability in response and receptiveness to TMS; it is unknown what the neural and behavioral consequences of continuous theta burst stimulation are to areas outside of primary motor cortex (Pabst et al., 2021). Additionally, subjects may have different scalp and skull thicknesses, and posterior parietal cortex may be localized differently across subjects, which is impossible to account for unless access to fMRI-guided neuro-navigation for individuals is provided. One way we addressed subject variability is learning strategies of the motor sequence. Participants in this experiment could have explicitly learned the motor sequence, which would initially disqualify them from participating in the study (as seen in Brown & Robertson, 2007 and Cohen & Robertson, 2011), and is only detectable after completion of the study by way of post-experiment questioning. Explicitly learning this sequence utilizes declarative networks instead of procedural networks, and thus could have downstream consequences on behavior, which is why Cohen and Robertson (2011) initially discarded this data, however we intend to analyze the differences between these two subject pools. Current results indicate that differences do not exist between these two categories of participants. Further research could provide interesting insight into how declaratively learned motor information impacts declarative knowledge for word-list learning, and vice versa.

The results from the mixed-effects modeling does indicate that the motor sequence was learned, indicated by significant reductions in reaction time across almost all groups, including the sham stimulation group in the DP task order. This indicates that stimulation may have not been the driving factor in 1) reduction of interference between the two tasks and 2) consolidation of the sequence. Simply, enough time may have passed where off-line consolidation occurred for the motor memory. However, prior work conducted by Robertson and colleagues (2007, 2011) indicates that the primary motor cortex is involved in motor sequence consolidation, and stimulation of this area reduced interference between declarative and procedural memories, allowing for consolidation of the motor sequence. Another key difference between the current study and previous research is that our stimulation protocol utilized cTBS and not rTMS. These two stimulation protocols differ in the pattern of pulses delivered and the length of time required, although the end result is similar in that these protocols inhibit neural activity. These two stimulation protocols may act on different neural

mechanisms for inhibition and may also be the cause of discrepancies between the results of this study and the results in prior work.

While these results are inconclusive in regard to the involvement of the lPPC in declarative and procedural consolidation, this does not negate the use of TMS for determining causal involvement in cognitive processes. When conducting future research on the functional role of the PPC in memory, utilizing neuronavigation methods with individual MRIs to determine the precise location of the PPC that are involved in memory processing, and target those areas for cortical modulation. Further, it would be beneficial to determine the differences in memory functioning across the distinct areas of the PPC, including the intraparietal sulcus, superior marginal gyrus, and superior parietal lobule to determine their respective roles in encoding, consolidation, and retrieval of procedural and declarative memories. Because the parietal lobe is involved in multisensory integration, it is likely that its role will differ depending on the nature of the information encoded. In conclusion, we recommend that these mechanisms of interference between memory systems be further investigated with much more fine grain control in determining stimulation location for TMS.

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Chapter 4
A systematic review of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement

Intermittent theta-burst stimulation (iTBS) has been used to focally regulate excitability of neural cortex over the past decade – however there is little consensus on the generalizability of effects reported in individual studies. Many studies use small sample sizes (n < 30), and there is a considerable amount of methodological heterogeneity in application of the stimulation itself. This systematic meta-analysis aims to consolidate the extant literature and determine if up-regulatory theta-burst stimulation reliably enhances cognition through measurable behavior. Results show that iTBS – when compared to suitable control conditions — may enhance cognition when outlier studies are removed, and there is a significant amount of heterogeneity across studies. Significant contributors to between-study heterogeneity include location of stimulation and method of navigation to the stimulation site. Surprisingly, the type of cognitive domain investigated was not a significant contributor of heterogeneity. The findings of this meta-analysis demonstrate that standardization of iTBS is urgent and necessary to determine if neuroenhancement of particular cognitive faculties is reliable and robust, and measurable through observable behavior.

Introduction

The invention of non-invasive brain stimulation (NIBS) is potentially one of the most important advances in neuroscience. NIBS enables researchers to investigate the causal relationships between brain activity and behavior, without cost and risk associated with direct intracranial stimulation methods. Several protocols of NIBS exist and have been used not only as interventions in studies regarding the relationships between basic neurophysiology and cognition (for review, see Brunoni & Vanderhasselt, 2014; Simonsmeier et al., 2018), but also in the advancement of clinical neuroscience and the treatment of several neurological conditions, including Parkinson's disease (Goodwill et al., 2017), Alzheimer's disease (Hsu et al., 2015), dementia and mild cognitive impairment (MCI; Inagawa et al., 2019), schizophrenia (Rogasch et al., 2014; Sloan et al., 2020), and seizure disorders (Boon et al., 2018; Shafi et al., 2015). In particular, the theta burst magnetic stimulation protocols (TBS) are utilized to mimic the natural firing patterns of the brain to up- or down-regulate excitability of focal areas on the surface of the cortex with relatively high precision (Diamond et al., 1988; Peinemann et al., 2004; Rounis et al., 2005, 2006). The TBS protocols are advantageous because the stimulation can be applied relatively quickly (40s - 190s), allowing for larger sample sizes from populations that may not be able to tolerate several minutes of stimulation, as is the case for repetitive transcranial magnetic stimulation (rTMS) protocols which can last up to 30 minutes (Maeda et al., 2000). Intermittent patterns of TBS (iTBS; 190s of stimulation with 3 50Hz pulses repeated every 10s, 600 total pulses) tend to increase neural excitability

and induce long-term potentiation (LTP) in targeted neural circuits, whereas continuous stimulation (cTBS; 40s of stimulation with 3 50Hz pulses administered every 200ms, 600 total pulses) tends to decrease neural excitability and induce long-term depression (LTD) in targeted circuits (Huang et al., 2005).

Interest in facilitatory stimulation (including iTBS) in healthy human populations has grown throughout the past decade, specifically within government and private sectors because NIBS is a potentially useful and efficient method to enhance human cognition (Nelson & Tepe, 2015; Wexler, 2017). However, there are several caveats to interpreting recent studies utilizing iTBS protocols as having successfully enhanced human cognition. First, the iTBS protocol (Huang et al., 2005) was standardized to the human motor cortex of the dominant hand, and enhancement was operationalized as changes in cortical excitability (measured as muscle-evoked potentials (MEPs)). Extending this protocol to areas outside of the dominant motor cortex has not been standardized within the field. While this has not impeded new experimental findings using the iTBS protocol, researchers need to be cautious in the interpretation of their results when targeting non-dominant motor and non-motor cortical areas.

Researchers should also take caution in how they measure behavior and cognition, especially if there are no secondary measurements to directly quantify neural excitability before and after stimulation to monitor cortical change (Miniussi and Thut, 2010; Sack and Linden, 2003). Second, there is a lack of consistency in how human subjects respond to facilitatory stimulation (López-Alonso et al., 2014). Subjects can be classified as ‘responders’ or ‘non-responders’ to NIBS, but the proportion of subjects who are classified in these categories is rarely reported in methods sections of published studies. Third, there is no standardization in the reporting of equipment such as coil diameter and manufacturer of the TMS equipment or stimulation parameters including motor threshold used for stimulation (RMT vs. AMT). The effects of manipulating these parameters are largely unknown, and under reporting is common. While these issues exist, it is important to assess the existing studies within this body of work to understand which reported parameters may be contributing to variation between study results, and how or if existing studies provide support for the hypothesis that iTBS generally enhances cognition.

In a review conducted by Wischnewski and Schutter (2015), the authors investigated the efficacy of theta-burst protocols on MEP size and duration. Intermittent theta burst stimulation was found to be efficacious for up to a duration of 60 minutes, whereas continuous theta burst stimulation was efficacious for 20-40 minutes, depending on the duration of stimulation. While insightful, the outcomes of their review are limited to interventions involving stimulation of primary motor cortices, and these results should not be extended to findings where stimulation is performed outside of the motor cortex. Another review conducted by Chung and colleagues (2016) investigated the efficacy of TBS on multiple measures of cortical excitability across time. Similar to Wischnewski and Schutter’s (2015) findings, Chung et al. found cTBS was

effective for reduction of MEP amplitudes for up to 60 minutes, peaking in efficacy at 5 minutes, and iTBS was found to be effective for the increase of MEP amplitudes for up to 30 minutes, remaining similarly effective at both early (5 minutes post-TBS) and mid (20-30 minutes post-TBS) time points.

At this time, no systematic review on the efficacy of iTBS for neuroenhancement has been conducted. Specifically, no systematic review has been done to assess whether or not iTBS enhances cognition through measurable behavior due to its ability to potentiate neural populations. In this case, enhancement of cognition refers to a myriad of behavioral measurements that determine improvement in a particular skill or aspect of cognition, specifically reaction time, accuracy, or performance enhancements. While this is limited in the scope of what cognition entails and the ways in which it can be measured, a meta-analysis of this scope is justified due to the lack of understanding in the field of how iTBS manipulations effect higher-order cognitive processes which exclude corticospinal excitability measures and are generally measured through behavioral response paradigms. A systematic review or meta-analysis on the efficacy of iTBS with measures of cognition as the variable of interest and location of stimulation, parameters of stimulation, and the type of cognitive phenomena studied as the primary covariates would allow researchers to fully utilize neurostimulation techniques while avoiding methodological pitfalls.

The primary objective of this systematic meta-analysis was to determine if iTBS – when compared with proper control conditions – reliably enhances cognitive functioning. We evaluated reported effect sizes across studies for a variety of measures of cognitive enhancement that are not merely measures of cortical and cortico-spinal excitability, which have been assessed in the aforementioned meta-analyses (Chung et al., 2016; Wischnewski and Schutter, 2015). Specific measures of cognitive enhancement evaluated here include behavioral measurements of performance, accuracy, and reaction time in healthy adults. A secondary objective of this meta-analysis was to determine the optimal and influential parameters which contribute to reliable effect sizes in studies of cognitive enhancement using iTBS. Specific parameters assessed include stimulation location, and stimulation protocols including: determination of motor threshold, determination of stimulation location, coil and stimulator features, and features of the control condition. We also investigated the distribution of effect sizes and to assess heterogeneity between studies using aforementioned parameters as factors in meta-analytic models. Additionally, indications of publication bias were also assessed through small sample bias methods, as well as p-curve analyses.

Methods

Protocol and registration

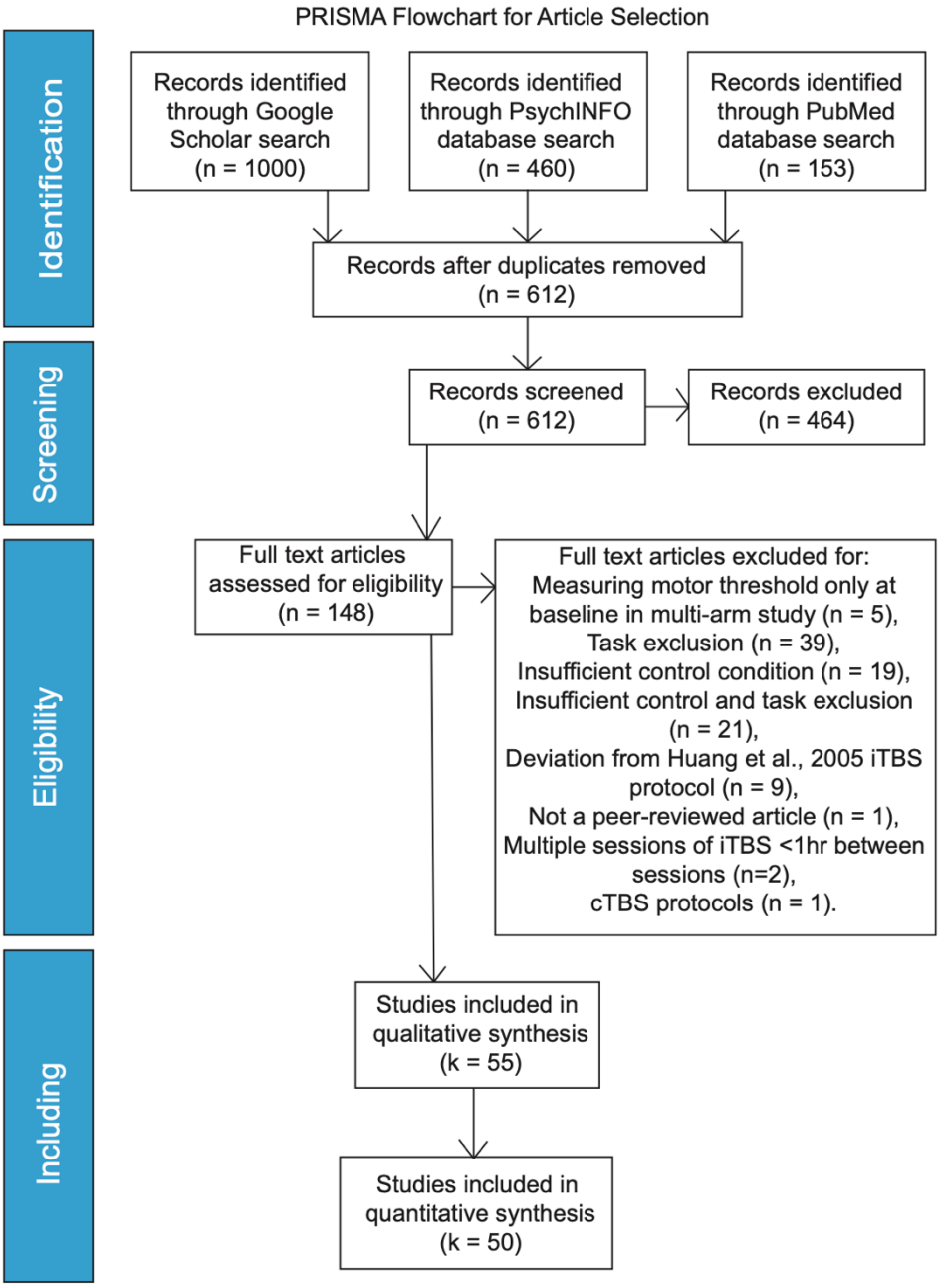
The meta-analysis adhered to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009).

Search strategy

The types of studies included in our search were: meta-analyses, original research articles, systematic reviews, and randomized controlled trials. All sources must have been peer reviewed and have high standards of methodological rigor to ensure that outside sources of variance are not contributing to the effects found in each study. Methodological rigor in this meta-analysis disqualified studies that did not provide details regarding motor threshold, an insufficient control condition, had a protocol deviating from the Huang et al. (2005) recommendation (including Goldsworthy et al., 2012), measured motor threshold at the beginning of the experiment and not during each session (if multiple sessions of iTBS), and had stimulation sessions more than once per day with less than an hour between sessions.

Reviewers first examined each database (Google Scholar, PsychINFO, and PubMed) and selected articles that contained the following topics/terms in their abstract or title: 1) iTBS, theta burst stimulation, TMS, or transcranial magnetic stimulation, 2) cognitive enhancement, neuroenhancement, or brain enhancement, and 3) healthy adults. The articles contained within each database that met the following criterion were added into a Google Spreadsheet that was shared across reviewers (AP, SP, DCC, BM, JMR). Two reviewers (AP, SP) assessed all screened articles in their entirety, adding information to a shared spreadsheet that would allow for determination of eligibility for each article. The information that was collected included the following: publication type, name of the journal, year of publication, mean and standard deviation of the studied sample, age range and gender of the studied sample, total sample size, experimental and control sample sizes, study design (between, mixed, or within-subjects), location of stimulated brain areas, stimulator and coil type, details of the control and experimental conditions, details of the motor thresholding process, percentage of motor threshold used for iTBS intensity, information about the type of cognitive task used, and the type of behavioral data collected. Pub-Med and PsychINFO databases were searched, and an additional search was conducted using Google Scholar. The Google Scholar search included the following terms: “intermittent theta burst stimulation AND iTBS OR theta burst stimulation OR TMS, enhancement OR cognitive enhancement OR neuroenhancement OR brain enhancement, healthy adults”. This search generated 1000 results, as that is the limit of Google Scholar’s search query. The PsychINFO database search used the following conditions: Record types: dissertation, dissertation chapter, journal articles, peer reviewed journals; Methodology: Brain imaging, clinical trial, empirical study, experimental replication, literature review, meta-analysis, quantitative study, systematic review; Language: English; Age group: adulthood; Population: human; Timeframe: 2010-2020; Search terms: In the abstract, must contain: “theta burst stimulation OR iTBS OR intermittent theta burst stimulation AND transcranial magnetic stimulation OR TMS AND healthy adults AND cognitive enhancement OR neuroenhancement OR brain enhancement”. This search query generated 460 results. For the PubMed database search, this used the same search terms as

the PsychINFO search, however the publication type was changed to include: “clinical study OR clinical trial OR comparative study OR controlled clinical trial OR journal article OR meta-analysis OR randomized controlled trial OR systematic review or validation study”. Limits for the PubMed search included no restrictions on gender, the age of the population studied must be 18 or above, the years of publication from January 2010 - April 2020, and language set to English for ease of reviewing for the reviewers. This search query generated 153 results. The final search query was performed April 14, 2020. In total, 1395 results were generated. After comparing the results of each query and checking for duplicates, 613 individual records were ready for initial review (see Figure 4.1 for study selection outline).



4.1. PRISMA Flowchart. Assessment of articles outlined in the Search Strategy section, beginning with identification of articles, the screening and eligibility process, and the number of included studies. Note that the definition of 'study' is a singular research finding, and multiple studies can be extracted from a single article.

Selection criteria and outcome measures

The population assessed included healthy adult subjects (aged 18+) with no neurological illness or reported contraindications to TMS (see Table 1 for specific inclusion and exclusion criteria). The intervention examined was the application of iTBS offline in relation to cognitive tasks. Cognitive tasks needed to include behavioral measurements of sensation, perception, cognition, or action in order to satisfy the inclusion criteria. Studies needed to include a sufficient control condition, which included sham stimulation, active stimulation of a region not involved in the task at hand, use of a placebo coil, or a separate no-stimulation condition. Study outcomes were required to pertain to the enhancement of cognitive abilities, specifically using behavioral measurements of performance, accuracy, or reaction time. The study designs that were included within the meta-analysis included between and within subject designs that compared control conditions with stimulation conditions. Criteria for dates were set to articles published after 2010, as safety guidelines for TMS were amended to include the use of theta-burst stimulation in 2009 (Rossi et al., 2009).

Table 4.1. PICOS Criteria for iTBS meta-analysis. This table describes the criteria required for a study to be eligible for inclusion in the meta-analysis, following PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) guidelines.

	Inclusion	Exclusion
Participants	○ Healthy adult subjects age 18 or over ○ No neurological illness ○ No contraindications to TMS	○ Non-human subjects ○ Any kind of neurological illness or contraindication to TMS ○ Subjects under age 18
Interventions	○ iTBS following the Huang et al., 2005 protocol (3 50Hz pulses applied every 10s for 190s, 600 total pulses) ○ Offline behavioral measurements ○ Cognitive tasks include behavioral measurements of sensation, perception, cognition, or action	○ iTBS administration deviating from Huang et al., 2005 protocol ○ Online measurements of cognition ○ Any other form of NIBS

Comparison	○ Sham condition (using placebo coil, reduction of stimulation intensity, coil rotation to point pulses away from cortex) ○ No stimulation condition ○ Active stimulation of a region not involved in the behavior measured	○ No comparison conditions ○ Active stimulation of regions involved in the measured behavior
Outcomes	○ Behavioral measurements of performance, reaction time, or accuracy	○ Cortico-spinal excitability measurements ○ fMRI, EEG, MEG, fNIRS measurements
Study Design	○ Post iTBS measurements compared to post-control measurements	○ Pre-post measurement studies with no control/sham conditions
Data Reported	○ Data that enables the estimation and calculation of effect sizes between comparator conditions and iTBS stimulation conditions including mean and standard deviation / standard error and effect sizes	○ Unpublished data ○ Published studies without enough data to enable effect size calculations
Type of Publications	○ Peer-reviewed journal articles ○ Written in English ○ Written between 2010 - 2020	○ Non-English journal articles ○ Grey literature, non-peer reviewed articles, preprints, case studies, review

		articles o Written before 2010

Data extraction

Each article was assessed in full text by five independent reviewers (AP, SP, BM, DC, JMR) to determine study eligibility. During this time, reviewers wrote questions in a collaborative document if an article posed additional questions that could change the determination of eligibility of an article, and any prior articles assessed before such questions arose were reassessed with the adapted criterion. Reviewers provided 'yes', 'no', or 'maybe' inclusion judgements, including reasons for 'no' and 'maybe' judgments. Reviewers were blind to each other's analysis eligibility decisions until all reviewers completed assessing the studies. At this point, the reviewers met and determined whether each study should be included in the meta-analysis. The inter-rater reliability was 86.23%. Any study that did not have unanimous agreement between reviewers was discussed until a consensus was formed.

Data were pulled from reported behavioral measurements taken in each study. If information was insufficient to calculate and estimate effect sizes, authors of that study were contacted to access the appropriate statistical information to estimate the effect size. Of the 55 eligible studies, 9 authors needed to be contacted for further information. Of the 9 authors contacted, 5 responded and shared information necessary for effect size calculation, and the rest (5 research findings in total) were excluded from quantitative analysis.

Meta-analysis

Calculating effect sizes

Effect size data and their respective standard errors, variances, and 95% confidence intervals were calculated by a single reviewer (AP), using standardized mean difference estimations of Cohen's d from reported means and standard deviations and tests of statistical significance. Hedges' g corrections were applied for small sample sizes (n < 30). 52 studies were included in the summative quantitative analysis. When standard deviations were not available but standard error was reported, the formula $SD = SE\sqrt{n}$, where n = sample size was used to calculate standard deviation (Higgins and Green, 2008). Meta-analyses were conducted in R (R version 4.0.3) and aided by Harrer and colleagues online guide and their "dmetar" R package (see Harrer et al., 2019 for a complete guide on performing meta-analysis). Prediction intervals, which are 95% confidence intervals that, given the present data, predict the significance of an effect in a subsequent study were calculated for each meta-analysis.

The meta-analysis models utilized all had the Hartung-Knapp adjustment set because it estimates the variance with improved coverage (Hartung and Knapp, 2001a,b; IntHout et al., 2014; Langen et al., 2019), especially when there is heterogeneity within the dataset, as we would expect given our a priori assumptions of the included studies. A Paule-Mandel estimator for tau

heterogeneity and Q-profile confidence interval estimation was used due to its robust performance and lack of requirement for fulfilling effect size distribution assumptions (Paule and Mandel, 1982; Veroniki et al., 2016).

Data analysis

The primary objective of this systematic meta-analysis was to determine if facilitatory stimulation using the iTBS protocol – when compared with proper control conditions – reliably enhances cognitive functioning. Due to the exploratory nature of the research question and the lack of consensus in the field regarding the true effects of facilitatory stimulation across research paradigms, all analyses were approached in an exploratory manner. First, meta-analysis was conducted across every effect regardless of cognitive task or behavior measured to establish if iTBS versus a properly controlled condition had an overall effect. Subsequent subgroup meta-analyses were then conducted across cognitive domains. Cognitive domains were established by independent reviewers during the eligibility screening process, with less than 100% consensus warranting a group discussion until agreement could be reached to place a study within a particular subgroup category. If a cognitive domain did not have a sufficient number of studies to allow for feasible effect-size analysis or publication bias, then they are mentioned in the discussion as a future direction worthy of pursuing but for the purposes of this meta-analysis, did not have the sufficient statistical power to address our research question directly. The cognitive domains that were established included attention (k=5), decision making (k=4), emotion (k=4), language (k=1), memory (k=5), motor skill (k=17), perception (k=4), social cognition (k=1), and working memory (k=9). Each study was limited to being placed in one category. Because each study had variation in how the dependent variables were measured and in the methodology employed, the standardized mean difference effect size measure was used to remove some of that variation and standardize measurements in the analysis.

Additional subgroup analyses were conducted to examine the impact of the chosen method of control, stimulation location, the type of measurement used, the percent of motor threshold used to set the iTBS settings, the use of active versus resting motor threshold, navigation to the stimulation location, and direction of current flow.

Test of heterogeneity

Between-study heterogeneity was assessed through the I^2 statistic of each model, with values of 25%, 50%, and 70% representing low, moderate, and substantial heterogeneity respectively. (Higgins et al., 2002). Due to the exploratory nature of the meta-analysis and the apparent heterogeneity in methodology utilized across studies (see Table 4.2 for a description of each study included in the meta-analysis), random-effects models were chosen for all analyses despite differing percentages of heterogeneity.

Outlier and influence analyses were conducted to determine which individual studies contributed substantial amounts of heterogeneity to the overall

effect, and to determine extreme effect sizes that have a large influence on the pooled effect of the meta-analysis. Outlier analyses were conducted by first examining extreme effect sizes where confidence intervals of individual studies did not overlap with the confidence interval of the pooled effect using the "dmetar" R package. Inference analyses were implemented using the "dmetar" package via a "leave-one-out" method, in which a meta-analysis is performed and its effect size is recalculated when a single study is left out of the analysis (Viectbauer and Cheung, 2010). Studies that were determined to be both outliers and have an unusually high influence on the effect size were removed from further analysis (see Baujat et al., 2002 for practical application of outlier analyses in meta-analysis). However, a sensitivity analysis was conducted and is included in the appendix of this dissertation.

Graphical displays of heterogeneity (GOSH) plots were generated to explore heterogeneity in the effect size data (Olkin, Dahabreh, and Trikalinos, 2012). GOSH plots fit a meta-analysis model to all possible subsets of included studies using the "metafor" R package (Viechtbauer 2010). Each of these models is then plotted, displaying the pooled effect size and between-study heterogeneity in which patterns and subgroups can be identified from the distribution of the data. The GOSH analyses did not influence our intention to pursue subgroup analyses; we intended to conduct exploratory analysis to determine which covariates, if any, had an influence on the heterogeneity of effect sizes or the effect sizes themselves. The particular covariates investigated included: study type (construct), control condition, stimulation location, dependent measure, percent of motor threshold used, AMT or RMT used, navigation to stimulation location, study design, and direction of current flow.

Further investigations into study heterogeneity and influence of subgroups on effect sizes were implemented by exploratory multiple meta-regression. Multiple meta-regression allows for the investigation of interactions and additive effects within a meta-regression model (Borenstein et al., 2011). This method allows the ability to combine and test all possible model predictor combinations and determines which predictors are the most important overall by comparing each model's corrected AIC value (Akaike Information Criterion; Akaike, 1974), creating an estimate for each predictor, and generating an estimate of predictor importance which ranges from 0-1 in value (Burnham & Anderson, 2002; Lindberg et al., 2015; Harrer et al., 2019). Multi-model inference was appropriate to use in this context due to the unknown nature of how each of our predictors influence the overall effect, as suggested by Higgins and Thompson for more robust models (Higgins and Thompson, 2004), and permutation tests were used to confirm the findings of the multiple meta-regression (Higgins and Thompson, 2004; Good, 2013; Viechtbauer et al., 2015).

4.2. Study Characteristics. Table depicting each study included in the quantitative analysis and characteristics of each study relevant to analysis, if reported

Studies	Size (n)	Gender Ratio	Mean Age ± SD (age range)	iTBS (current flow)	Control	Area (Nav. To location)	Task	Coil type (diameter), Stimulator
Bogdanov et al., 2018	32*	35F:30M	24.52 ± 0.36 (19 – 32)	80% RMT	No Stim	Infero-lateral rPFC (Ind. MRI)	Motor Skill (Acc)	Fig 8 coil (70mm), Magstim SuperRapid 2
Cardenas-Morales et al., 2010	17	17M	23.7 ± 2.6 (24 – 33)	90% AMT (AP)	No Stim	lM1 (Ind. Mapping)	Decision Making (RT)	MCFB70 (97mm), MagProX100
Che et al., 2019 (1)	20	12F:8M	26.45 ± 4.54	70% RMT	Rotated coil	ldmPFC (10-20 system)	Emotion (Score)	Cool-B65 (75mm)
Che et al., 2019 (2)	20	12F:8M	26.45 ± 4.54	70% RMT	Rotated Coil	ldmPFC (10-20 system)	Perception (Score)	Cool-B65 (75mm)
Chung et al., 2018 (1)	18	10F:8M	25.6 ± 7	75% RMT (PA)	Rotated Coil	ldmPFC (10-20 system)	Working Memory (Score)	Cool-B65 (75mm)
Chung et al., 2018 (2)	18	10F:8M	25.6 ± 7	75% RMT (PA)	Rotated Coil	ldmPFC (10-20 system)	Working Memory (Score)	Cool-B65 (75mm)
Conte et al., 2012	53*	40F:42M	32.9	80% RMT (PA)	Rotated Coil	lM1 (Ind. Mapping)	Motor Skill (Score)	Fig 8 coil (100mm), MagPro RapidRate
Crescentini et al., 2015	14	8F:6M	22.07 ± 2.12	80% AMT (PA)	Rotated Coil	rIPL (Ant. Landmarks)	Decision Making (Acc.)	Air-cooled Fig 8 (70mm), Magstim SuperRapid 2
de Dreu et al., 2016	36	36M	25.16 ± 2 (20-28)	80% AMT	imTBS	rIFG (Ind MRI)	Decision Making (Score)	Fig 8 (70mm), 3.5T Magstim SuperRapid 2
Debarnot et al., 2015	20*	iTBS 7F:3Mcontrol 6F:4M	iTBS 70.2 ± 5.5; control 70.2 ± 4.8	80% AMT	Active control	lBA10 (Ind MRI)	Memory (Score)	Fig 8 (70mm), Magstim SuperRapid
Depperma nn et al., 2016	42*	74F:9M	26.46 ± 8.47	80% MT (PA)	Rotated Coil	lDLPFC (10-20 system)	Emotion (RT)	MCFB65 (75mm), MagOption/

								MagproX100
Duffy et al., 2019	56	37F:19M	24.6 ± 5.3 (18-40)	80% AMT	Rotated Coil	rTPJ (Ind. MRI)	Social Cognition (Score)	Cool-BCF65 (75mm), MagProX100
Finkel et al., 2019	14	7F:7M	27.3 (22-35)	80% AMT (AP)	Active Control	rS1 larynx (Ind. MRI)	Perception (Acc.)	Fig 8 (70mm), Magstim Rapid2
Gan et al., 2019 (1)	22	14F:8M	(18-40)	80% RMT (AP)	Sham tDCS	lPPC (10-20 system)	Working Memory (Score)	Circular (114 mm), MagProX100
Gan et al., 2019 (2)	22	14F:8M	(18-40)	80% RMT (AP)	Sham tDCS	lPPC (10-20 system)	Attention (Score)	Circular (114mm), MagProX100
Gan et al., 2019 (3)	22	14F:8M	(18-40)	80% RMT (AP)	Sham tDCS	lPPC (10-20 system	Emotion (RT)	Circular (114mm), MagProX100
Gheysen et al., 2016 (1)	67	8F:7M*	24.4 ± 3.1	80% AMT (AP)	No Stim	lCerebellum (Ind MRI)	Motor Skill (Acc)	Fig 8 Airfilm (70mm), Magstim Rapid2
Gheysen et al., 2016 (2)	71	12F:7M*	24.6 ± 3.1	80% AMT (AP)	No Stim	rCerebellum (Ind MRI)	Motor Skill (Acc)	Fig 8 Airfilm (70mm), Magstim Rapid2
Giboin et al., 2016	10	10M	26 ± 2	80% AMT (AP)	Rotated coil	lM1 Lower Limb (Ind Mapping)	Motor Skill (Score)	MCB70 (97mm), MagPro R30
He et al., 2013 (1)	60	30F:30M	20.1 (19-23)	80% RMT (AP)	Rotated Coil	lPPC (10-20 system)	Attention (RT)	Nitrogen-cooled Fig 8 (70mm), YirudeCCY-I
He et al., 2013 (2)	60	30F:30M	20.1 (19-23)	80% RMT (AP)	Rotated Coil	rPPC(10-20 system)	Attention (RT)	Nitrogen-cooled Fig 8 (70mm), YirudeCCY-I
He et al., 2013 (3)	60	30F:30M	20.1 (19-23)	80% RMT (PA)	Rotated Coil	lDLPFC (10-20 system)	Attention (RT)	Nitrogen-cooled Fig 8 (70mm), YirudeCCY-I
He et al., 2013 (4)	60	30F:30M	20.1 (19-23)	80% RMT (PA)	Rotated Coil	rDLPFC (10-20 system)	Attention (RT)	Nitrogen-cooled Fig 8 (70mm),

								YirudeCCY-I
Hoy et al., 2016 (1)	19	9F:10M	22.16 ± 2.93	80% RMT	Rotated Coil	lDLPFC (10-20 system)	Working Memory (score)	Fig 8 (70mm) MagVenture R30/X100
Hoy et al., 2016 (2)	19	9F:10M	22.16 ± 2.93	80% RMT	Rotated Coil	lDLPFC (10-20 system)	Working Memory (score)	Fig 8 (70mm) MagVenture R30/X100
Jelić et al., 2015 (1)	20*	12F:18 M	26 ± 3	80% AMT (PA)	Placebo Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Fig 8 (70mm) Magstim Rapid
Jelić et al., 2015 (2)	20*	12F:18 M	26 ± 3	80% AMT (PA)	Placebo Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Fig 8 (70mm) Magstim Rapid
Koch et al., 2020 (1)	24*	20F:16 M	26.2 ± 3.9	80% AMT (AP)	Rotated Coil	rCerebellum (Ant Landmarks)	Motor Skill (Acc)	Fig 8 (70mm) Magstim Rapid
Koch et al., 2020 (2)	12	6F:6M	25.6 ± 2.9	80% AMT (AP)	Rotated Coil	rCerebellum (Ant Landmarks)	Motor Skill (Acc)	Fig 8 (70mm), Magstim Rapid
López-Alonso et al., 2015	56	6F:50M	20.51 ± 1.52	80% AMT (PA)	Non-Responder Participants	lM1 (Ind Mapping)	Motor Skill	Fig 8 (70mm), Magstim SuperRapid
López-Alonso et al., 2018	14*	16F:12 M	27.21 ± 6.93	80% AMT	Sham tDCS	lM1 (Ind Mapping)	Motor Skill	Fig 8 (70mm), Magstim SuperRapid
Mioli et al., 2018 (1)	28	16F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rPMv (Opto Electric NeuroNav)	Perception (Score)	Fig 8 (90mm), DuoMagXT 100
Mioli et al., 2018 (2)	28	16F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rIPL (Opto Electric NeuroNav)	Perception (Score)	Fig 8 (90mm), DuoMagXT 100
Mioli et al., 2018 (3)	28	16F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rPMv (Opto Electric NeuroNav)	Perception (Acc)	Fig 8 (90mm), DuoMagXT 100
Mioli et al., 2018 (4)	28	16F:12 M	26.68 ± 4.66	80% AMT	Rotated Coil	rIPL (Opto Electric	Perception (Acc)	Fig 8 (90mm), DuoMagXT 100

						NeuroNav)		
Notzon et al., 2018	41	21F:20M	iTBS: 24.7 (19-29) Control: 27.2 (21-45)	80% RMT	Rotated Coil	rDLPFC (10-20 system)	Emotion (RT)	Fig 8 (70mm), MagProX100 Option
Restle et al., 2012	18	NA	26 ± 4.7	80% AMT	Active Control	lpIFG (Ind MRI)	Language (Acc)	Fig 8 (65mm), MagProX100
Si et al., 2019	24*	25F:35M	22.03 (18-26)	80% MT	Rotated Coil	FZ (10-20 System)	Decision Making (Score)	Fig 8 (70mm), Magstim SuperRapid 2
Stöckel et al., 2015	24	14F:10M	iTBS: 28.1 ± 6.7 Control: 24.3 ± 5.1	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill	Fig 8 (70mm) Magstim SuperRapid 2
Stöckel et al., 2016 (1)	24*	13F:11M	iTBS: 24.4 ± 5.9 Control: 24.4 ± 5	80% AMT (PA)	Rotated Coil	rM1 (Ind Mapping)	Motor Skill (Score)	Fig 8 (70mm), Magstim SuperRapid 2
Stöckel et al., 2016 (2)	24*	14F:10M	iTBS: 26.2 ± 5.6 Control: 24.4 ± 5	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill (Score)	Fig 8 (70mm), Magstim SuperRapid 2
Turriziani et al., 2012 (1)	20*	78F:22M	(20-35)	80% AMT	Rotated Coil	rDLPFC (10-20 system)	Memory (Acc)	Fig 8 (70mm), Magstim SuperRapid
Turriziani et al., 2012 (2)	20*	78F:22M	(20-35)	80% AMT	Rotated Coil	lDLPFC (10-20 system)	Memory (Acc)	Fig 8 (70mm), Magstim SuperRapid
Vidal-Piñeiro et al., 2014 (1)	22	NA	71.75 ± 6.81 (61-80)	80% AMT	Placebo Coil	lIFG (Ind MRI)	Memory (Acc)	Fig 8, MagProX100
Vidal-Piñeiro et al., 2014 (2)	22	NA	71.75 ± 6.81 (61-80)	80% AMT	Placebo Coil	lIFG (Ind MRI)	Memory (Acc)	Fig 8, MagProX100
Viejo-Sobera et	24*	26F:10M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLFPC (Ind MRI)	Working Memory (Acc)	Fig 8 (70mm), Magstim

al., 2013 (1)								SuperRapid 2
Viejo-Sobera et al., 2013 (2)	24*	26F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory (Score)	Fig 8 (70mm), Magstim SuperRapid 2
Viejo-Sobera et al., 2013 (3)	24*	26F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory (Score)	Fig 8 (70mm), Magstim SuperRapid 2
Viejo-Sobera et al., 2013 (4)	24*	26F:10 M	29.22 ± 9.7	80% AMT	Rotated Coil	lDLPFC (Ind MRI)	Working Memory	Fig 8 (70mm), Magstim SuperRapid 2
Wilkinson et al., 2010	16	10F:6M	iTBS: 27.63 ± 4.44 Control: 27.63 ± 4.44	80% AMT (PA)	Rotated Coil	lM1 (Ind Mapping)	Motor Skill	Fig 8 (70mm), Magstim Rapid

Publication bias

Publication bias was investigated through both p-curve methods and small sample bias methods. P-curve methods investigate the likelihood of publication bias occurring due to significance levels and p-hacking (Simonsohn, Nelson, and Simmons, 2014a), whereas small-sample bias methods investigate the likelihood of publication bias occurring when small-sampled studies that have very large effects are published, leaving small-sampled studies whose effects are small and non-significant to contribute to the 'file-drawer' problem (Dickersin, 2005). Publication bias influences the pooled effect, and thus can contribute to a poor estimation of the true effect size of a given intervention in meta-analyses. Both of these methods were used to determine if any amount of publication bias exists regardless of theoretical assumptions.

Results

Selection of studies

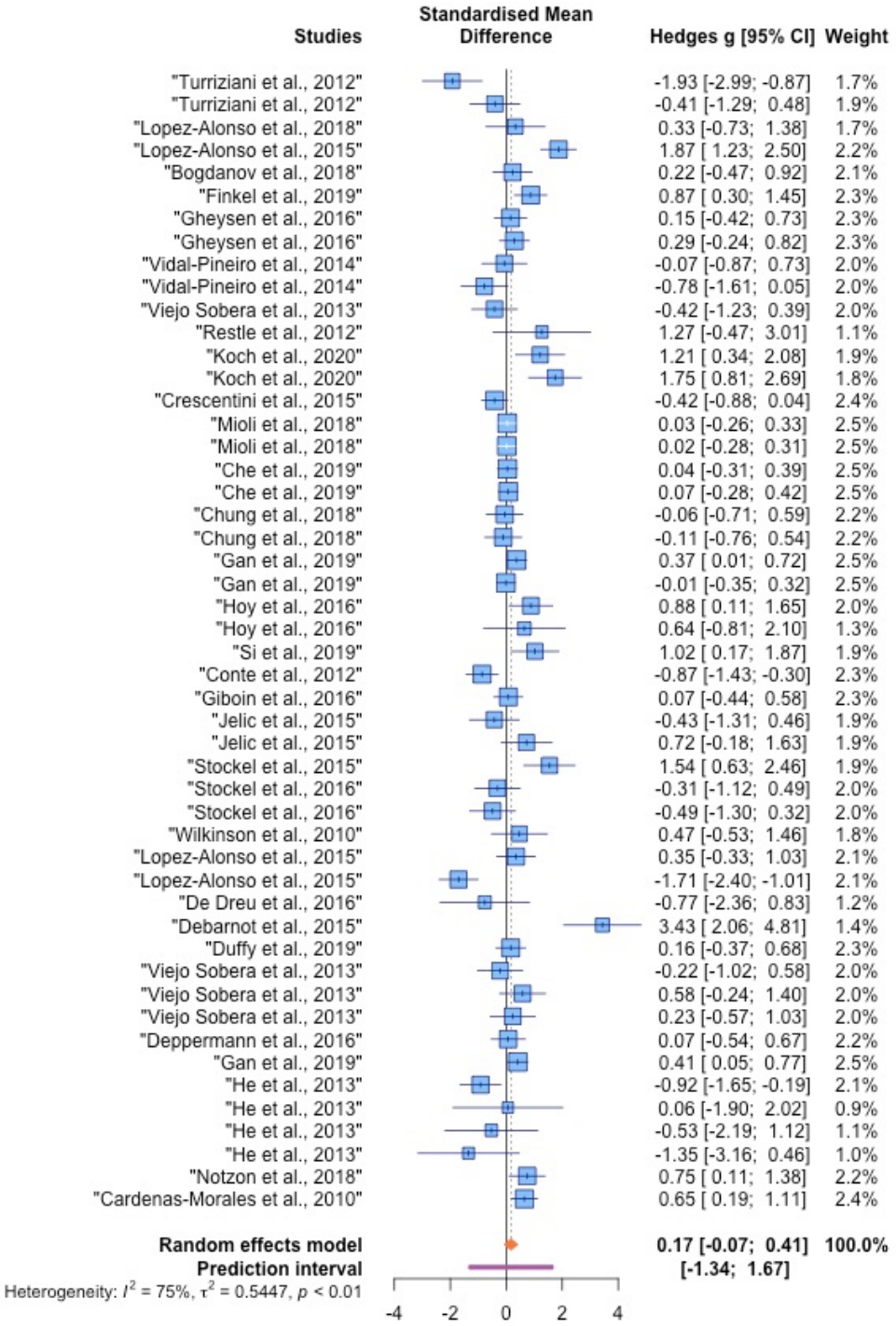
After duplicate removal from the set of studies generated through electronic query of journal article databases and the web, a total of 612 studies underwent initial review. Abstracts and titles were screened against the aforementioned selection criteria, and a total of 464 articles were removed for not meeting the inclusion criteria. Of the 148 articles that underwent full-text screening of eligibility, 5 were removed for not meeting the methodological standards of establishing motor threshold or a baseline measurement prior to iTBS, 39 were removed for not meeting the task requirements, 19 were removed for having insufficient control conditions, 21 were removed for both having insufficient control conditions and not meeting the task requirements, 9 were

removed for not adhering to the Huang et al., 2005 iTBS protocol, 1 was removed for being a conference abstract and not being a peer-reviewed journal article, 2 were removed for applying iTBS within an hour of having received a first dose of iTBS, which may impact cortical excitability (Tse et al., 2018), and 1 was excluded for being an inhibitory protocol. This left 52 articles (55 total studies, as some articles contributed more than one eligible research finding) to be included within the qualitative synthesis of studies, and finally 50 research findings from those articles were included in the quantitative assessment of the meta-analysis (see Table 2 for list of included articles and their study characteristics). The 55 research findings included in the qualitative synthesis reflect the total number of studies deemed eligible, and the 50 research findings included in the quantitative synthesis of results reflects all the studies that provided sufficient data to estimate effect sizes.

Synthesized findings

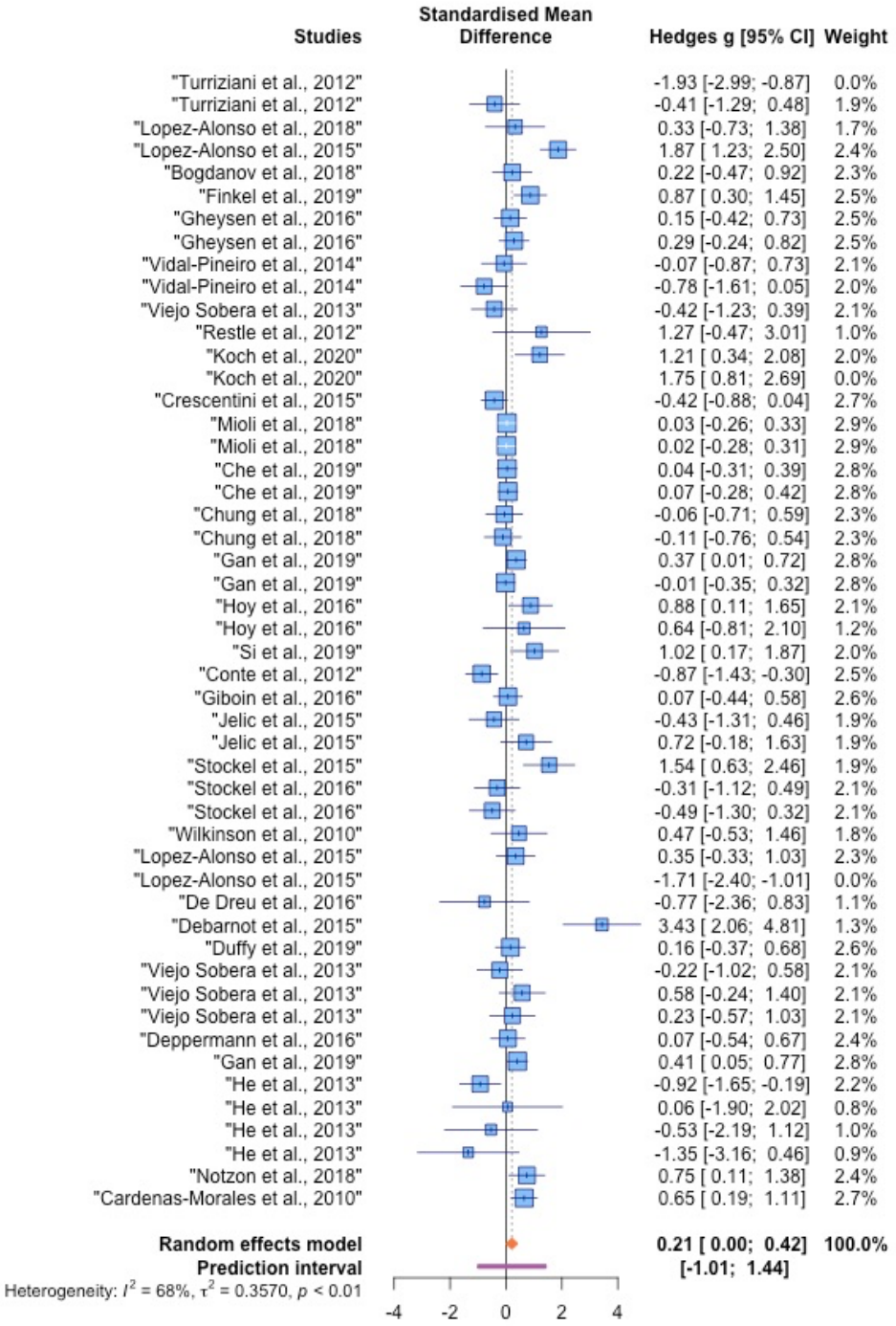
iTBS versus control

Figure 4.2 provides a summary of the effect sizes across all studies, regardless of cognitive domain or methodological parameters. The effect of iTBS is small compared to control conditions and is non-significant (pooled SMD = 0.17, 95% CI [-0.07, 0.41], $p = 0.17$). Additionally, the prediction interval was non-significant (95% CI [-1.34, 1.67]). Heterogeneity of the studies was determined to be significant ($tau^2 = 0.54$, 95% CI [0.31, 0.99]; $I^2 = 75.3\%$, 95% CI [67.6%, 81.2%]; Q = 198.58, $p < 0.0001$).



4.2. iTBS versus Control. Forest plot of Hedges' g pooled effect size for iTBS versus control conditions across all studies.

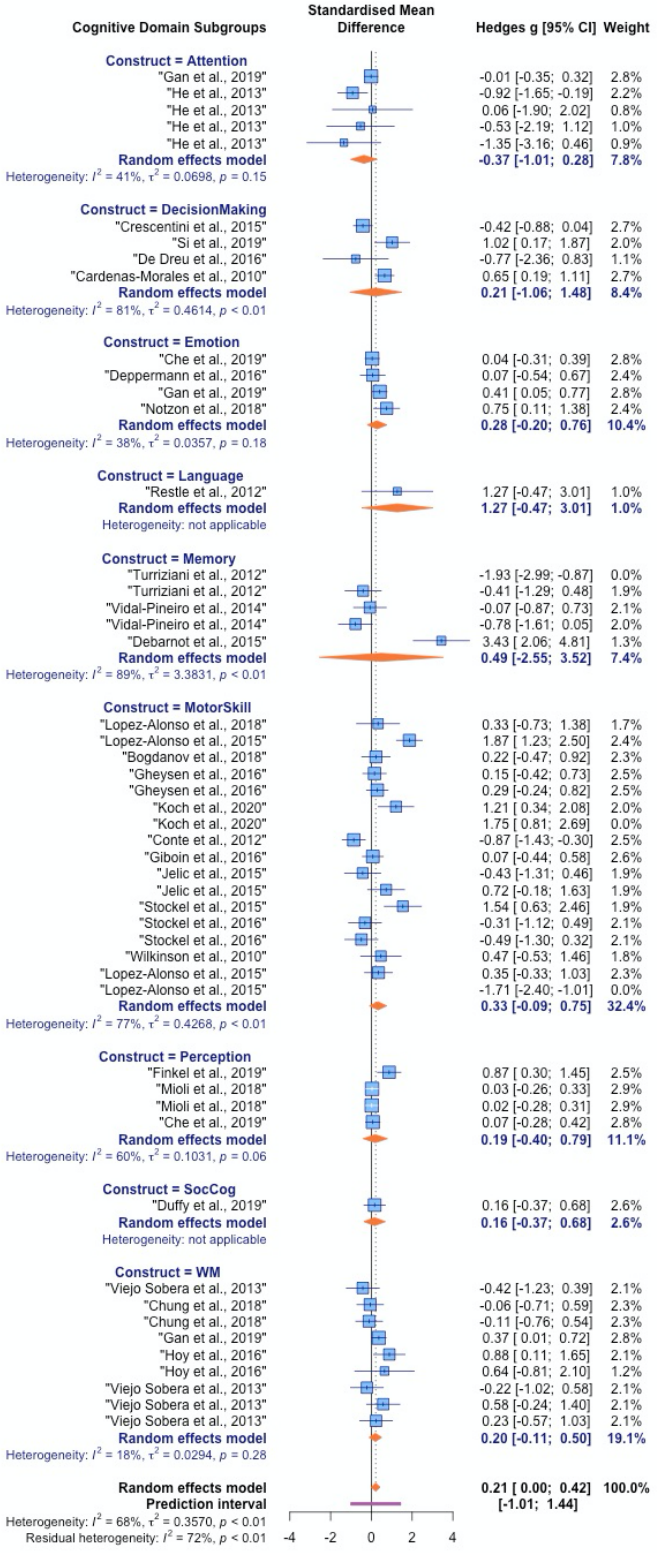
Outlier and influence analyses were conducted to determine which studies contribute significantly to the heterogeneity and size of the pooled effect. Further influence analyses using GOSH plots to identify naturally occurring clusters in the data. Confidence interval boundary outlier analyses tagged 8 studies as having potentially significant influence on the effect size. K-means algorithm, DBSCAN (density-based spatial clustering of applications with noise) algorithm, and a Gaussian Mixture Model found 5, 25, and 6 studies respectively which significantly influenced the effect size. The three studies that overlapped between the outlier analysis and the influence analyses were removed from subsequent analyses. An updated meta-analysis was conducted with the following studies removed: Koch et al., 2020 (2), Turriziani et al., 2012 (1), and López-Alonso et al., (2015; 3) (see Table 2 for study characteristics). The updated meta-analysis, shown in Figure 4.3, (k = 47) revealed a significant effect (SMD = 0.21, 95% CI [0.003, 0.42], $p = 0.047$), however the prediction interval maintained no significant effects would be produced in future studies on the basis of the data present (95% CI [-1.01, 1.44]). Heterogeneity measures indicate a sizeable decrease in the outlier-reduced model compared to the full model ($tau^2 = 0.36$, 95% CI [0.18, 0.71]; $I^2 = 68.3\%$, 95% CI [57.2%, 76.5%]; Q = 145.09, $p < 0.001$). This indicates that overall, when iTBS is compared to control conditions, there may be very small significant effects. However, this may be dependent on the context of the study conducted, as heterogeneity measures indicate a moderate to substantial presence of heterogeneity. This warrants further investigation using subgroup analyses to determine the specific variables and contexts in which studies using iTBS compared to control may have significant effect sizes.



4.3. iTBS versus Control – Outlier-reduced Model. Forest plot of outlier-extracted meta-analysis comparing iTBS versus control conditions.

Subgroup analyses: cognitive domain

Cognitive domain covariates included attention (k = 5), decision-making (k =4), emotion, (k = 4), language (k = 1), memory (k = 4), motor skill (k = 15), perception (k = 4), social cognition (k = 1), and working memory (k = 9). The factor of cognitive domain was not found to have significant differences between groups (Q = 8.07, p = 0.43). None of the subgroups were found to significantly influence effect size (see Figure 4).



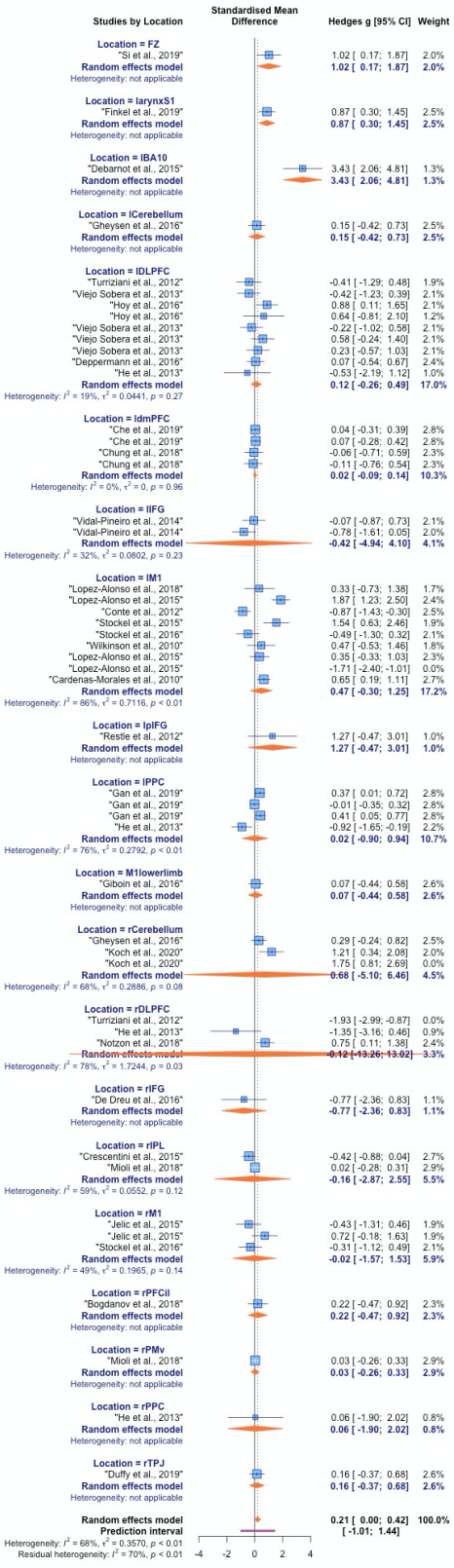
4.4 iTBS versus Control: Cognitive Domain Subgroups. Forest plot distinguishing pooled effects for each cognitive domain of iTBS versus control conditions.

Subgroup analyses: control conditions

The type of control condition used in each iTBS study was included as a factor for contributions to between-study heterogeneity. The control conditions used were active control (k = 3), intermediate theta burst stimulation (imTBS; k = 1), non-responding control populations (k = 3), no stimulation condition (k = 4), placebo coil (k = 4), rotation of the coil away from cortex (k = 29), and sham transcranial direct current stimulation (sham tDCS; k = 4). Marginally significant differences were found between groups (Q = 11.89, p = 0.06), however none of the subgroups of the control conditions were found to significantly influence effect size. This could be because the control condition of rotation with the coil included many more studies than other covariates.

Subgroup analyses: stimulation location

Location of non-control stimulation was included as a factor for contributions to between-study heterogeneity. The location subgroups included FZ (k = 1), larynx sensory cortex (k=1), left BA10 (k = 1), left cerebellum (k=1), left dorsolateral prefrontal cortex (DLPFC; k = 9), left dorsomedial prefrontal cortex (dmPFC; k = 4), left inferior frontal gyrus (IFG; k = 2), left primary motor cortex (M1; k = 8), left posterior inferior frontal gyrus (pIFG; k = 1), left posterior parietal cortex (PPC; k = 4), lower limb motor cortex (k = 1), right cerebellum (k = 2), right DLPFC (k = 2), right IFG (k=1), right inferior parietal lobule (IPL; k = 2), right M1 (k = 3), right inferolateral PFC (k = 1), right ventral premotor cortex (PMv; k = 1), right PPC (k = 1), right temporoparietal junction (TPJ; k = 1). Significant differences were found between groups for location of stimulation (Q = 46.53, p = 0.0004; see Figure 4.5). Locations FZ and larynx sensory cortex, and left BA10 were found to significantly influence effect size (FZ: SMD = 1.02, 95% CI [0.17, 1.87]; larynx S1: SMD = 0.87, 95% CI [0.30, 1.45]; lBA10: SMD = 3.43, 95% CI [2.06, 4.81]), however each of these location subgroups only had one study contribution to that location and should not be considered to generalize to future studies or the population.


Studies by Location
Standardised Mean Difference
Hedges g [95% CI]
Weight
Location = FZ
"Si et al., 2019" 1.02 [0.17; 1.87] 2.0%
Random effects model 1.02 [0.17; 1.87] 2.0%
Heterogeneity: not applicable
Location = larynxS1
"Finkel et al., 2019" 0.87 [0.30; 1.45] 2.5%
Random effects model 0.87 [0.30; 1.45] 2.5%
Heterogeneity: not applicable
Location = lBA10
"Debarnot et al., 2015" 3.43 [2.06; 4.81] 1.3%
Random effects model 3.43 [2.06; 4.81] 1.3%
Heterogeneity: not applicable
Location = lCerebellum
"Gheysen et al., 2016" 0.15 [-0.42; 0.73] 2.5%
Random effects model 0.15 [-0.42; 0.73] 2.5%
Heterogeneity: not applicable
Location = lDLPFC
"Turriziani et al., 2012" -0.41 [-1.29; 0.48] 1.9%
"Viejo Sobera et al., 2013" -0.42 [-1.23; 0.39] 2.1%
"Hoy et al., 2016" 0.88 [0.11; 1.65] 2.1%
"Hoy et al., 2016" 0.64 [-0.81; 2.10] 1.2%
"Viejo Sobera et al., 2013" -0.22 [-1.02; 0.58] 2.1%
"Viejo Sobera et al., 2013" 0.58 [-0.24; 1.40] 2.1%
"Viejo Sobera et al., 2013" 0.23 [-0.57; 1.03] 2.1%
"Deppermann et al., 2016" 0.07 [-0.54; 0.67] 2.4%
"He et al., 2013" -0.53 [-2.19; 1.12] 1.0%
Random effects model 0.12 [-0.26; 0.49] 17.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.0441, p = 0.27
Location = ldmPFC
"Che et al., 2019" 0.04 [-0.31; 0.39] 2.8%
"Che et al., 2019" 0.07 [-0.28; 0.42] 2.8%
"Chung et al., 2018" -0.06 [-0.71; 0.59] 2.3%
"Chung et al., 2018" -0.11 [-0.76; 0.54] 2.3%
Random effects model 0.02 [-0.09; 0.14] 10.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96
Location = lIFG
"Vidal-Pineiro et al., 2014" -0.07 [-0.87; 0.73] 2.1%
"Vidal-Pineiro et al., 2014" -0.78 [-1.61; 0.05] 2.0%
Random effects model -0.42 [-4.94; 4.10] 4.1%
Heterogeneity: I^2 = 32%, τ^2 = 0.0802, p = 0.23
Location = lM1
"Lopez-Alonso et al., 2018" 0.33 [-0.73; 1.38] 1.7%
"Lopez-Alonso et al., 2015" 1.87 [1.23; 2.50] 2.4%
"Conte et al., 2012" -0.87 [-1.43; -0.30] 2.5%
"Stockel et al., 2015" 1.54 [0.63; 2.46] 1.9%
"Stockel et al., 2016" -0.49 [-1.30; 0.32] 2.1%
"Wilkinson et al., 2010" 0.47 [-0.53; 1.46] 1.8%
"Lopez-Alonso et al., 2015" 0.35 [-0.33; 1.03] 2.3%
"Lopez-Alonso et al., 2015" -1.71 [-2.40; -1.01] 0.0%
"Cardenas-Morales et al., 2010" 0.65 [0.19; 1.11] 2.7%
Random effects model 0.47 [-0.30; 1.25] 17.2%
Heterogeneity: I^2 = 86%, τ^2 = 0.7116, p < 0.01
Location = lpIFG
"Restle et al., 2012" 1.27 [-0.47; 3.01] 1.0%
Random effects model 1.27 [-0.47; 3.01] 1.0%
Heterogeneity: not applicable
Location = lPPC
"Gan et al., 2019" 0.37 [0.01; 0.72] 2.8%
"Gan et al., 2019" -0.01 [-0.35; 0.32] 2.8%
"Gan et al., 2019" 0.41 [0.05; 0.77] 2.8%
"He et al., 2013" -0.92 [-1.65; -0.19] 2.2%
Random effects model 0.02 [-0.90; 0.94] 10.7%
Heterogeneity: I^2 = 76%, τ^2 = 0.2792, p < 0.01
Location = M1lowerlimb
"Giboin et al., 2016" 0.07 [-0.44; 0.58] 2.6%
Random effects model 0.07 [-0.44; 0.58] 2.6%
Heterogeneity: not applicable
Location = rCerebellum
"Gheysen et al., 2016" 0.29 [-0.24; 0.82] 2.5%
"Koch et al., 2020" 1.21 [0.34; 2.08] 2.0%
"Koch et al., 2020" 1.75 [0.81; 2.69] 0.0%
Random effects model 0.68 [-5.10; 6.46] 4.5%
Heterogeneity: I^2 = 68%, τ^2 = 0.2886, p = 0.08
Location = rDLPFC
"Turriziani et al., 2012" -1.93 [-2.99; -0.87] 0.0%
"He et al., 2013" -1.35 [-3.16; 0.46] 0.9%
"Notzon et al., 2018" 0.75 [0.11; 1.38] 2.4%
Random effects model -0.12 [-13.26; 13.02] 3.3%
Heterogeneity: I^2 = 78%, τ^2 = 1.7244, p = 0.03
Location = rIFG
"De Dreu et al., 2016" -0.77 [-2.36; 0.83] 1.1%
Random effects model -0.77 [-2.36; 0.83] 1.1%
Heterogeneity: not applicable
Location = rIPL
"Crescentini et al., 2015" -0.42 [-0.88; 0.04] 2.7%
"Mioli et al., 2018" 0.02 [-0.28; 0.31] 2.9%
Random effects model -0.16 [-2.87; 2.55] 5.5%
Heterogeneity: I^2 = 59%, τ^2 = 0.0552, p = 0.12
Location = rM1
"Jelic et al., 2015" -0.43 [-1.31; 0.46] 1.9%
"Jelic et al., 2015" 0.72 [-0.18; 1.63] 1.9%
"Stockel et al., 2016" -0.31 [-1.12; 0.49] 2.1%
Random effects model -0.02 [-1.57; 1.53] 5.9%
Heterogeneity: I^2 = 49%, τ^2 = 0.1965, p = 0.14
Location = rPFCil
"Bogdanov et al., 2018" 0.22 [-0.47; 0.92] 2.3%
Random effects model 0.22 [-0.47; 0.92] 2.3%
Heterogeneity: not applicable
Location = rPMv
"Mioli et al., 2018" 0.03 [-0.26; 0.33] 2.9%
Random effects model 0.03 [-0.26; 0.33] 2.9%
Heterogeneity: not applicable
Location = rPPC
"He et al., 2013" 0.06 [-1.90; 2.02] 0.8%
Random effects model 0.06 [-1.90; 2.02] 0.8%
Heterogeneity: not applicable
Location = rTPJ
"Duffy et al., 2019" 0.16 [-0.37; 0.68] 2.6%
Random effects model 0.16 [-0.37; 0.68] 2.6%
Heterogeneity: not applicable
Random effects model 0.21 [0.00; 0.42] 100.0%
Prediction interval [-1.01; 1.44]
Heterogeneity: I^2 = 68%, τ^2 = 0.3570, p < 0.01
Residual heterogeneity: I^2 = 70%, p < 0.01
-4
-2
0
2
4

4.5. iTBS versus Control: Stimulation Location Subgroups. Forest plot of location subgroups.

Subgroup analyses: measurement variable

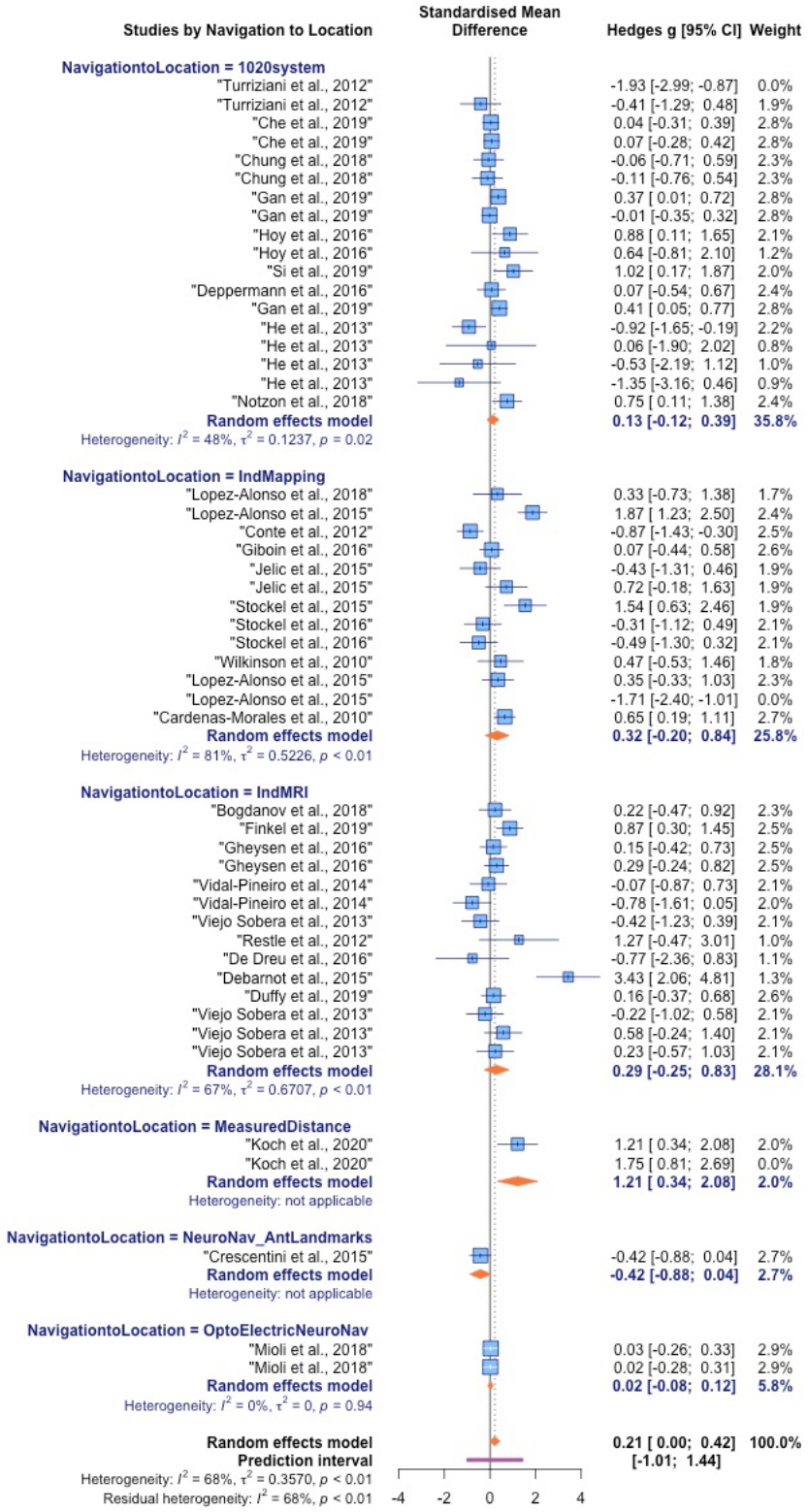
The measurement variable used was included as a factor for contributions of between-study heterogeneity. The measurement variable subgroups included studies that measured reaction time (k = 8), accuracy (k = 15), and performance (k = 24). No differences were found across subgroups (Q = 0.32, *p* = 0.85; see Figure 7). No significant differences in effect size were found for any of the groups.

Subgroup analyses: AMT versus RMT

The motor thresholding technique used to set iTBS intensity was investigated to determine if between-group differences exist for active motor threshold versus resting motor threshold. The subgroups included studies that used AMT (k = 29), unspecified MT (k = 2), and RMT (k = 16). No differences were found between subgroups (Q = 2.07, *p* = 0.35). No significant differences in effect size were found for any of the groups.

Subgroup analyses: navigation to stimulation location

Navigation to stimulation location was included in subgroup analyses to determine if any differences existed between subgroups due to navigation techniques. The conditions included using the 10-20 system (k = 17), individual mapping of the cortex (k = 12), individualized MRI scans (k = 14), measured distance from primary motor cortex (k = 1), neuronavigation using anatomical landmarks (k = 1), and opto-electric neuronavigation (k = 2). Significant differences were found between groups (Q = 14.12, *p* = 0.01; see Figure 4.6). Measured distance methods of navigation had a significant influence on effect size (SMD – 1.21, 95% CI [0.34, 2.08]), however this finding should be taken with caution and not extended to generalize to population effects because only one research finding was contributed to that subgroup. Individual mapping contributed the most heterogeneity to the distribution of effect sizes (Q = 59.32, tau^2 = 0.52), followed by individualized MRI (Q = 39.22, tau^2 = 0.67) and use of the 10-20 system (Q = 20.49, tau^2 = 0.12). Heterogeneity measures could not be calculated for the other conditions as their sample sizes were too small.



4.6. iTBS versus Control: Navigation to Location Subgroups. Forest plot of effect sizes grouped by navigation to location factor.

Subgroup analyses: study design

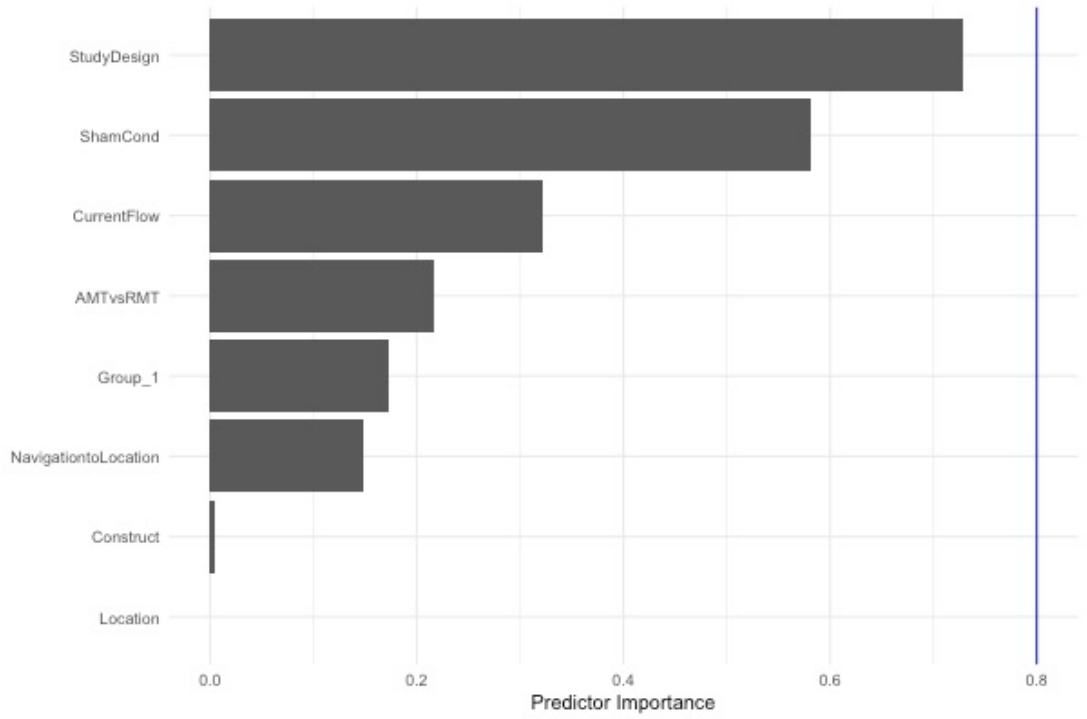
The experimental design was also taken into account as a factor for subgroup analyses. Covariates included between subject design (k = 25), mixed design (k = 1), and within subject design (k = 21). No significant differences were found between groups (Q = 2.97, p = 0.23), and no groups significantly contributed to overall effect size.

Subgroup analyses: current flow

The orientation of the coil and the direction of the flow of current were investigated with subgroup analyses. The subgroups included anterior-posterior current flow (AP; k = 11), posterior-anterior current flow (PA; k = 15), and unknown current flow (k = 21). No differences between subgroups were found (Q = 0.68, p = 0.71). No current flow subgroups had a significant impact on effect size.

Multiple meta-regression

The multi-model inference method suggests that study design (importance value = 0.73), sham condition (importance value = 0.58), and current flow (importance value = 0.32) were the most important predictors to consider in a multiple meta-regression model (see Fig. 4.7). The top 5 models out of all possible combinations from the 8 chosen covariates were compared to each other using ANOVA comparisons, and the model with the lowest AIC value was interpreted. Interaction terms were included in all models. The meta-regression model that performed best included the control condition and study design covariates that were modeled with an interaction. The permutation test (run with 1000 iterations) indicated a marginally significant trend ($F(11,38) = 1.94$, p = 0.09) and marginal interaction effects: for no stimulation control condition and within study designs (estimate = 2.87, SE = 1.37, p = 0.05, 95% CI [0.09, 5.65]; for coil rotation control condition and within study designs (estimate = 2.24, SE = 1.16, p = 0.07, 95% CI [-0.09, 4.59]). This indicates that within study designs (which generally tend to have less between-subjects variance due to the nature of the design) paired with specific kinds of control conditions (no stimulation and coil rotation away from cortex) tend to result in larger positive effect sizes.



4.7. Multimodel Inference. Graphical representation of multimodel inference analysis categorizing all predefined predictors by their importance with respect to effect size.

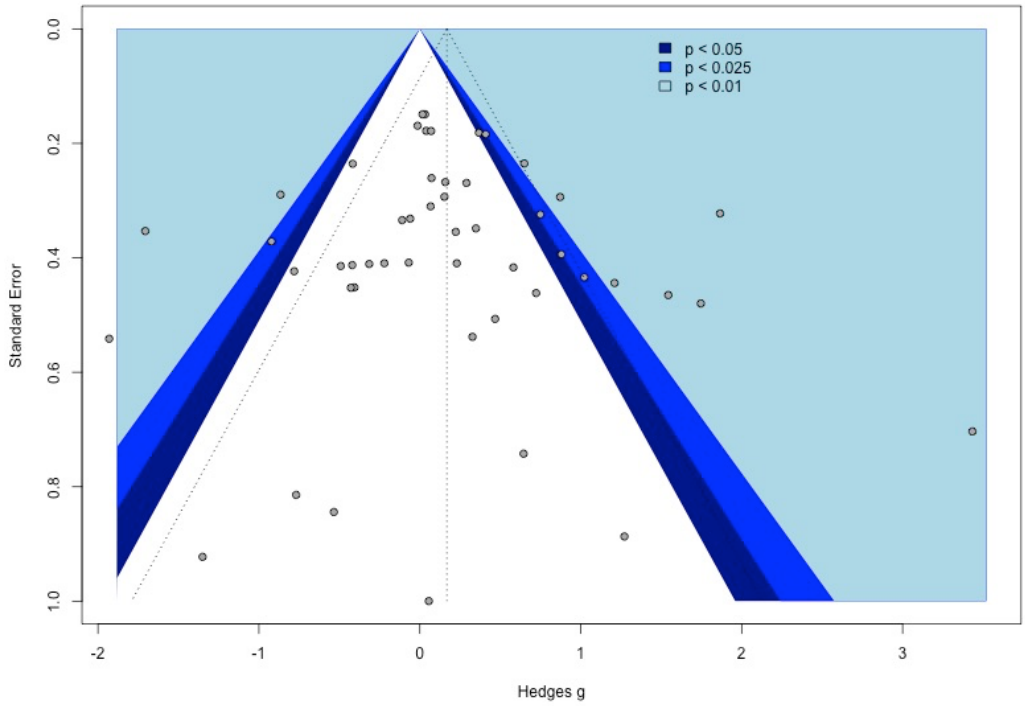
Publication Bias

Publication bias results included the full model (not outlier reduced) to determine the full scope of publication bias if it exists. While we do not have any a priori reasons to believe that publication bias exists in this subsection of neuroscience (see Chung et al., 2016 for recent assessment of publication bias in iTBS studies on MEP and cortical excitability measurements), in psychology and science generally, it is an understood assumption that research studies are only published when significant effects are found. Emphasis has been placed on the p-value rather than the overall effect of an intervention to determine the meaningfulness of an experimental result. Dubbed the ‘file-drawer’ problem, publication of small-sampled studies with large & significant effects, but not small-sampled studies with small or non-significant effects, can increase the pooled effect of a given intervention (Dickersin, 2005). Recently alternative methods for reporting informative statistics have been suggested (Dirnagl, 2019; Halsey, 2019), and it remains important to evaluate the possibility of ‘file-drawer’ publication bias in studies using the iTBS protocol occurring due to non-publication according to this significance standard.

Small sample bias methods were utilized to assess publication bias, which are able to determine if small studies with small effect sizes are missing (Borenstein et al., 2011). The assumptions required to run these analyses include 1) Large studies are likely to be published regardless of significance, 2)

moderately sized studies with insignificant findings are at greater risk of not being published but are more represented in the literature as compared to small studies, and 3) small studies are at the greatest risk of not being published because of non-significant findings and thus should have the largest proportion of missing values.

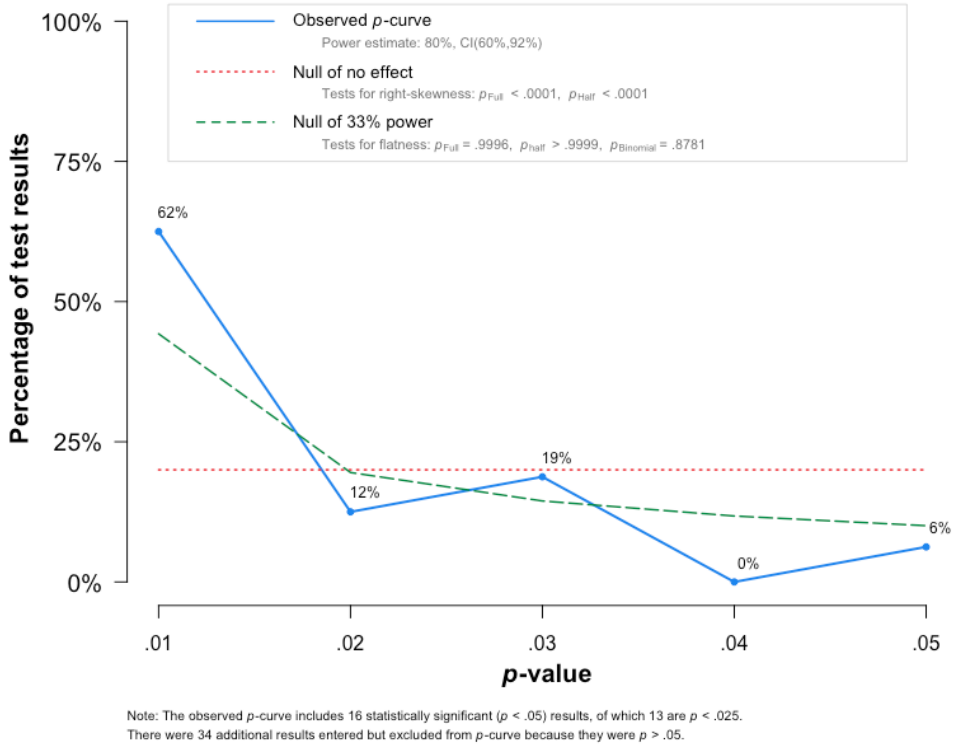
Publication bias was not present in the overall evaluation (see Fig. 4.8). While the plot is slightly asymmetrical, which may visually indicate publication bias, an Egger's test of the intercept which quantifies funnel plot asymmetry was found to be non-significant (0.29, 95% CI [-1.02, 1.60], $p = 0.66$).



4.8. Small Sample Bias Funnel Plot. Funnel plot of the studies included in the overall meta-analysis. Larger studies, which have an inherently smaller standard error are plotted on top of the y-axis, and the x-axis shows the effect size of each study. The shaded areas indicate levels of significance, with many studies reporting non-significant findings.

P-curve methods of analysis were also used to determine publication bias. This method assumes that publication bias is generated by p-hacking and/or exploratory forms of data analysis until findings become significant. Figure 9 displays the observed p-curve versus null effects and sufficient power. We found that of the total 50 studies included, 16 presented significant findings. The evidential value, or the true effect size, was found to be present, indicating that these findings are not the product of publication bias and p-hacking. Were p-hacking present, the graph in Figure 4.9 would be inverted, with a higher

percentage of findings being located closer to p = 0.05. This bodes well for researchers utilizing iTBS, signaling that the significant effects found in these studies are likely the result of finding a true effect.



4.9. P-Curve Analysis. P-curve of significant findings included in the meta-analysis.

Discussion

Conclusions of iTBS efficacy

The primary aim of this meta-analysis was to determine if facilitatory brain stimulation experiments — following the protocol set by Huang and colleagues (2005) — have shown reliable and effective results in cognitive enhancement for healthy adults after a single session of iTBS. Secondary aims were to determine which factors may contribute to heterogeneity in the effects of iTBS on cognition between studies, and if certain factors were predictive of effect size outcomes. Meta-analytic approaches until this point have confirmed that iTBS enhances motor cortex excitability and facilitates MEPs (Chung et al., 2016), but questions regarding how facilitatory theta burst stimulation affects behavior which is mediated through higher-order cognition have until now remained unanswered. Our findings indicate that in an outlier-reduced model, there is an indication that iTBS has a small positive effect on measures of cognitive enhancement compared to control conditions, indicating that facilitatory stimulation may indeed be effective. However, substantial heterogeneity in effect sizes was present

across these studies, indicating variability in the effect of iTBS on cognitive tasks. This variability arises from a number of researcher decisions which must be made when implementing TMS studies, such as the specific cognitive domain in question, the measurement variable for that cognitive domain, the motor thresholding strategy, TMS current flow, study design, the target of stimulation, type of control condition, and the method for navigation to the stimulation site. Subgroup analyses on these factors revealed three factors which contribute significantly to this heterogeneity— summarized below. Based on the results of these subgroup analyses, we conclude with a list of recommendations for future studies using the iTBS protocol as a causal method for investigating cognitive enhancement.

Factors that influence iTBS efficacy, conclusions from subgroup analyses

Subgroup analyses on a number of factors were run to determine the distribution of heterogeneity among effect sizes, and to determine which factors influence effect size for iTBS experiments of cognitive enhancement. These results should be referenced by researchers using the iTBS protocol to understand how experimental parameters can influence study outcomes. Notably, the specific brain region targeted, the method for navigating to the targeted brain region, and the type of control condition used were found to be influential factors for the effects of iTBS interventions on cognitive enhancement. Of the factors investigated, meta-regression analyses determined that study design and control condition were the two most important parameters in predicting effect size.

Cognitive domain

Grouping studies based on cognitive domain revealed no significant between-group differences, and no group contributed significantly to the distribution of effect sizes. This signal that there may be no differences in the efficacy of iTBS across cognitive domains. However, an alternative explanation is that the heterogeneity of studies between cognitive domains may be so disparate and the number of studies so small within each domain that the efficacy of iTBS is not accurately captured by the meta-analytic model. Some cognitive domains (social cognition and language) had only one research contribution, which does not allow for accurate estimations on how studies in these domains may or may not differ from cognitive domains with more published works.

Control condition

Marginal differences were found between groups based on the type of control condition used, however no single group was found to significantly influence effect size. These results are to be interpreted with caution, as most studies implemented coil rotation away from the cortex as their control method ($k = 29$), while other control methods were used in a smaller number of studies, making interpretation of the individual impacts of other control methods on effect size difficult. In practice, our finding that there are differences between sham

conditions demonstrates that the methods researchers use to control for stimulation may be lacking. If there were no differences between control groups, this would indicate that each method of controlling for stimulation acts as a control in the same way - this does not seem to be the case based on present findings. However, this does indicate that there may be reason to include a variety of control conditions in future iTBS studies. Recent work has investigated the effectiveness of sham conditions in TMS studies more broadly (Duecker & Sack, 2015), arguing that multiple control conditions should be utilized due to suboptimal performance of singular sham conditions as effective controls.

Target stimulation location

It may seem intuitive that target stimulation location is an important factor in iTBS studies – different regions of the brain may respond differently when provided with targeted facilitatory stimulation, and different cognitive tasks are associated with different brain regions. The findings of this meta-analysis related to target location do not support this intuition that particular target regions are more susceptible to the effects of iTBS on cognitive enhancement than other regions. On the contrary, it seems that iTBS effects may generally translate across target regions. However, target stimulation location is an important factor in the magnitude of the subsequent effect size of the measured behavior. Further investigation into how stimulation affects behavior, cortical excitability, and brain activity using simultaneous EEG, fMRI, or fNIRS technology could elucidate how different regions of the brain respond to stimulation at different time points.

Navigation to stimulation sites

Significant differences found between groups with different methods for navigating to stimulation location indicates that this is an important factor to consider when conducting iTBS studies. While no groups had a significant impact on effect size, we would expect differences to naturally arise due to the preciseness of each technique. For example, the 10-20 system is not as precise as individualized MRI or motor cortex mapping methods. One study has shown that the error of coil placement when using the 10-20 system can extend up to two centimeters in three dimensions, and approximately 10% of individuals had coil placement that bordered on functionally distinct areas (Herwig et al., 2003). Another study cited the 10-20 system as being the least-accurate targeting system when compared to fMRI-guided neuronavigation, probabilistic neuronavigation, and TMS-mapping methods for stimulation of the motor cortex (Sparing et al., 2008). This prior evidence is not to suggest that the 10-20 system should be thrown out, but we suggest other mapping approaches should be investigated in tandem to determine how exactly navigation to a stimulation location generates the effect of interest.

Meta regression - study design and control condition

Significant and marginal interactions with positive effect sizes were found for studies utilizing no-stimulation control conditions and coil-rotation control

conditions with within-subjects experimental designs, as compared to an active stimulation control condition with between-subject experimental designs. Although within-subject studies have less inherent variability due to the nature of the design, these interactions were puzzling. We believe this finding may support placebo effects when subjects are not naïve to TMS. It is relatively easy for a participant to determine if a sham condition is being used, especially in no-stimulation conditions and in coil rotation conditions due to perceivable differences in the sensory aspects of stimulation (Rossi et al., 2009). Active control conditions may be indistinguishable from non-control conditions, however research regarding blindness of subjects or experimenters across control conditions remains sparse. Many experimental researchers do not report this data, however small systematic analyses have been conducted regarding clinical outcomes (Berlim et al., 2013; Broadbent et al., 2011). The lack of placebo effect with sham stimulation is a well-known issue in the field (Davis et al., 2013; Loo et al., 2000). The use of active controls, non-responder populations, and alternative forms of sham stimulation that are less likely to be correctly identified as control conditions, while problematic in their own ways (Duecker and Sack, 2015), are useful when working with subjects who are not naïve to stimulation.

Limitations of the current meta-analysis

It may be called into question whether studies which used disparate methodologies and measures can be compared within a single meta-analysis. Collapsing studies into a generalized cognitive domain category or measured behaviors can certainly muddy effects, especially considering that these findings were independent from one another, and it is likely that each researcher used different methods to investigate their variable of interest. While this is a sensible critique, the increasing use of and reliance on iTBS as an intervention to investigate cognitive enhancement renders the need to consolidate and evaluate these findings with a high degree of clarity and methodological rigor — as done here. Some of the variability across study subgroups from this aggregation was accounted for by using random-effects meta-analytic modeling, and this variability was further investigated by performing subgroup analyses and meta-regression, which can evaluate interactions between predictors. This does not account for all variability across studies; however, we believe these findings are novel contributions to the field – specifically for determining important factors that contribute to variability between studies and which parameters of iTBS influence effect sizes.

It should be noted that individuals themselves could be highly variable in their responses to iTBS, as some subjects do not have the expected facilitation of MEPs to iTBS (Hinder et al., 2014). A recent meta-analysis on subject response to NIBS found that factors that influence corticospinal excitability include genetic variation – specifically the BDNF genotype – age differences between older and younger adults, menstrual cycle variation, skull thickness and brain morphology (Pellegrini et al., 2018). These particular factors were out of the scope of the present meta-analysis due to low reporting of BNDF polymorphism,

two studies having investigated older adults (Debarnot et al., 2015; Vidal-Pineiro et al., 2014) , no studies reporting menstrual cycle characteristics of their samples, and no availability of data regarding brain structure and skull structure.

A related limitation of this meta-analysis was the exclusion of additional cortical excitability measurements, namely modulation of MEP and EEG transcranial evoked potential (TEP) amplitudes after stimulation. While we do consider cortico-spinal and cortical excitability measurements to be a component of cognitive processing and note that these are indeed measurements related to cognitive enhancement, the focus of this meta-analysis was to investigate behavioral measurements that were not direct indices of cortical excitability. Recent meta-analyses have already investigated the influence of iTBS on cortico-spinal and cortical excitability (Wischnewski and Schutter, 2015; Chung et al., 2016). Additionally, EEG-based studies were excluded, as there were not enough studies with post-iTBS EEG measurements with proper controls, making quantitative assessment infeasible.

This meta-analysis also excluded studies that utilized pre-post measurements when conducting iTBS interventions without additional control conditions. These studies use each individual subject's performance pre-iTBS as a measure of behavior at baseline, which is a valid way to control for subject-dependent variability. However, these pre-post studies require the estimation and calculation of the standardized mean gain, which is an effect size that should not be combined with the standardized mean difference which is the measure that was compared in this meta-analysis. To evaluate the efficacy of iTBS on cognitive enhancement for pre-post test methodologies would require conducting an additional protocol and separate meta-analysis. Therefore, evaluating the efficacy of pre-post iTBS procedures on cognitive enhancement was outside of the scope of the current meta-analysis. Future investigation should be conducted with these data, as the use of pre-iTBS baseline measurements as a way to control for variability could help reduce heterogeneity in meta-analytic models.

The lack of standardization in the field for reporting many iTBS parameters created some difficulty in conducting this meta-analysis. Specifically, nine published studies did not provide adequate information to calculate effect sizes. In these instances, outreach to authors was necessary so as to include as many research findings as possible. But this outreach was not always successful. In addition to published articles not providing sufficient information for effect size estimation, many studies did not report parameters that would aid meta-analytic modeling, including coil dimensions (k = 2), coil and stimulator manufacturer (k = 4), method for calculating motor threshold (k = 2), and coil orientation (k = 25).

Specific recommendations for future iTBS research

The findings from this meta-analysis should be used to inform future studies utilizing iTBS in efforts to enhance particular aspects of cognition. These findings provide a consensus on the state of the field regarding the efficacy of iTBS interventions to cognitive measures, beyond cortical excitability. Moreover, both the findings and limitations of this meta-analysis have resulted in a list of

recommendations for researchers conducting future studies using the iTBS protocol as a causal method for investigating cognitive enhancement.
Based on the current findings, we suggest the following prescriptions for future research using iTBS to enhance cognition. Researchers should use strict methodological rigor and careful attention when determining: the location of stimulation, the type of control condition to be used, and how navigation to the stimulated location is chosen.

These factors were found to contribute to differences between studies. The location of stimulation and the type of navigation used should also be backed by prior literature – and ideally multiple control conditions should be implemented in experimental designs to account for potential placebo effects and variability across control conditions. This will aid future research by advancing our knowledge regarding the inadequacies of particular sham and control methods.

Authors contributing to the field of non-invasive brain stimulation should utilize effect size calculations in the statistical packages used to analyze their data, and report those statistics, even if the findings are not significant. Further, authors should make their data readily available to researchers who are attempting to conduct systematic reviews. Researchers should report the following methodological parameters: details of the control condition used, the location stimulated and how navigation to this location was determined motor threshold determination and parameters of motor threshold used for theta burst stimulation (% output of stimulator, and whether resting or active motor threshold was used), coil orientation and the direction of current flow, and coil specifications and stimulator manufacturer.

We encourage researchers to report sham-blindness measures experiments using both within-subjects and between-subjects designs. This can easily be adopted by asking participants what condition they perceived to be in post-stimulation. Reporting the aforementioned parameters enables successful replication of studies, which in turn enables the determination of a true effect regarding the enhancement of cognition after intervention with the iTBS protocol. An important area for future TBS research involves the inclusion of simultaneous neural recording through the use of EEG or MEG to determine how stimulation of regions outside of the motor cortex impacts cortical excitability of those regions, whether we can assume that iTBS facilitates neural activity across the entire cortex, and for determining if and how inter-individual variability plays a role in cortical excitability across the cortex.

Endnote: *indicates a subset of the total recruited subjects; RMT – resting motor threshold; AMT – active motor threshold; MT – unspecified motor threshold; AP – anterior-posterior; PA – posterior-anterior; rPFC – right prefrontal cortex; lM1 – left primary motor cortex; ldmPFC – left dorsomedial prefrontal cortex; rIPL – right inferior parietal lobe; rIFG – right inferior frontal gyrus; lBA10 – left Brodmann's area 10; lDLPFC – left dorsolateral prefrontal cortex; rTPJ – right temporoparietal junction; rS1 – right primary somatosensory cortex; lPPC – left

posterior parietal cortex; rPPC – right posterior parietal cortex; rDLPFC – right dorsolateral prefrontal cortex; rM1 – right primary motor cortex; rPMv – right ventral premotor cortex; lpIFG – left posterior inferior frontal gyrus; FZ – electrode location FZ (10-20 system)

Epilogue

In this dissertation, I have shown how humans adapt to a wide variety of perturbations, including ones generated internally, external perturbations from the environment, and from perturbations applied directly to the brain. In Chapter 1, I demonstrated how the extension and holding phases of movement during finger tapping serve as correction processes to internally generated errors during synchronization and syncopation to auditory and visual rhythms. Humans may be better at synchronizing to auditory rhythms compared to visual rhythms due to audio-motor integration. The neural mechanisms underlying this process are purported to be within the parietal cortex and consist of fast processes (see ASAP hypothesis in Patel & Iversen, 2014), whereas the neural correlates underlying visuomotor timing are thought to be much slower (resulting in larger variance) and are largely unexplored. In Chapter 2, I showed evidence of desynchronization between the limbs when elastic and viscous perturbations were applied to the hands. Bimanual reaching behavior has been shown before to be synchronous despite differences difficulty or reaching distance, and that we compensate for changes in distance by aligning the velocities of the limbs so that we arrive to end targets at the same time (Kelso et al., 1979). However, under conditions that are not a ubiquitous part of the human experience (force applications), the hands desynchronize to complete the intended goal. In Chapter 3, I provide evidence that directly applying perturbations to the brain via transcranial magnetic stimulation may influence memory consolidation mechanisms, but due to the variability across participants and their responses, this work requires further research. Finally in Chapter 4, myself and several co-authors assessed the state of facilitatory transcranial magnetic stimulation to determine if this direct perturbation can enhance healthy human cognition. We found that there is a small positive effect of facilitatory TMS, however, these effects are heavily influenced by researcher-determined methodological applications of stimulation, and we argue that standardization of the field is necessary to ensure true effects. Overall, this dissertation contributes to our understanding of how human brains and bodies are intertwined with the environment, and how we utilize information to predict how to act. I hope that this work influences future research to understand how humans adapt to both internally and externally generated perturbations.

Future research should take predictive processing theoretical frameworks into account to determine which of these theories is best equipped to explain behavior and adaptation in response to perturbations. These theoretical accounts include predictive coding frameworks proposed by Friston (2002; 2005) and the newly established active inference framework (Friston 2010; Parr & Friston, 2019). Work from our lab demonstrates that musical and beat processing can be accounted for by these frameworks (Proksch et al., 2020), and it would be interesting to extend this approach to memory and cognition processes, similar to work I demonstrate here. Additionally, I would encourage future researchers to

utilize mixed-methods approaches in their studies of adaptation, as collecting neurological and behavioral data simultaneously will provide much more insight into the mechanisms that control adaptation in a variety of circumstances. Further, the evoked behavior should be as naturalistic as possible and be contained within ecologically valid scenarios. Cognitive science is slowly starting to extend research outside of the laboratory and into reality, and this will help elucidate further insight into how neurological mechanisms enable real-world adaptation.

Let's think back to the scenario initially presented at the start of this dissertation. The lights go on, the audience quiets, and the curtains open. Your photoreceptors have adjusted to the darkness backstage, and with the stage lights on, you can barely see the first row of the audience. This isn't an issue though – you've practiced with stage lights before and have anticipated this change in perception. As you begin reciting your lines, the cilia in your ears receive feedback from your voice being projected across the room and back to you – this is a full audience, and your voice isn't carrying as far as it needs to. You update your internal model to engage your diaphragm much more, and within a second or two, you have adjusted your speaking volume. Other actors have appeared on stage – as you had predicted, this is how you've rehearsed for the past three months, and now you need to integrate visual information and proprioceptive information. As an actor – it is incredibly important to never turn your back to the audience, but you need to be aware of others moving around on stage with you without necessarily seeing them. Another actor falls on stage – this was not anticipated – a complete accident! But the audience laughs, and you and the rest of the actors on stage must go on with it to preserve the audience's understanding of the show and not break the fourth wall. The performance draws on, and at the end of the night, you've recovered lines that other actors forgot, you've remembered all of your songs and dances, and even put your stage props back in their proper place. It is curtain call now, and you and the other actors make your way to the stage for a bow. You thank the musicians, and you thank the light crew, but don't forget to thank your brain and body for updating your internal models. They've done quite a bit of work tonight, and they deserve applause too. All there's left to do is to exit stage left and prepare for the next performance.

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Appendix A: Additional Materials for Chapter 4

Outlier analysis

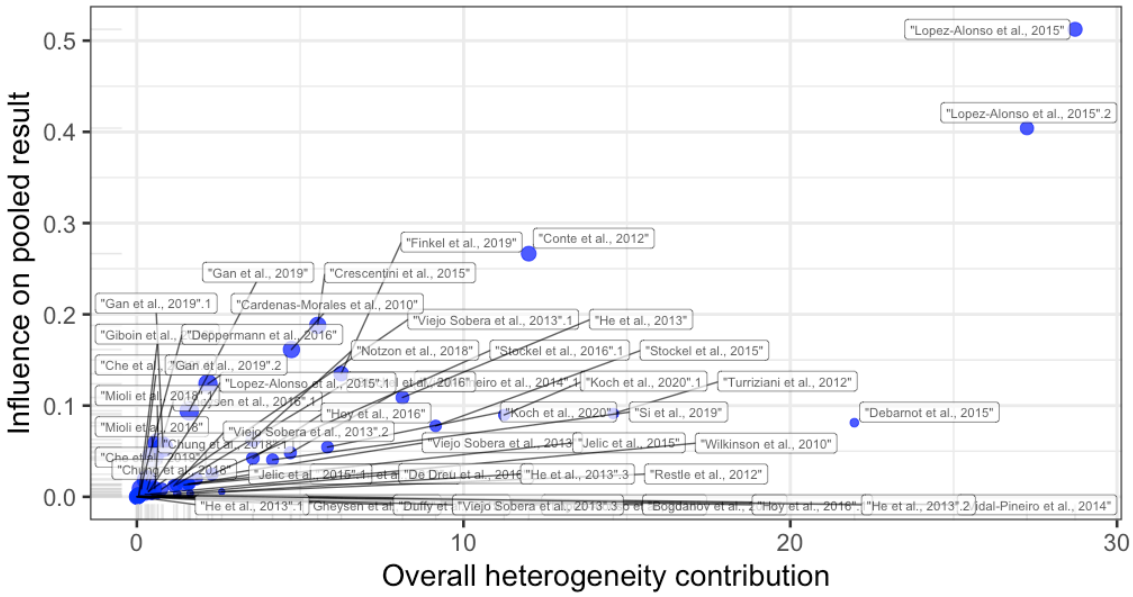
The purpose of this sensitivity analysis is to compare the results of models with no outliers removed versus models with outliers removed. Each step of the meta-analysis follows the flow of the meta-analysis written in the results section of Chapter 4.

As stated in the Chapter 4, a random-effects meta-analytic model with a Hartung-Knapp adjustment (Hartung and Knapp, 2001a,b) was used with a Paule-Mandel estimator for tau heterogeneity measurement and Q-profile confidence interval estimation (Paule and Mandel, 1982; Veroniki et al., 2016). Both the outlier-reduced model and the full model have these predefined features.

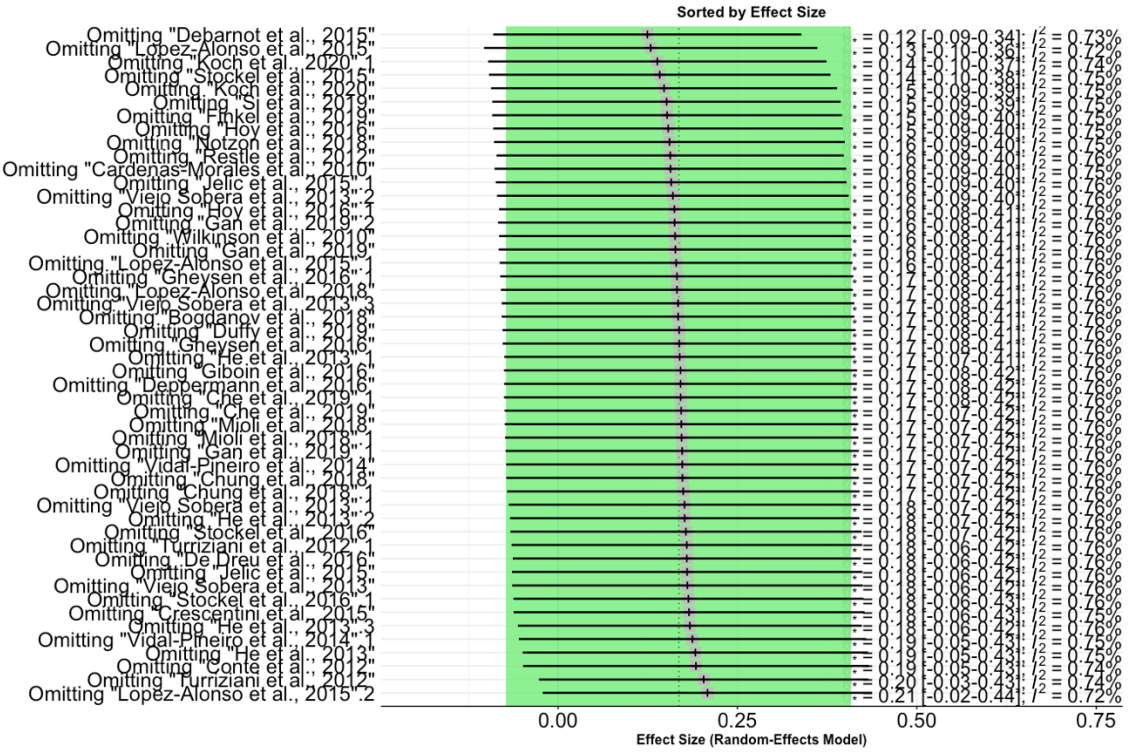
The outlier analysis from the 'dmetar' package (Harrer et al., 2019) detected these studies as outliers:

Conte et al., 2012
Debarnot et al., 2015
Koch et al., 2020 (2)
Stockel et al., 2015
Turriziani et al., 2012 (1)
Lopez Alonso et al., 2015 (2)
Lopez Alonso et al, 2015 (3)
He et al., 2013 (1)

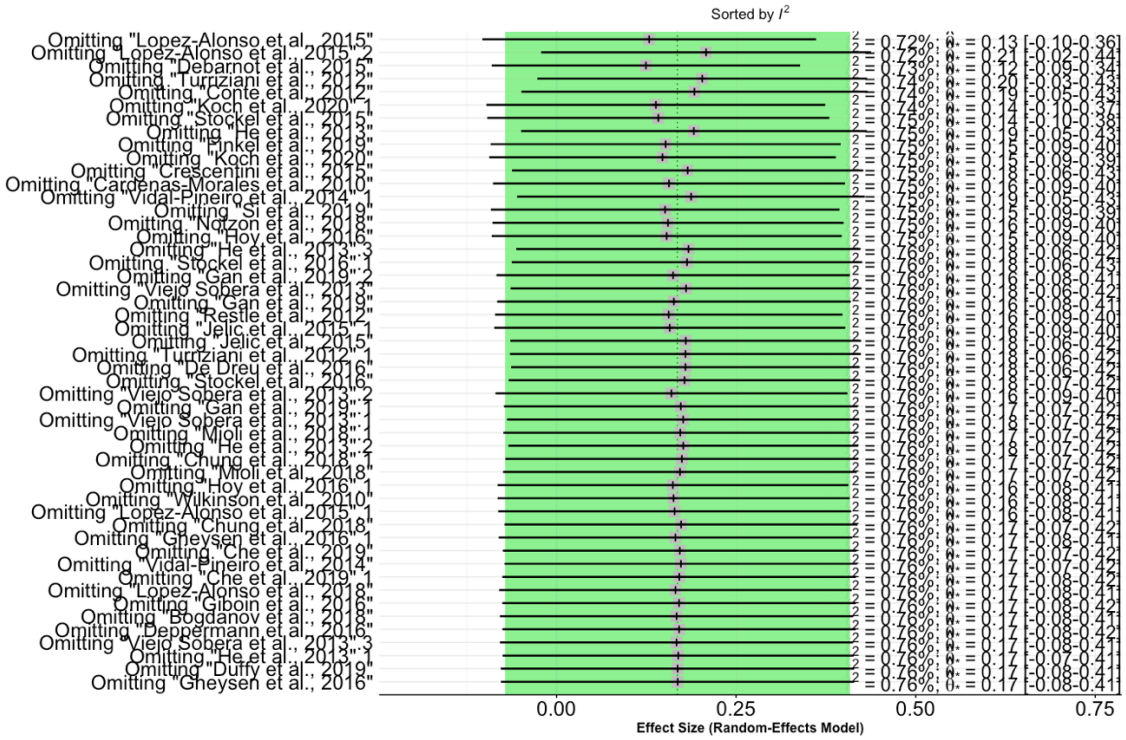
Where the number following the author's name and year signifies the research finding, which is defined in Table 4.2.



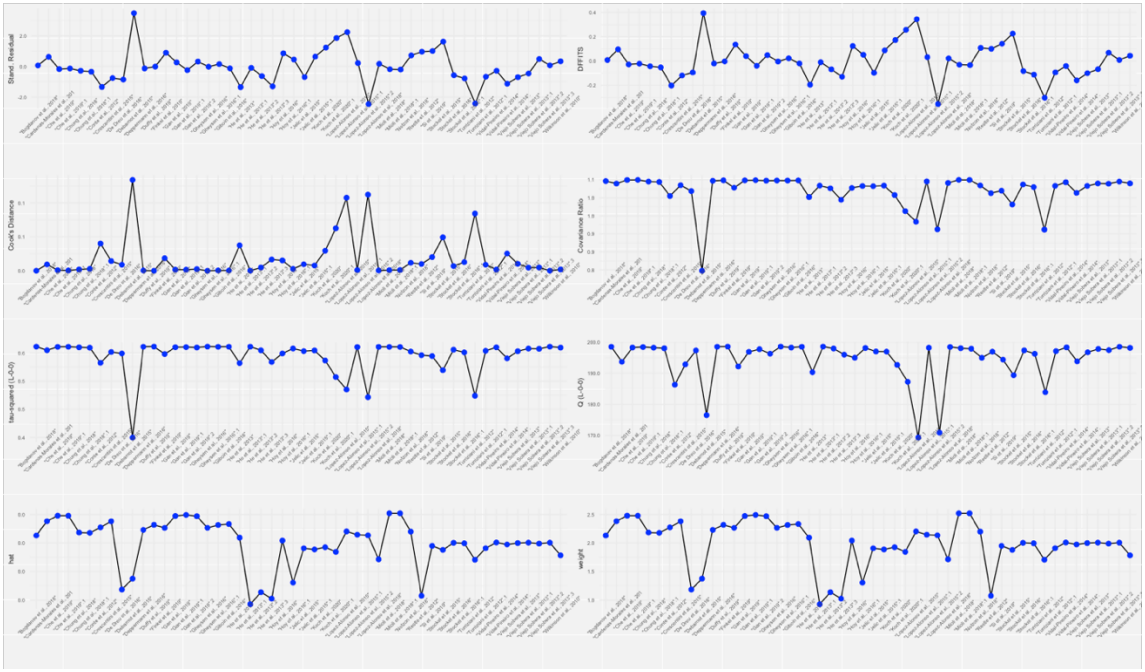
A.1. Baujat plot of the influence analysis, displaying each research finding's contribution to overall heterogeneity of the pooled effect, along with a measure of each study's influence on the overall pooled effect. Points on the right half of the plot are of particular importance, as these studies contribute significant heterogeneity and may influence the outcome of the meta-analysis.



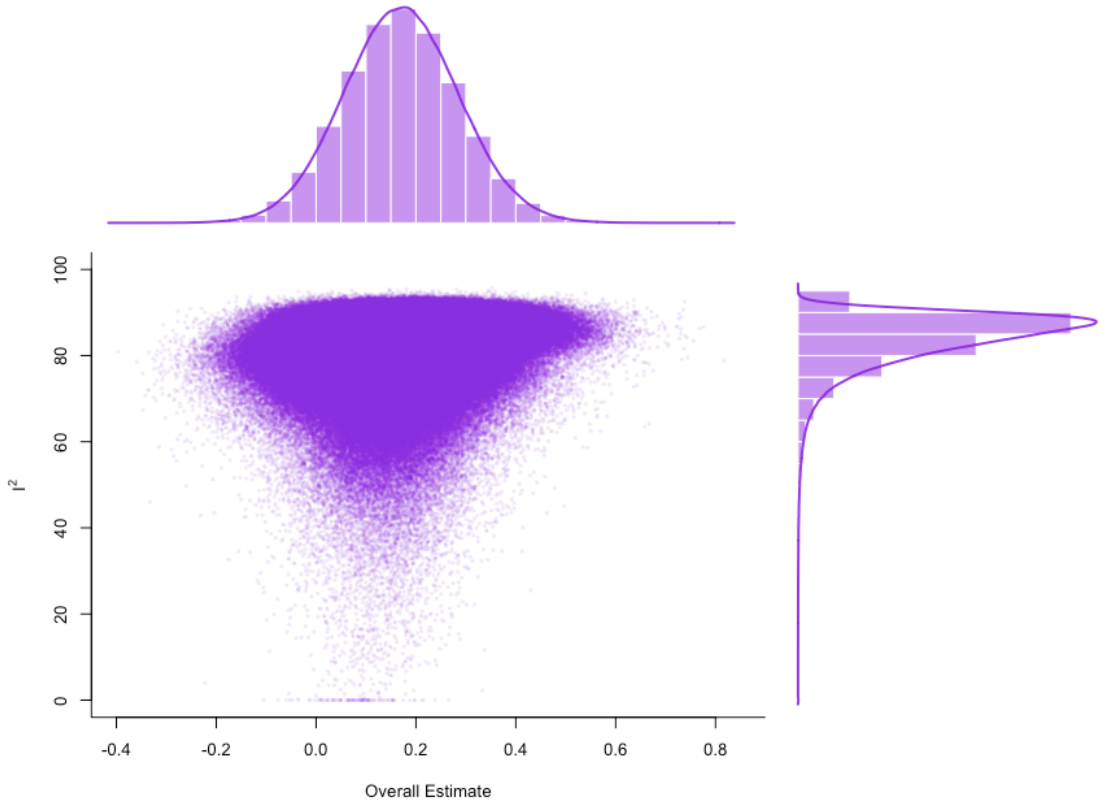
A.2. Results of the “leave-one-out” influence analysis, sorting the results of each analysis by effect size.



A.3. Results of the “leave-one-out” analysis, sorted by I^2, a measure of study heterogeneity. Studies which have the largest heterogeneity contributions to the pooled effect size are at the top of the plot.



A.4. Influence diagnostics proposed by Viechtbauer & Cheung (2010), specifically standard residuals, Cook's distance, tau-squared, hat, DFFITS, covariance ratio, Q, and weight. No studies were found to be particularly influential on effect size.

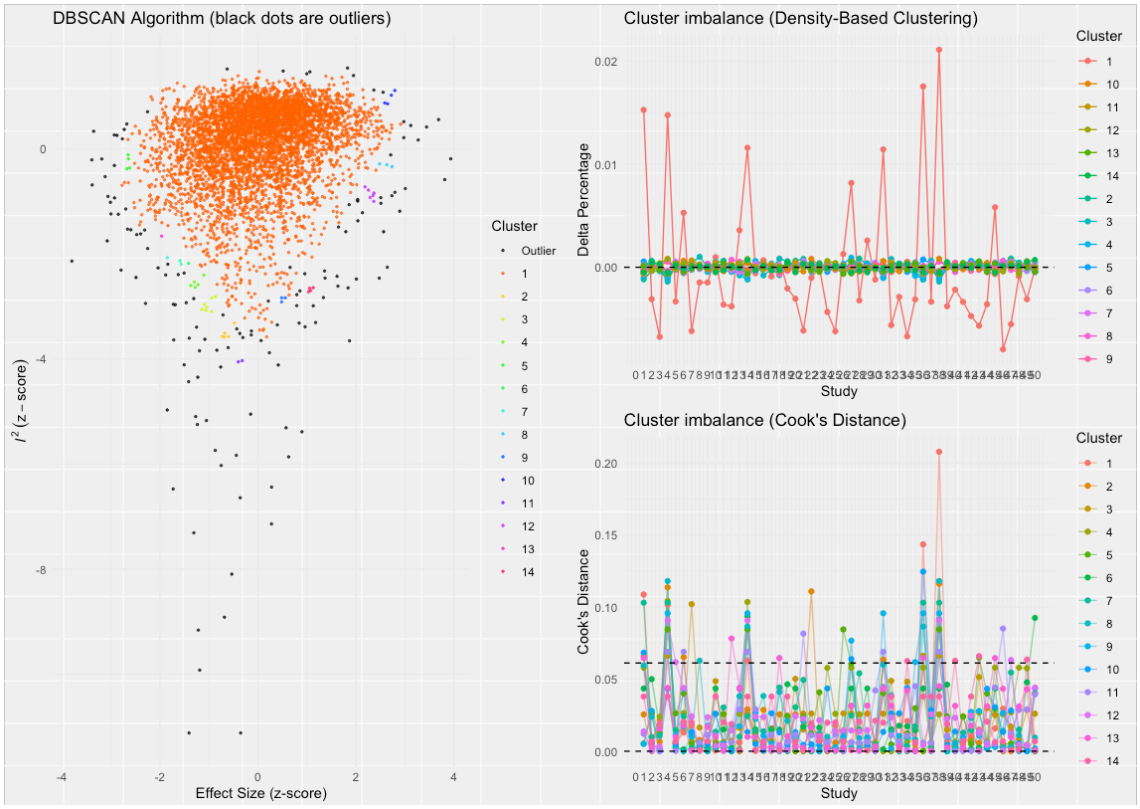


A.5. Graphical Display of Heterogeneity (GOSH) plot. GOSH plot analyses fit the meta-analytic model to all possible subsets of included studies, displaying the pooled effect size on the x-axis and the between-study heterogeneity on the y-axis. These plots would indicate if naturally occurring subsets existed in the data.

K-means clustering algorithm identified the following studies as outliers:
Study 1: Turriziani et al., 2012 (1)
Study 4: Lopez-Alonso et al., 2015 (2)
Study 36: Lopez-Alonso et al., 2015 (3)
Study 48: He et al., 2013 (4)
Study 14: Koch et al., 2020 (2)

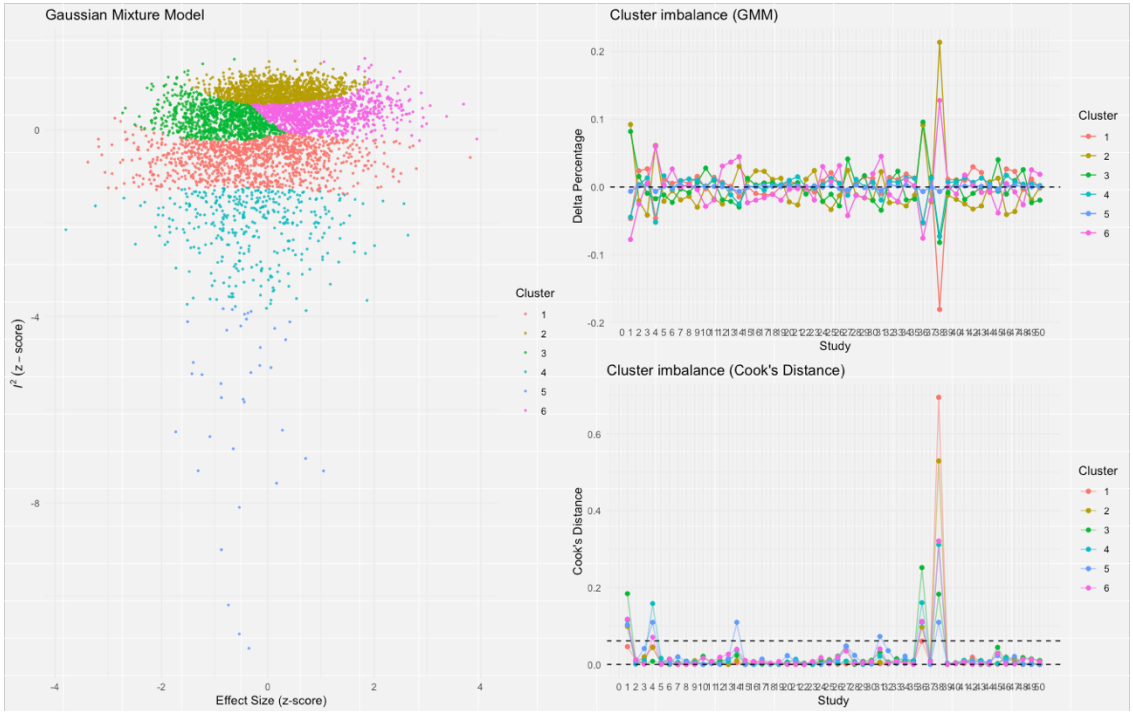
A.6. K-means clustering algorithm to detect naturally occurring clusters within the data. K-means clustering used 3 clusters, plotting possible effect sizes on the basis of these combined studies according to I^2 measure of heterogeneity, delta percentage as determined from the K-means algorithm, and Cook's distance.

DBSCAN clustering algorithm identified the following studies as outliers:
Study 1: Turriziani et al., 2012 (1)
Study 4: Lopez-Alonso et al., 2015 (2)
Study 14: Koch et al., 2020 (2)
Study 36: Lopez-Alonso et al., 2015 (3)
Study 6: Finkel et al., 2019
Study 22: Gan et al., 2019 (1)
Study 31: Stockel et al., 2015
Study 7: Gheysen et al., 2016 (1)
Study 26: Si et al., 2019
Study 43: Viejo Sobera et al., 2013 (3)
Study 50: Cardenas-Morales et al., 2010
Study 8: Gheysen et al., 2016 (2)
Study 27: Conte et al., 2012
Study 35: Lopez-Alonso et al., 2015 (1)
Study 21: Chung et al., 2018 (2)
Study 46: He et al., 2013 (2)
Study 5: Bogdanov et al., 2018
Study 47: He et al., 2013 (3)
Study 12: Restle et al., 2012
Study 18: Che et al., 2019
Study 45: He et al., 2013 (1)
Study 34: Wilkinson et al., 2010
Study 40: Viejo Sobera et al., 2013 (1)
Study 49: Notzon et al., 2018



A.7. Results of the DBSCAN clustering algorithm to detect outliers.

Gaussian Mixture Modeling (GMM) clustering algorithm identified the following studies as outliers:
Study 38: Debarnot et al., 2015
Study 1: Turriziani et al., 2012 (1)
Study 36: Lopez-Alonso et al., 2015 (3)
Study 14: Koch et al., 2020 (2)
Study 31: Stockel et al., 2015



A.8. Gaussian Mixture Model Clustering results.

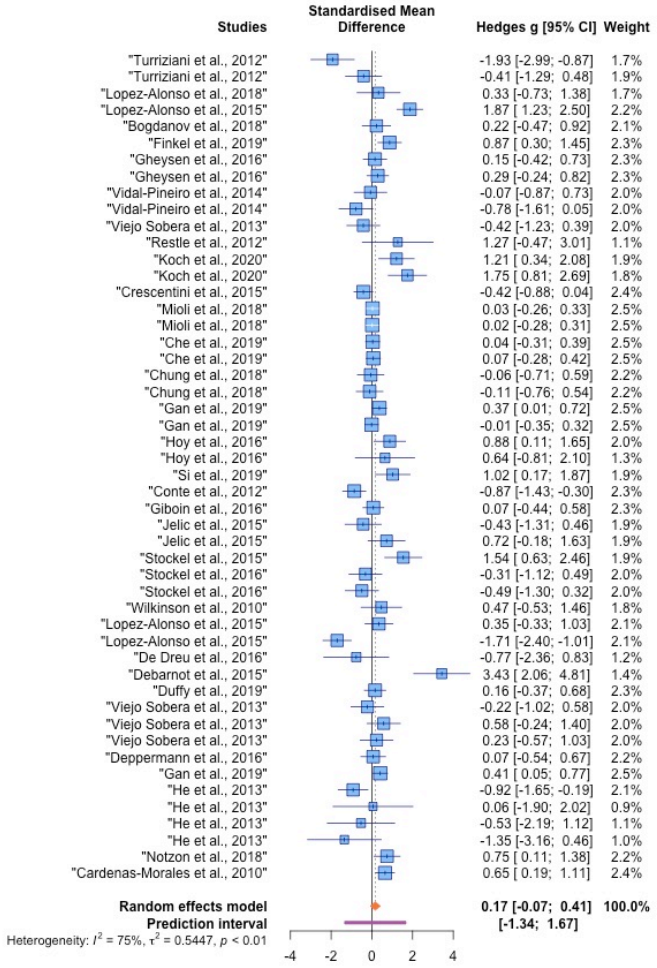
After examining all outlier and influence analyses, commonly identified outliers across all analyses were removed and a new meta-analytic model was constructed, the results of which are reported in the manuscript. The outliers that were removed included: Turriziani et al., 2012 (1), Lopez Alonso et al, 2015 (3), and Koch et al., 2020 (2).

The following section will detail the results of the study with the full model as a sensitivity analysis. We do not believe that the interpretation of the outcome of the study substantially differs from our interpretations of the outlier-reduced model. Outlier reduction was warranted, as an aim of the meta-analysis was to determine sources of heterogeneity across studies and their impact on the effect of iTBS versus control conditions. As such, the outlier-reduced model was utilized in the results of the main manuscript.

Full Model Results and Discussion

In the full model (k = 50) comparing iTBS treatment to control conditions, no significant effect was found (SMD = 0.17, 95% CI [-0.07, 0.41], p = 0.17). Additionally, the prediction interval was not significant (95% CI [-1.34, 1.67]), indicating that if an additional study was conducted, on the basis of the information available from these studies, we would not expect to find a significant effect. Heterogeneity was significant (tau^2 = 0.54, 95% CI [0.31, 0.99]; I^2 = 75.3%, 95% CI [67.6%, 81.2%]; Q = 198.58, p < .0001). In the outlier-reduced model, a significant effect was found, however due to the amount of heterogeneity present in both models, subgroup analyses were warranted to determine specific contributors to heterogeneity across studies. Our interpretation of these analyses

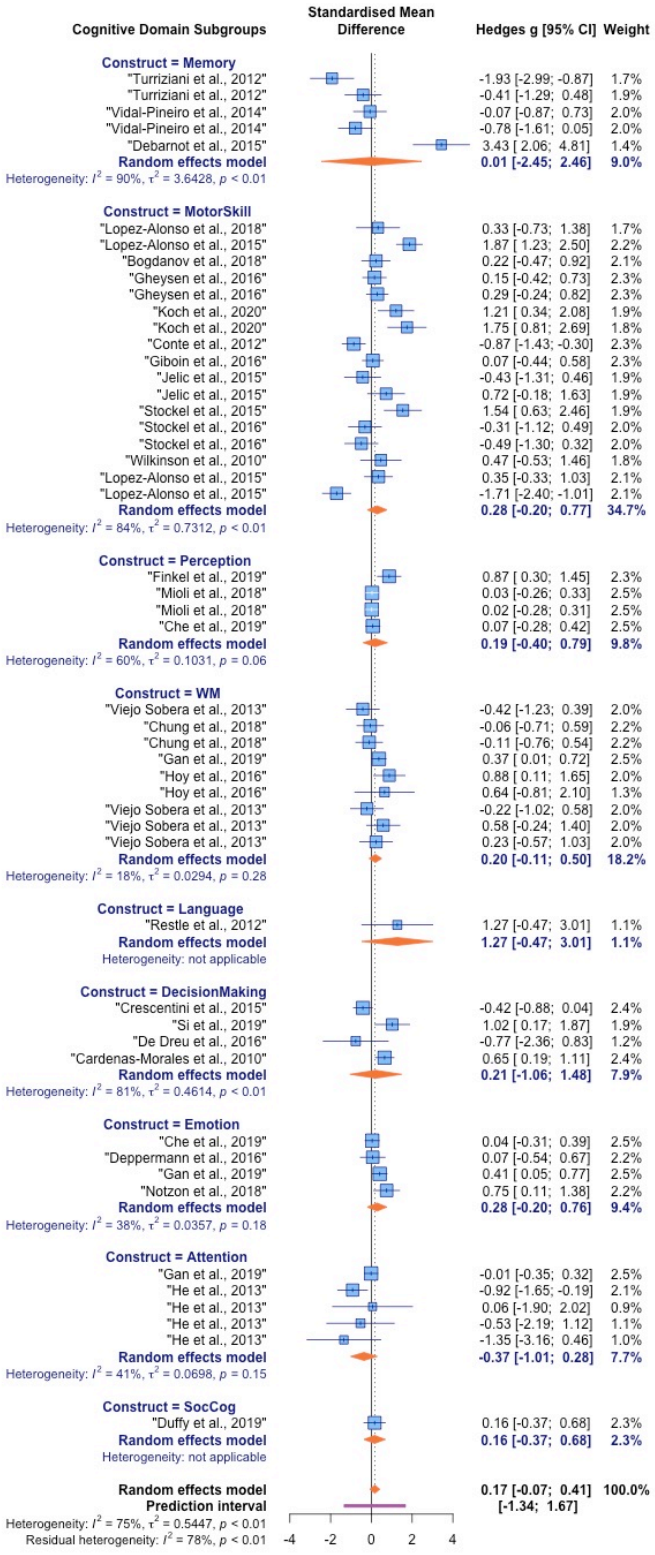
remains the same – specifically that if there is a true effect of iTBS on cognitive enhancement, due to the heterogeneity across all studies additional investigation was needed to determine what may influence the effect size.



A.9. Forest plot of all studies that were determined eligible for the meta-analysis, despite significant contributions to heterogeneity measures or influence on the overall effect size.

Subgroup analysis: cognitive domain

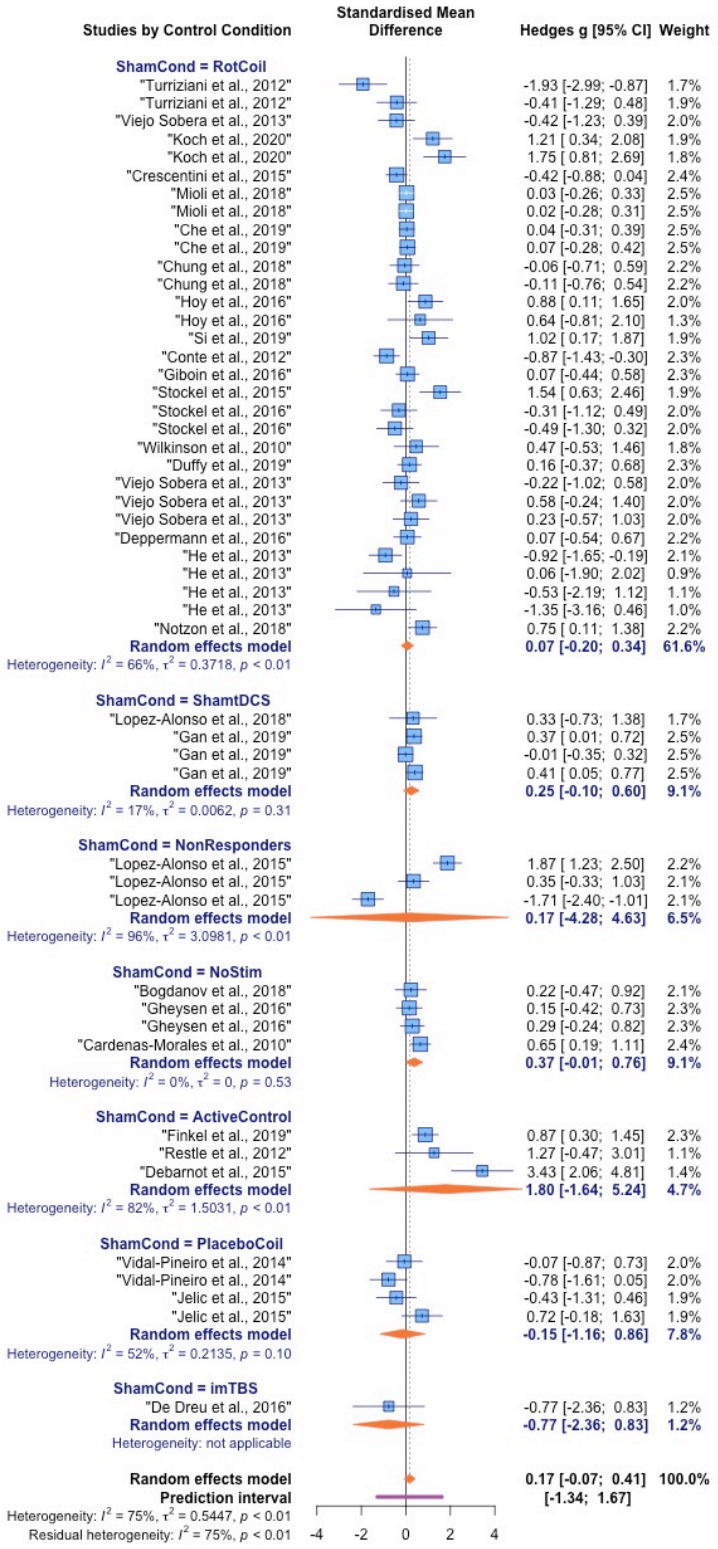
No significant differences were found between groups for cognitive domain (Q = 7.66, p = 0.47). Additionally, no specific groups were found to have a significant influence on effect size.



A.10. Forest plot of all eligible studies categorized by cognitive domain subgroup.

Subgroup analysis: control condition

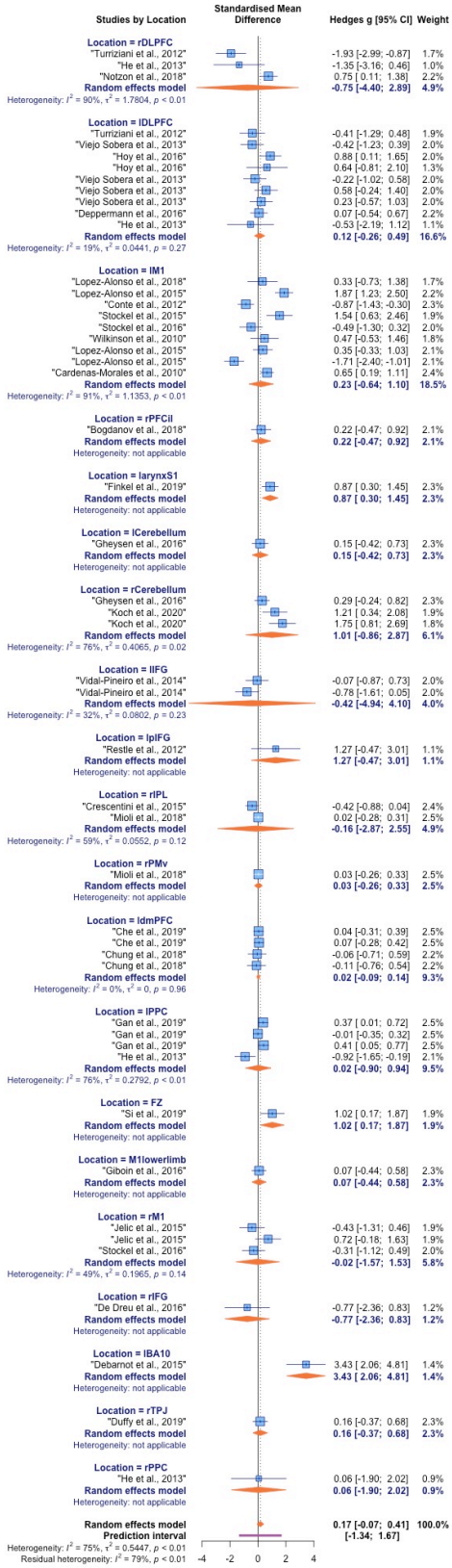
No differences were found between groups for control condition ($Q = 9.84$, $p = 0.13$), and no groups were found to have a significant influence on effect size. While the outlier-reduced model did find that control condition had marginal differences between groups, our interpretation of the influence of control condition on outcomes related to iTBS remains the same. Researchers should utilize multiple methods of control conditions to account for potential differences between shams, researched by Duecker and Sack (2015).



A.11. Forest plot of all eligible studies categorized by control condition.

Subgroup analysis: location of stimulation

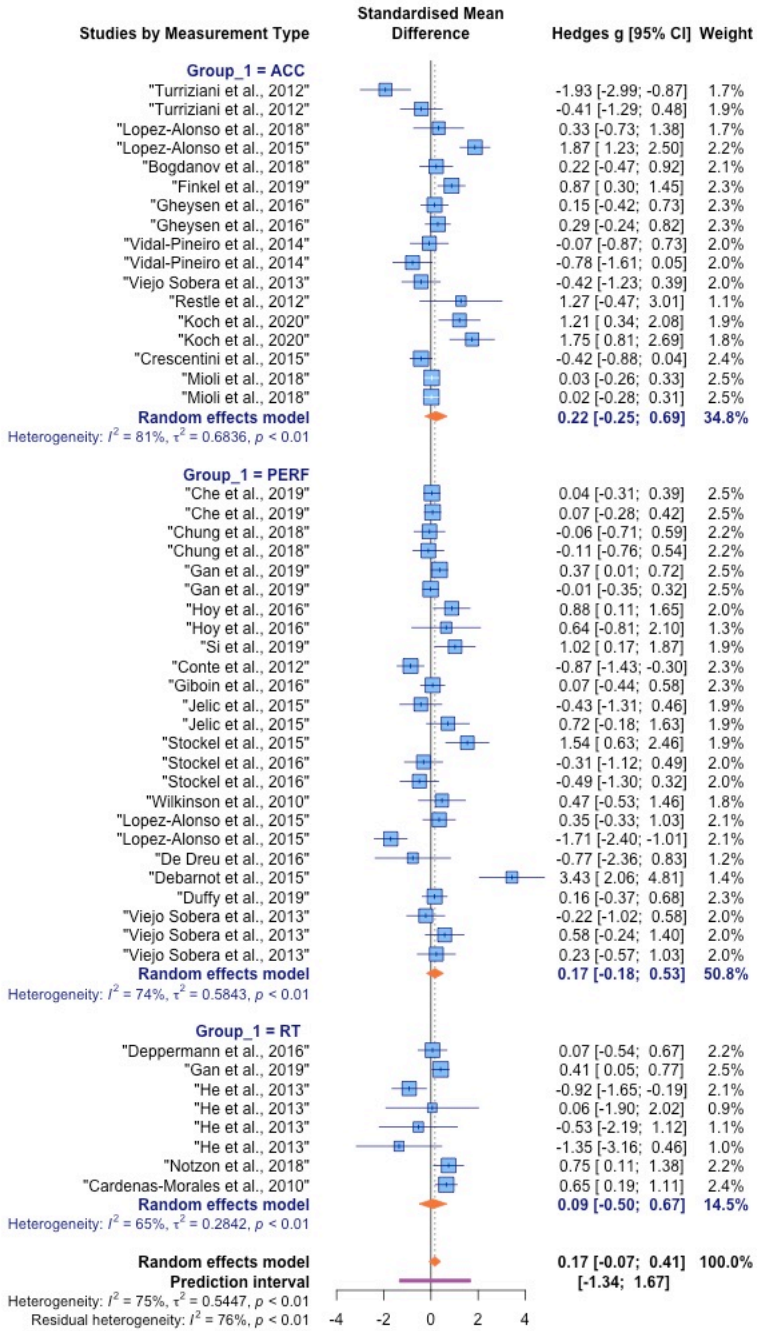
Significant differences were found between groups for stimulation of location ($Q = 48.9$, $p = 0.0002$). Larynx primary somatosensory cortex, electrode location FZ, and left Brodmann's area 10 were found to have significant positive effects on effect size, however, these locations only had one research contribution to each location. Therefore, the interpretation that these areas do indeed have positive effects relating to cognitive enhancement cannot be justified, and further research is required to determine the efficacy of stimulating these locations across a broad range of tasks.


Studies by Location
Standardised Mean Difference
Hedges g [95% CI]
Weight
Location = rDLPFC
"Turriziani et al., 2012" -1.93 [-2.99; -0.87] 1.7%
"He et al., 2013" -1.35 [-3.16; 0.46] 1.0%
"Notzon et al., 2018" 0.75 [0.11; 1.38] 2.2%
Random effects model -0.75 [-4.40; 2.89] 4.9%
Heterogeneity: I^2 = 90%, τ^2 = 1.7804, p < 0.01
Location = lDLPFC
"Turriziani et al., 2012" -0.41 [-1.29; 0.48] 1.9%
"Viejo Sobera et al., 2013" -0.42 [-1.23; 0.39] 2.0%
"Hoy et al., 2016" 0.88 [0.11; 1.65] 2.0%
"Hoy et al., 2016" 0.64 [-0.81; 2.10] 1.3%
"Viejo Sobera et al., 2013" -0.22 [-1.02; 0.58] 2.0%
"Viejo Sobera et al., 2013" 0.58 [-0.24; 1.40] 2.0%
"Viejo Sobera et al., 2013" 0.23 [-0.57; 1.03] 2.0%
"Deppermann et al., 2016" 0.07 [-0.54; 0.67] 2.2%
"He et al., 2013" -0.53 [-2.19; 1.12] 1.1%
Random effects model 0.12 [-0.26; 0.49] 16.6%
Heterogeneity: I^2 = 19%, τ^2 = 0.0441, p = 0.27
Location = lM1
"Lopez-Alonso et al., 2018" 0.33 [-0.73; 1.38] 1.7%
"Lopez-Alonso et al., 2015" 1.87 [1.23; 2.50] 2.2%
"Conte et al., 2012" -0.87 [-1.43; -0.30] 2.3%
"Stockel et al., 2015" 1.54 [0.63; 2.46] 1.9%
"Stockel et al., 2016" -0.49 [-1.30; 0.32] 2.0%
"Wilkinson et al., 2010" 0.47 [-0.53; 1.46] 1.8%
"Lopez-Alonso et al., 2015" 0.35 [-0.33; 1.03] 2.1%
"Lopez-Alonso et al., 2015" -1.71 [-2.40; -1.01] 2.1%
"Cardenas-Morales et al., 2010" 0.65 [0.19; 1.11] 2.4%
Random effects model 0.23 [-0.64; 1.10] 18.5%
Heterogeneity: I^2 = 91%, τ^2 = 1.1353, p < 0.01
Location = rPFCll
"Bogdanov et al., 2018" 0.22 [-0.47; 0.92] 2.1%
Random effects model 0.22 [-0.47; 0.92] 2.1%
Heterogeneity: not applicable
Location = larynxS1
"Finkel et al., 2019" 0.87 [0.30; 1.45] 2.3%
Random effects model 0.87 [0.30; 1.45] 2.3%
Heterogeneity: not applicable
Location = lCerebellum
"Gheysen et al., 2016" 0.15 [-0.42; 0.73] 2.3%
Random effects model 0.15 [-0.42; 0.73] 2.3%
Heterogeneity: not applicable
Location = rCerebellum
"Gheysen et al., 2016" 0.29 [-0.24; 0.82] 2.3%
"Koch et al., 2020" 1.21 [0.34; 2.08] 1.9%
"Koch et al., 2020" 1.75 [0.81; 2.69] 1.8%
Random effects model 1.01 [-0.86; 2.87] 6.1%
Heterogeneity: I^2 = 76%, τ^2 = 0.4065, p = 0.02
Location = lIFG
"Vidal-Pineiro et al., 2014" -0.07 [-0.87; 0.73] 2.0%
"Vidal-Pineiro et al., 2014" -0.78 [-1.61; 0.05] 2.0%
Random effects model -0.42 [-4.94; 4.10] 4.0%
Heterogeneity: I^2 = 32%, τ^2 = 0.0802, p = 0.23
Location = lpIFG
"Restle et al., 2012" 1.27 [-0.47; 3.01] 1.1%
Random effects model 1.27 [-0.47; 3.01] 1.1%
Heterogeneity: not applicable
Location = rIPL
"Crescentini et al., 2015" -0.42 [-0.88; 0.04] 2.4%
"Mioli et al., 2018" 0.02 [-0.28; 0.31] 2.5%
Random effects model -0.16 [-2.87; 2.55] 4.9%
Heterogeneity: I^2 = 59%, τ^2 = 0.0552, p = 0.12
Location = rPMv
"Mioli et al., 2018" 0.03 [-0.26; 0.33] 2.5%
Random effects model 0.03 [-0.26; 0.33] 2.5%
Heterogeneity: not applicable
Location = ldmPFC
"Che et al., 2019" 0.04 [-0.31; 0.39] 2.5%
"Che et al., 2019" 0.07 [-0.28; 0.42] 2.5%
"Chung et al., 2018" -0.06 [-0.71; 0.59] 2.2%
"Chung et al., 2018" -0.11 [-0.76; 0.54] 2.2%
Random effects model 0.02 [-0.09; 0.14] 9.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.96
Location = lPPC
"Gan et al., 2019" 0.37 [0.01; 0.72] 2.5%
"Gan et al., 2019" -0.01 [-0.35; 0.32] 2.5%
"Gan et al., 2019" 0.41 [0.05; 0.77] 2.5%
"He et al., 2013" -0.92 [-1.65; -0.19] 2.1%
Random effects model 0.02 [-0.90; 0.94] 9.5%
Heterogeneity: I^2 = 76%, τ^2 = 0.2792, p < 0.01
Location = FZ
"Si et al., 2019" 1.02 [0.17; 1.87] 1.9%
Random effects model 1.02 [0.17; 1.87] 1.9%
Heterogeneity: not applicable
Location = M1lowerlimb
"Giboin et al., 2016" 0.07 [-0.44; 0.58] 2.3%
Random effects model 0.07 [-0.44; 0.58] 2.3%
Heterogeneity: not applicable
Location = rM1
"Jelic et al., 2015" -0.43 [-1.31; 0.46] 1.9%
"Jelic et al., 2015" 0.72 [-0.18; 1.63] 1.9%
"Stockel et al., 2016" -0.31 [-1.12; 0.49] 2.0%
Random effects model -0.02 [-1.57; 1.53] 5.8%
Heterogeneity: I^2 = 49%, τ^2 = 0.1965, p = 0.14
Location = rIFG
"De Dreu et al., 2016" -0.77 [-2.36; 0.83] 1.2%
Random effects model -0.77 [-2.36; 0.83] 1.2%
Heterogeneity: not applicable
Location = lBA10
"Debarnot et al., 2015" 3.43 [2.06; 4.81] 1.4%
Random effects model 3.43 [2.06; 4.81] 1.4%
Heterogeneity: not applicable
Location = rTPJ
"Duffy et al., 2019" 0.16 [-0.37; 0.68] 2.3%
Random effects model 0.16 [-0.37; 0.68] 2.3%
Heterogeneity: not applicable
Location = rPPC
"He et al., 2013" 0.06 [-1.90; 2.02] 0.9%
Random effects model 0.06 [-1.90; 2.02] 0.9%
Heterogeneity: not applicable
Random effects model 0.17 [-0.07; 0.41] 100.0%
Prediction interval [-1.34; 1.67]
Heterogeneity: I^2 = 75%, τ^2 = 0.5447, p < 0.01
Residual heterogeneity: I^2 = 79%, p < 0.01
-4
-2
0
2
4

A.12. Forest plot of all eligible studies categorized by location of target stimulation.

Subgroup analysis: measurement type

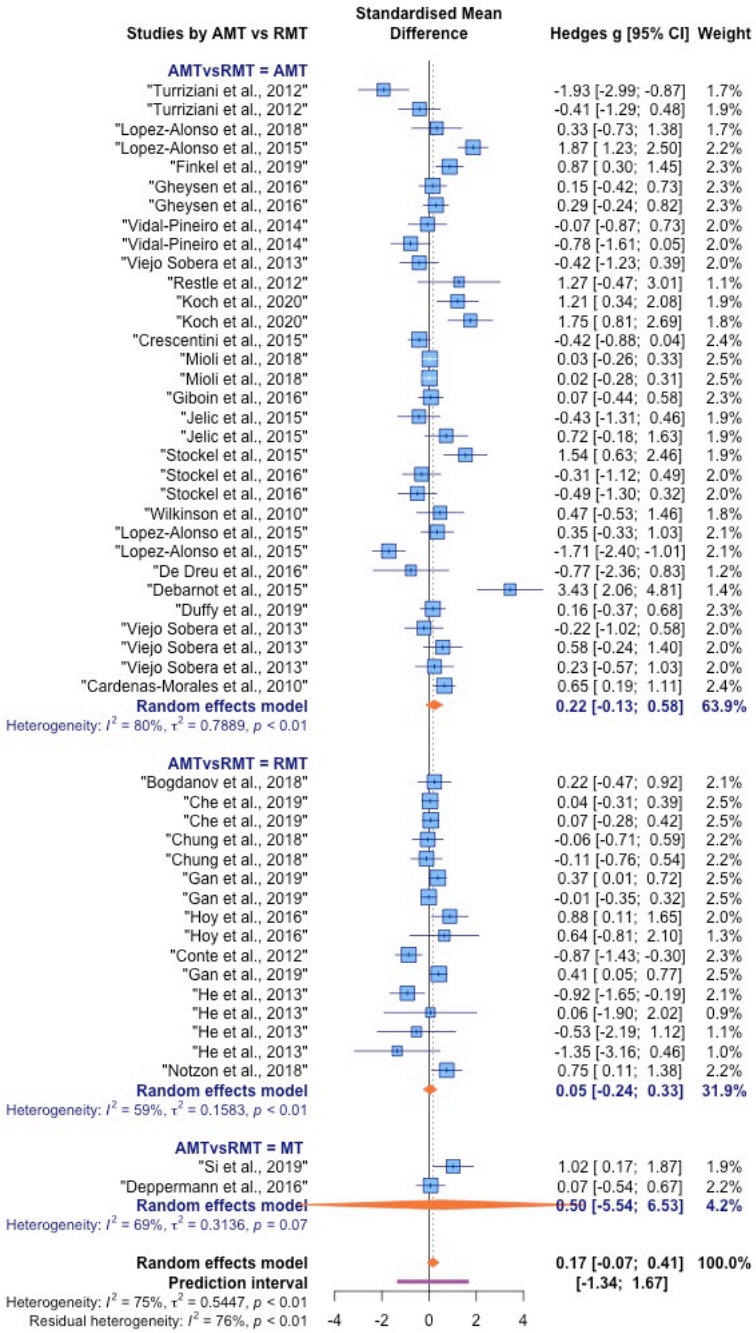
No significant differences were found between groups (Q = 0.16, p = 0.92), and no subgroup was found to have a significant effect on effect size.



A.13. Forest plot of all eligible studies categorized by measurement type, where “ACC” denotes accuracy measurements, “PERF” denotes performance measurements, and “RT” denotes reaction time measurements.

Subgroup analysis: AMT vs RMT

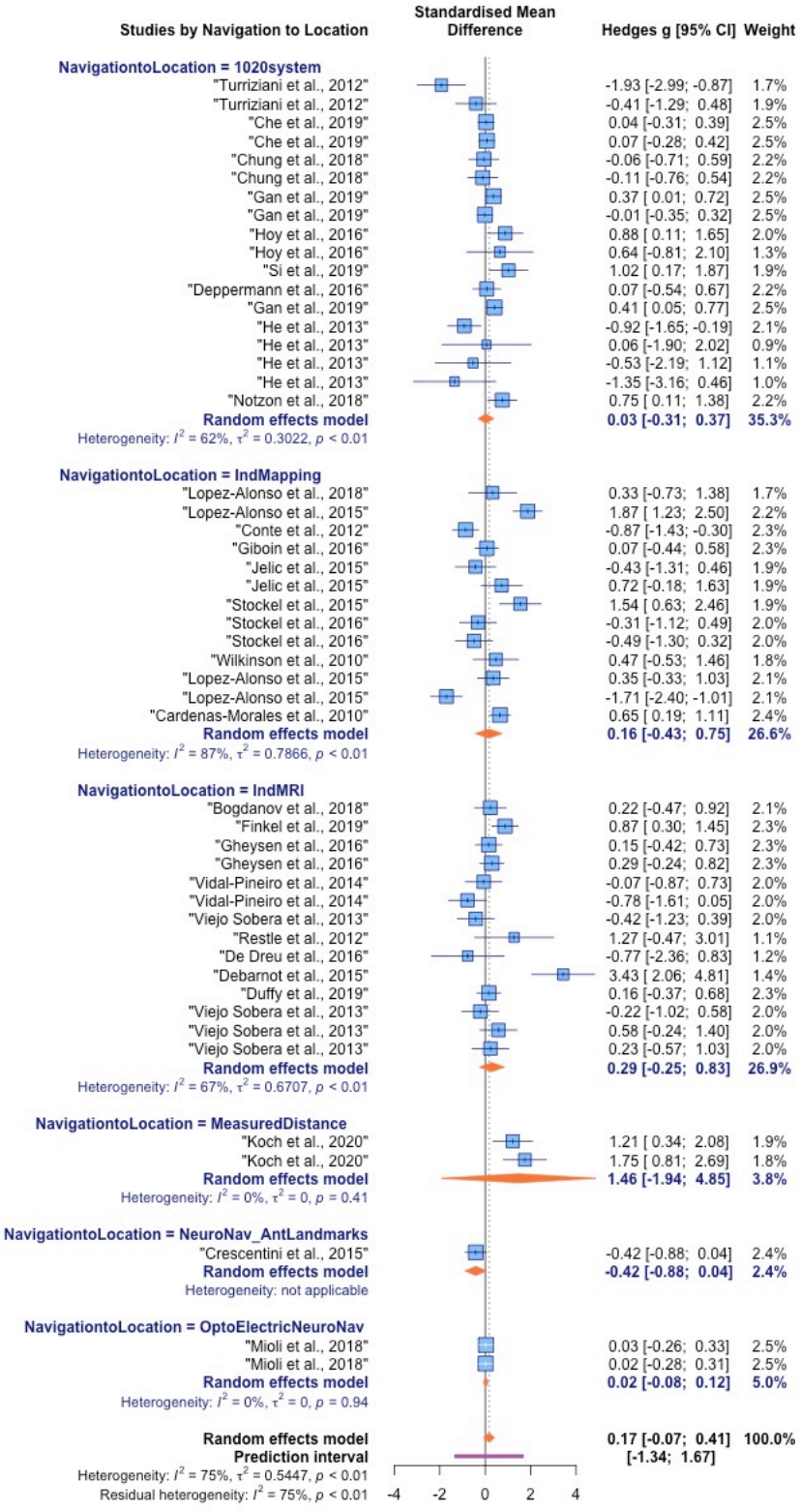
No significant differences were found between groups for methods of determining motor threshold ($Q = 1.27$, $p = 0.53$). No groups were found to contribute significantly to effect size.



A.14. Forest plot of all eligible studies categorized by use of AMT versus RMT determination. “AMT” denotes use of active motor threshold, “RMT” denotes use of resting motor threshold, and “MT” denotes unspecified use of motor threshold.

Subgroup analysis: navigation to location

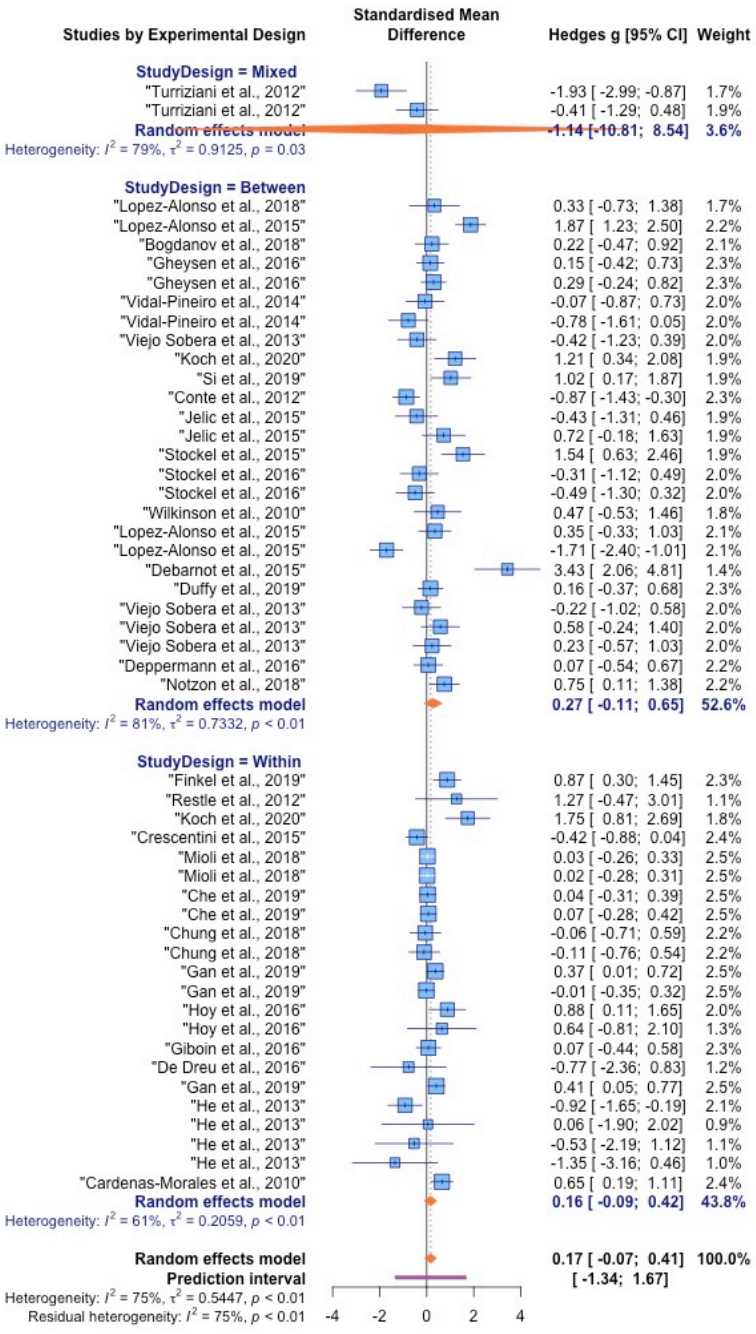
Significant differences were found between groups for navigation to the target location for stimulation ($Q = 33.64$, $p < 0.0001$). No groups were found to significantly impact effect size.


Studies by Navigation to Location
Standardised Mean Difference
Hedges g [95% CI] Weight
NavigationtoLocation = 1020system
"Turriziani et al., 2012" -1.93 [-2.99; -0.87] 1.7%
"Turriziani et al., 2012" -0.41 [-1.29; 0.48] 1.9%
"Che et al., 2019" 0.04 [-0.31; 0.39] 2.5%
"Che et al., 2019" 0.07 [-0.28; 0.42] 2.5%
"Chung et al., 2018" -0.06 [-0.71; 0.59] 2.2%
"Chung et al., 2018" -0.11 [-0.76; 0.54] 2.2%
"Gan et al., 2019" 0.37 [0.01; 0.72] 2.5%
"Gan et al., 2019" -0.01 [-0.35; 0.32] 2.5%
"Hoy et al., 2016" 0.88 [0.11; 1.65] 2.0%
"Hoy et al., 2016" 0.64 [-0.81; 2.10] 1.3%
"Si et al., 2019" 1.02 [0.17; 1.87] 1.9%
"Deppermann et al., 2016" 0.07 [-0.54; 0.67] 2.2%
"Gan et al., 2019" 0.41 [0.05; 0.77] 2.5%
"He et al., 2013" -0.92 [-1.65; -0.19] 2.1%
"He et al., 2013" 0.06 [-1.90; 2.02] 0.9%
"He et al., 2013" -0.53 [-2.19; 1.12] 1.1%
"He et al., 2013" -1.35 [-3.16; 0.46] 1.0%
"Notzon et al., 2018" 0.75 [0.11; 1.38] 2.2%
Random effects model 0.03 [-0.31; 0.37] 35.3%
Heterogeneity: I^2 = 62%, τ^2 = 0.3022, p < 0.01
NavigationtoLocation = IndMapping
"Lopez-Alonso et al., 2018" 0.33 [-0.73; 1.38] 1.7%
"Lopez-Alonso et al., 2015" 1.87 [1.23; 2.50] 2.2%
"Conte et al., 2012" -0.87 [-1.43; -0.30] 2.3%
"Giboin et al., 2016" 0.07 [-0.44; 0.58] 2.3%
"Jelic et al., 2015" -0.43 [-1.31; 0.46] 1.9%
"Jelic et al., 2015" 0.72 [-0.18; 1.63] 1.9%
"Stockel et al., 2015" 1.54 [0.63; 2.46] 1.9%
"Stockel et al., 2016" -0.31 [-1.12; 0.49] 2.0%
"Stockel et al., 2016" -0.49 [-1.30; 0.32] 2.0%
"Wilkinson et al., 2010" 0.47 [-0.53; 1.46] 1.8%
"Lopez-Alonso et al., 2015" 0.35 [-0.33; 1.03] 2.1%
"Lopez-Alonso et al., 2015" -1.71 [-2.40; -1.01] 2.1%
"Cardenas-Morales et al., 2010" 0.65 [0.19; 1.11] 2.4%
Random effects model 0.16 [-0.43; 0.75] 26.6%
Heterogeneity: I^2 = 87%, τ^2 = 0.7866, p < 0.01
NavigationtoLocation = IndMRI
"Bogdanov et al., 2018" 0.22 [-0.47; 0.92] 2.1%
"Finkel et al., 2019" 0.87 [0.30; 1.45] 2.3%
"Gheysen et al., 2016" 0.15 [-0.42; 0.73] 2.3%
"Gheysen et al., 2016" 0.29 [-0.24; 0.82] 2.3%
"Vidal-Pineiro et al., 2014" -0.07 [-0.87; 0.73] 2.0%
"Vidal-Pineiro et al., 2014" -0.78 [-1.61; 0.05] 2.0%
"Viejo Sobera et al., 2013" -0.42 [-1.23; 0.39] 2.0%
"Restle et al., 2012" 1.27 [-0.47; 3.01] 1.1%
"De Dreu et al., 2016" -0.77 [-2.36; 0.83] 1.2%
"Debarnot et al., 2015" 3.43 [2.06; 4.81] 1.4%
"Duffy et al., 2019" 0.16 [-0.37; 0.68] 2.3%
"Viejo Sobera et al., 2013" -0.22 [-1.02; 0.58] 2.0%
"Viejo Sobera et al., 2013" 0.58 [-0.24; 1.40] 2.0%
"Viejo Sobera et al., 2013" 0.23 [-0.57; 1.03] 2.0%
Random effects model 0.29 [-0.25; 0.83] 26.9%
Heterogeneity: I^2 = 67%, τ^2 = 0.6707, p < 0.01
NavigationtoLocation = MeasuredDistance
"Koch et al., 2020" 1.21 [0.34; 2.08] 1.9%
"Koch et al., 2020" 1.75 [0.81; 2.69] 1.8%
Random effects model 1.46 [-1.94; 4.85] 3.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.41
NavigationtoLocation = NeuroNav_AntLandmarks
"Crescentini et al., 2015" -0.42 [-0.88; 0.04] 2.4%
Random effects model -0.42 [-0.88; 0.04] 2.4%
Heterogeneity: not applicable
NavigationtoLocation = OptoElectricNeuroNav
"Mioli et al., 2018" 0.03 [-0.26; 0.33] 2.5%
"Mioli et al., 2018" 0.02 [-0.28; 0.31] 2.5%
Random effects model 0.02 [-0.08; 0.12] 5.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.94
Random effects model 0.17 [-0.07; 0.41] 100.0%
Prediction interval [-1.34; 1.67]
Heterogeneity: I^2 = 75%, τ^2 = 0.5447, p < 0.01
Residual heterogeneity: I^2 = 75%, p < 0.01
-4
-2
0
2
4

A.15. Forest plot of all eligible studies categorized by the method of navigation to the target location for stimulation.

Subgroup analysis: experimental design

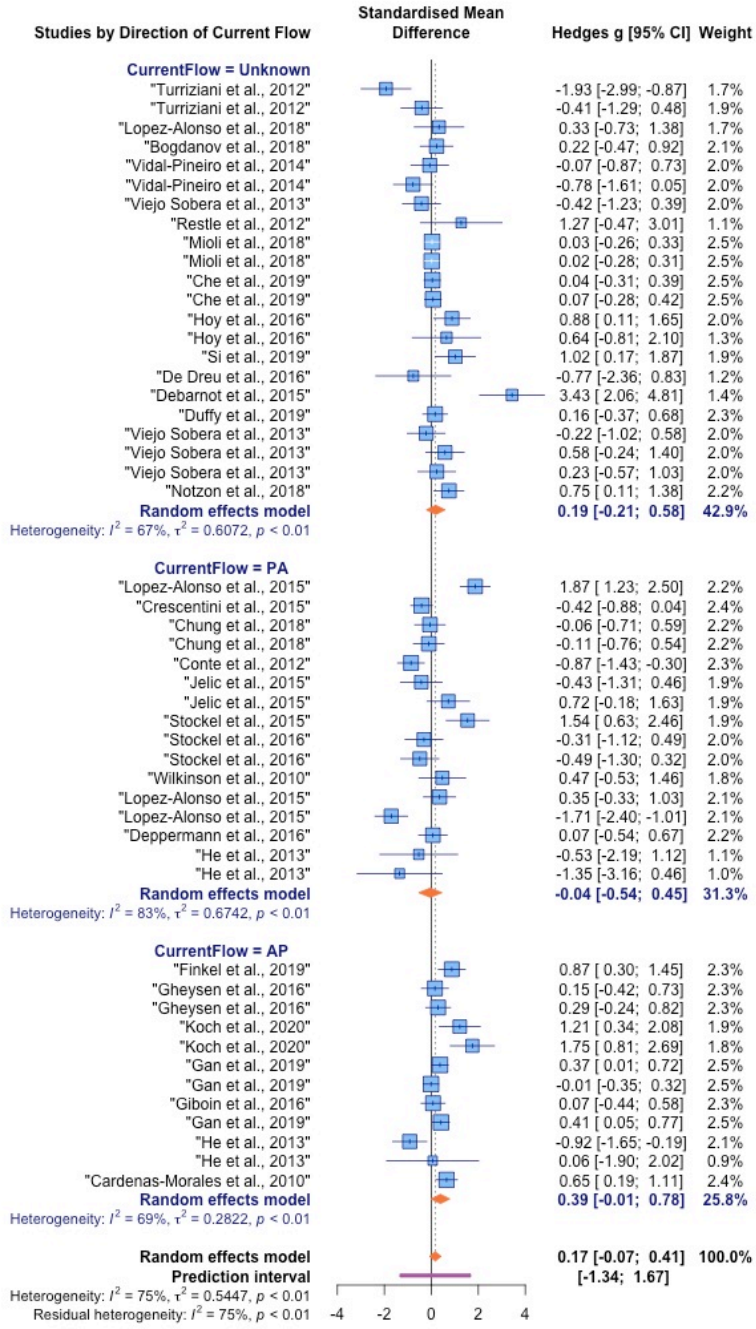
No differences were found between groups that differed by experimental design (Q = 3.25, p = 0.20), and no groups were found to significantly influence effect size.



A.16. Forest plot of all eligible studies categorized by experimental design.

Subgroup analysis: direction of current flow

No significant differences were found between groups that differed by the direction of current flow (Q = 2.17, p = 0.34), and no groups were found to significantly influence effect size.



A.17. Forest plot of all eligible studies categorized by the direction of current flow. “Unknown” refers to unspecified direction of current flow within the study, “PA” denotes posterior-anterior direction of current flow, and “AP” denotes anterior-posterior direction of current flow.

According to the results of both the outlier-reduced model and the full model, effect size of iTBS when compared to control conditions on the enhancement of cognition seems to be influenced by experimenter-determined parameters. In the full model, we did not find a significant effect of iTBS on the enhancement of cognition, whereas in the outlier-reduced model we did find a significant, but small, effect. Our interpretation in the manuscript stands – while on the basis of the present studies we may not expect to find a significant effect in a future study (determined by the prediction interval), we aimed to understand what parameters influenced effect size due to the substantial heterogeneity present in both models. We found that the location of stimulation and the way in which researchers navigate to that location have significant differences across groups. What is not clear is the influence of the control condition – in the outlier reduced model we found marginal differences between groups, whereas in the full model no differences were found between groups. We stand by our interpretation that multiple methods of control and sham should be used in iTBS experiments to determine if there are any tangible differences in behavior after stimulation, as mentioned by Duecker and Sack (2015) in their article that compared the efficacy of popular control conditions.

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From: Alexandria Pabst, PhD Candidate, Cognitive & Information Sciences
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Appendix D: Memorandum on Dissertation Format

To: Chris Kello, Dean of Graduate Education
From: Alexandria Pabst, PhD Candidate, Cognitive and Information Sciences
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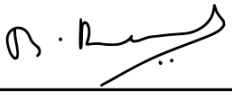

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