

Attentional effects on visual-tactile crossmodal
enhancement at early stages of cortical
processing

by

Esteban Salazar

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Sensory processing can be facilitated through bimodal interactions between relevant visual-tactile sensory inputs in order to achieve goal-oriented behaviours. While the specific neural mechanisms contributing to this modulation remain unclear, the dorsolateral prefrontal cortex (DLPFC) may have a role in regulating the observed processing facilitation seen in the somatosensory cortex (S1), though the extent is not yet clear. We used electroencephalography (EEG) to observe the temporal contributions of visual priming to the enhancement of S1 responses. We hypothesized that inhibiting DLPFC cortical activity would result in a diminished facilitation of tactile processing in S1 (represented by the P50), observed by a visual-tactile stimuli onset with a 200-300 ms time delay. Somatosensory modulation was inferred through amplitude and latency shifts in tactile event-related potentials (ERPs) recorded while participants performed a sensory integration task that required scaled motor responses dependent on the amplitudes of tactile and visual stimuli. Tactile stimuli were discrete vibrations (25 Hz) presented to the left index finger, visual stimuli were presented as a central horizontal bar on a computer screen at varying heights, and graded motor responses were made by squeezing a pressure-sensitive rubber bulb. Healthy adults completed a training session to become familiar with the stimulus-response relationships for both visual and tactile stimuli prior to completing a task where pairs of discrete stimuli with random amplitudes were presented: Tactile-tactile (TT, 500 ms each, 30 ms ISI), visual-tactile with a 200-300 ms delay (vTd 200-300 ms), and visual-tactile with a 300-400 ms delay (vTd 300-400 ms). Stimuli pairs were administered in a block setting, where each block contained 60 trials, with 20 trials for each of the discrete stimuli presented in a randomized order. The study design consisted of 10 blocks, with a short transcranial

magnetic stimulation (TMS) intervention at the halfway mark. Participants were randomly assigned to either an intervention group (n=16) or control group (n=16) where TMS modalities of theta burst stimulation (TBS); continuous TBS (cTBS) was given to the intervention group and intermittent TBS (iTBS) was given to the control group, both applied to the right DLPFC. Results revealed that P50 upregulation observed in condition vTd (200-300 ms) is significantly lower following cTBS on the right DLPFC but still greater than unimodal TT stimulation. Following iTBS, bimodal facilitation was observed in condition vTd (300-400 ms) for P50 and N70. These findings improve our understanding of the role right DLPFC plays regarding crossmodal facilitation observed in visual-tactile processing.

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List of Abbreviations

FMRI – Functional magnetic resonance imaging

BOLD – Blood oxygenated level dependent [signal]

DLPFC – Dorsolateral prefrontal cortex

S1 – Primary somatosensory cortex

S2 – Secondary somatosensory cortex

ERPs – Event related potentials

EEG – Electroencephalography

RA2 – Rapidly adapting 2 [mechanoreceptor]

DCML – Dorsal column medial lemniscus

VPLN – Ventral posterior lateral nucleus [thalamus]

BA – Brodmann area

LGN – Lateral geniculate nucleus [thalamus]

V1 – Primary visual cortex

PFC – Prefrontal cortex

TRN -Thalamic reticular nucleus [thalamus]

MD – Mediodorsal [thalamic nucleus]

SIM – Simultaneous

vTd -Visual-tactile delay onset

tVd – Tactile-visual delay onset

TT – Tactile-tactile

TMS – Transcranial magnetic stimulation

TBS – Theta burst stimulation

cTBS – Continuous theta burst stimulation

iTBS – intermittent theta burst stimulation

MT – Motor threshold

APB – Abductor pollicis brevis

EMG – electromyography

AMT – Active motor threshold

LP – Parietal lobule

1.0 Introduction

Consider your environment at any given moment in time. Visually, you may see people walking past you; you may notice their body language, their facial expressions, the clothing they are wearing or even something they are carrying. Concurrently, you notice how they fit into the environment relative to you. Within yourself, you notice your body positioning, any weight or pressure from objects you may be carrying or wearing. Your nervous system needs to process these various sensory inputs coming in from multiple systems, integrate them in an effective manner to be able to react appropriately to your environment, and any stimuli that may arise.

The different sensory modalities presented to your nervous system can be overwhelming. As such, need to be filtered throughout so only the information that is relevant to the task at hand is processed, whether that be safely crossing a road, carrying groceries in, or having a conversation. Since our external environment contains objects, animals and other people that can present multiple sensory modalities at once, our nervous system needs to be equipped at suppressing or enhancing said modalities.

Studies in the early 2000s explored the interaction a sensory modality could have in a different cortical region and found that the presence of vibrotactile stimuli coupled with a visual input on the ipsilateral hemifield resulted in an altered processed signal at the level of the visual cortex (Macaluso et al., 2000, 2002). In a study using functional magnetic resonance imaging (fMRI), Staines et al. (2002) found that vibrotactile stimulation to the left hand resulted in an increased blood oxygenated level dependent (BOLD) signal on ipsilateral dorsolateral prefrontal cortex (DLPFC) and contralateral primary somatosensory area (S1), with a decrease in BOLD signal to ipsilateral S1. Dionne et al. (2010) explored the effects a second stimulus modality could have on the processing of a single modality. Dionne used an experimental paradigm where

participants would be exposed to either a unimodal visual or tactile stimulus, or a visual-tactile bimodal stimuli. Through whole-brain imaging and region of interest imaging techniques collected with fMRI, she discovered a significant increase of percent BOLD signal in S1 contralateral to where the tactile stimulus was presented, relative to BOLD percent levels in unimodal tactile or unimodal visual. This increase in BOLD signal provided the first indication that coupling a visual stimulus with a tactile stimulus could enhance how the tactile stimulus is processed in S1.

In a subsequent study, Dionne et al. (2013) sought to investigate the role task-relevance would have on event related potentials (ERPs) from crossmodal enhancement noted in S1. Using electroencephalography (EEG) and a similar experiment task conducted by the same group in 2010, participants were asked to judge the summed amplitude of the visual-tactile sensory stimuli and use a pressure-sensitive bulb to record their graded motor response. After analysing, she discovered that when a visual stimulus is present and task-relevant; a crossmodal enhancement occurs between visual and tactile modalities resulting in a significant P50 amplitude increase in S1. Using a similar experimental paradigm, I am now seeking to explore the attentional weight required for the aforementioned visual-tactile crossmodal upregulation and distinguish whether this phenomenon is dependent on attentional resources, physiological connections between the two modality cortices, or a combination of the two.

2.0 Literature Review

2.1 Somatosensation and Vision

The somatosensory system can be broken down into three major components: proprioception, exteroception and interoception. Proprioception refers to the ability to sense oneself, specifically the sensation of movement and joint position, and is achieved through receptors found in the skin (cutaneous mechanoreceptors), muscle fibres (muscle spindles), in muscle tendons (golgi tendon organs) and in the joint capsule (joint receptors). These types of receptors activate when there is a physical deformation to them, whether it be via stretch, pressure, or vibrations. Exteroception is the interaction between the external environment and its relation to the body. Skin mechanoreceptors can encode, and process sense of touch, thermal detection and painful stimuli termed nociception. Lastly, interoception allows for regulation of internal organs and physiological responses including cardiovascular, respiratory, digestive and renal control; monitored mainly by chemoreceptors.

Regarding our ability to perceive touch, there are four skin mechanoreceptors that can process skin deformation including stretch, pressure, and vibrations. Two major properties of these receptors are (1) the size of their receptive field and (2) their adaptive speed for stimuli duration. Superficial skin receptors will have a smaller receptive field and therefore will have a higher acuity for stimulus discrimination. Higher discrimination allows for recognizing small differences within a stimulus/stimuli presented, with a lower discrimination rate fine sensory information may be lost. Regarding adaptive speed, skin receptors can be slow adapting (SA) (Merkel's disk, Ruffini endings) or can be fast adapting (FA) (Meissner corpuscles, Pacinian corpuscles) for either a prolonged stimulus in the case of SA or a short stimulus presentation in the case of RA. Of the four, Pacinian corpuscles, a deeper layer, fast adaptive (RA2) receptor is

the best at processing vibrotactile stimulus. Discrimination tasks using vibrotactile input use Meissner Corpuscles to generate the appropriate signal which will eventually end in the somatosensory cortex.

When a vibrotactile stimulus is applied to the skin, the intensity of the vibration will produce a receptor potential of a similar size where the RA2 receptor will convert the vibrations into electrical energy, resulting in a depolarization of large cutaneous afferent fibers of the median or ulnar nerve, belonging to the dorsal column tract. The electrophysiological signal will flow ipsilaterally until it reaches the cuneatus nuclei at the level of the medulla. The tracts will synapse onto the arcuate fibers, decussate, and continue to flow contralaterally along the medial lemniscus tract until it reaches the thalamus. These two tracts make up the dorsal column medial lemniscus (DCML) pathway. Once the thalamus is reached, the tracts will synapse onto the ventral posterior lateral nucleus (VPLN) of the thalamus. From the thalamus, projections will travel to the primary somatosensory cortex (S1) where the final afferent synapse will occur; specifically, onto Brodmann area (BA) 3b and 1. S1 is topographically organized, and this organization can be referred to as the sensory homunculus. Hand representation in S1 is found medially, with the second digit having the largest neuronal representation among all digits. This makes the second digit (innervated by the median nerve) a strong stimulus site for electrophysiological studies.

Visual information is processed when photoreceptors within the fovea are stimulated by light photons and hyperpolarized, there is a decrease of glutamate release from the cell. With a decrease of glutamate, bipolar cells become active which allows for passive flow of an electrical current onto ganglion cells. Ganglion cells will generate an action potential and synapse onto fibers of the optic nerve. Once the signal is flowing through the optic nerves, it will cross the

optic chiasm, where visual sensory input located on the right visual field will continue along the left optic tract; sensory input located on the left visual field will travel along the right optic tract. The optic tracts will synapse onto its ipsilateral lateral geniculate nucleus (LGN), then the signal will travel along the optic radiation, and finally synapse onto the primary visual cortex (V1).

2.2 Sensory Gating

Mentioned in the pathways of visual and vibrotactile sensory modalities, when a signal goes beyond the thalamus and reaches its specific cortical region; based on the level of cortical excitability, there will be modulations on how the signal gets processed. This phenomenon is termed sensory gating which allows for incoming sensory information to be inhibited during its path from the periphery to its primary cortical receptive zones (Staines et al., 2000). This allows for any irrelevant sensory input to be filtered out and prevent oneself from being overwhelmed within their environment. Observed in all modalities (Staines et al., 2000), one of the main drivers in sensory gating appears to be task-relevancy (Adams et al., 2019) which modulates how an afferent signal is processed in the cortex; either by facilitating the signal and thus enhancing cortical activity or suppressing the signal and diminishing cortical brain activity.

Sensory gating can be modulated by both bottom-up and top-down signals. Top-down modulation comes from the cortex, includes higher order regions from various cortices, one being the prefrontal cortex (PFC) which has been linked to attentional modulation (Zikopoulos & Barbas, 2007). Top-down modulation is task dependent and can be shifted by the focus of attention within the task (Wielsman & Wilson, 2020). The implication that top-down modulation of sensory gating can be affected by attention raises the question of what attention is and how it can be defined. In this case, attention would be defined as the relevant sensory cues needed to successfully achieve a task at hand. Attention has been shown to modulate sensory processing

within the visual modality (Motter, 1993; Gazzaley et al., 2007; Andersen et al., 2008) as well as somatosensation (Josiassen et al., 1990; Hsiao & Johnson, 1993; Johansen-Berg et al., 2000; Staines et al., 2002). Both these systems share a common anatomical structure which is tasked with sensory gating, the thalamus.

The thalamic reticular nucleus (TRN) are a thin veil made up of inhibitory GABAergic neurons, encasing most of the dorsal thalamus along its entire antero-posterior extent, separating the thalamus from the cortex (Zikopoulos & Barbas, 2007). It receives excitatory signals from collateral branches of both thalamocortical and corticothalamic tracts, and projects inhibitory connections to the thalamus. It can be influenced by cortical regions as well as the thalamus itself. TRN influences the thalamus by inhibiting or disinhibiting distinct thalamic nuclei by upregulating or downregulating inhibitory interneurons respectively to modulate how the thalamus interacts with incoming sensory input. This change in inhibition/disinhibition is modulated by higher order neurons carrying signals from S1. Inhibition of the thalamus would diminish the strength of the signal or eradicate it entirely, limiting or preventing the stimulus from being processed in the cortex respectively. Disinhibiting the thalamus would allow for afferent input to proceed onto the cortex for processing (Zikopoulos & Barbas, 2007). Proof of such modulation includes an increased TRN activity during attentional task in monkeys with an increased spike amplitude for transient visual responses when attention shifts for auditory to visual input (McAlonan et al., 2006). Increased TRN activity, subserving in thalamic modulation during attentional tasks adds to the likelihood of sensory gating being linked to attention; requiring the enhancement of relevant input, while decreasing irrelevant input to attain a goal-oriented response.

The thalamus plays a central role in the modulation of both top-down and bottom-up modulation (Zikopoulos & Barbas, 2007). From a top-down approach, it is considered the driver since its ability to modulate the incoming peripheral input is influenced by intra-thalamic and cortical input (Zikopoulos & Barbas, 2007). The thalamus has reciprocal connection with the TRN via open and closed loop circuits. Open loops refer to incoming input from the thalamus to the TRN, then outputted onto a different thalamic nucleus. Closed loops refer to the same thalamic nucleus and same TRN region modulating each other. The thalamus also has a reciprocal loop with cortical areas like S1, where projections from the VPLN synapse onto layer IV of S1, and projections from layer VI of S1 synapse back onto the VPLN. Though there is a direct connection between layer VI at the cortex to thalamic nuclei, the connection does not appear to have a strong limiting control (Sherman, 2016). Centrifugal projections from different cortical layer V have collateral connections to different brainstem regions that can also modulate incoming input; like the trigeminothalamic axon branch that innervates the superior colliculus, which synapses to the LGN (Sherman, 2016). This is also seen from S1, where branches will innervate different brainstem regions (Sherman, 2016). Depending on task requirements, cortical regions can directly or indirectly modulate the excitability of the thalamus, controlling the flow of sensory input to enter the processing stream.

The thalamus receives input from higher order cortical areas, resulting in a modulated thalamic state while receiving sensory information from all sensory modalities (except olfactory) and selects which of these signals will reach the cortex, effectively gating the incoming information. This filtering process is not done at random, the thalamus received input from layer VI of all sensory cortices, as well as TRN which help regulate the thalamus to appropriately filter out irrelevant information and enhance relevant input (Zikopoulos & Barbas, 2007). With the

thalamus in this modulated state, when multiple stimuli from different modalities are presented concurrently or within a brief time-window, the presence of the second stimuli has been shown to have no effect, attenuate the response, or behave as a primer to enhance the response for the task-relevant stimuli (Popovich & Staines, 2014; Adams et al., 2017). The enhancement response resulting from the presence of a priming sensory modality has been shown with a bimodal coupling of visual-tactile stimuli (Popovich & Staines, 2014; Adams et al., 2017; Adams et al., 2019).

2.3 PFC/DLPFC

Beyond the reciprocal projections of specific thalamic nuclei to their respective sensory cortex, different cortical regions can also influence attentional sensory gating. The PFC has 3 key functions in attentional modulation: direct cortical and thalamic modulation, incoming input enhancement, and incoming input suppression (Zikopoulos & Barbas, 2007). With a mix of large and small axonal terminals directly on the TRN, PFC can inhibit reticular neuron activity depending on the signals received from higher order neurons from S1, increasing salient stimuli input. it can also disinhibit the activity of reticular neurons, inhibiting open and closed reticulothalamic loops. PFC has also been shown to have modulatory effects in visual and somatosensory processing (Bolton & Staines, 2014; Adams et al., 2019). Altering cortical excitability at S1 can modulate how each cortex interacts with the thalamus, as well as prime the cortical region itself to receive incoming sensory input. Lastly it can activate the mediodorsal (MD) thalamic nucleus to enhance the transmission of relevant stimuli and suppress distracting stimuli. Within the PFC, the dorsolateral prefrontal cortex (DLPFC) has also been shown to influence sensory gating, although its extent is not fully understood (Knight et al., 1999; Bolton & Staines, 2011; Bolton & Staines, 2014; Brown et al., 2015).

The DLPFC plays a role on cognitive processing including language, motor control, attention, and executive function (Knight et al., 1999). A study explored the effects of lesions to the sulcus principalis in primates, an analogous structure to the human DLPFC (Jacobsen 1935, as cited in Knight et al., 1999). Results showed an impaired ability to successfully perform a delayed response task. A delayed response task requires subjects to be able to sustain instructions for task performance for a brief period of time, prior to performing the task. This would require subjects to hold task instructions within their working memory. Lesions to the sulcus principalis revealed an impaired working memory, thus linking the efficacy of working memory to the DLPFC. Knight suggested this cause and effect is not related to a direct link between both areas, but instead is caused by the multiple cortical interactions between the DLPFC and different specific modalities (Knight et al., 1999). Relating the effects of working memory to the sensory gating phenomena, Gazzaley et al. (2008) found that older adults demonstrate a sort of 'load-shift' where visual gating happens later in time, compared to the 100 ms time window in which it occurs in healthy, young adults. Gating incoming visual information later than 200 ms post stimulus onset has been revealed to negatively affect working memory and decreases task completion (Gazzaley et al., 2008). This is further explained by Hannula et al. (2010) with the explanation that in goal-oriented tasks, remembering the properties of perceived tactile stimulus for seconds or even minutes requires working memory, which has links to S1, S2 and various regions within the PFC and premotor cortex.

It was noted during a unilateral and bilateral task-relevancy experiment, that right DLPFC BOLD response was increased (Staines et al., 2002). Since then, Bolton and Staines (2011) and Brown et al. (2015) have found that DLPFC inhibition resulted in a reduction of attentionally-based modulation within S2 ERPs and movement-related gating within S1 ERPs

respectively, compared to their control groups. Bolton found a decrease in attentionally-based modulation, which could be related to a decrease in working memory (Bolton & Staines, 2011). Brown reported that once DLPFC neurons were inhibited, there was a reduction in the facilitation of relevant movement related gating in participants, implying that the DLPFC has a role in regulating sensory gating (Brown et al., 2015). All this suggests that the DLPFC has a key role to play in somatosensory sensory gating, especially tactile sensory gating; however, a mechanistic explanation of how this phenomenon is achieved is not yet fully understood.

2.4 Bimodal Sensory Presentation

ERPs are the summation of electrical cortical excitability evoked from a specific event triggering a modal response. Focusing on somatosensory ERP, specifically vibrotactile ERPs, the main ERPs generated in S1 are P50 and N70, while the main ERPs generated in S2 are P100 and N140. With the use of EEG, maximal peak ERP amplitudes are found overlying electrodes CP3/4, with some activity seen in surrounding electrodes C3/4 and P3/4.

P50 (with peak amplitude found within a 40-70 ms range) waveform is generated on the contralateral S1 to the stimulated limb and is unilateral in nature. P50 can be evoked in most participants by both pulses and vibratory stimuli (Hamalainen et al., 1990). It is an example of a unimodal ERP, since it is only generated in the presence of a tactile stimuli (Hamalainen et al., 1990; Bolton & Staines, 2014; Adams et al., 2017). Literature suggests that P50 is not generally modulated by attention unless the task is perceived difficult enough to increase cognitive demand (Schubert et al., 2008; Bolton & Staines, 2014), but can be modulated by the presence of a second stimulus modality (Popovich & Staines, 2014). Popovich conducted a study where a bimodal presentation of visual-tactile stimuli was presented with different temporal organizations. The stimuli were presented concurrently (SIM) or with a 100 ms delay, with either

visual preceding tactile (VTd) or tactile preceding visual (TVd). A control tactile-tactile (TT) condition was also included for comparison of P50 peak amplitude. Popovich found that P50 amplitude was significantly upregulated in the VTd condition, inferring that two conditions were needed for crossmodal upregulation: a temporal window suggestive of a processing period needed and a stimuli presentation order suggestive of a primer stimulus required (Popovich & Staines, 2014).

N70 (70-100 ms) waveform follows after P50, and similar to it is generated contralateral to the stimulated limb, and unilateral in nature (Hamalainen et al., 1990). Only generated by tactile stimuli, this waveform amplitude is larger when generated by a unimodal tactile stimulus presentation, relative to a bimodal visual-tactile stimuli presentation (Adams et al., 2017; Adams et al., 2019). In a bimodal presentation, when the visual stimulus is the distracter, it will attenuate the waveform (Adams et al., 2019) suggesting a split in attention. A comparison of N70 waveform pre and post continuous theta burst stimulation (cTBS) intervention to DLPFC showed a decrease in N70 when responding to a unimodal tactile stimulus (Adams et al., 2019). No significant enhancement of N70 processing have been reported after bimodal stimulus onset, suggesting that N70 is not altered by crossmodal processing.

P100 (90-125 ms) waveform will follow after N70 and is the first waveform to be generated from S2, with bilateral activation (Hamalainen et al., 1990). This waveform appears to have its greatest peak when it is evoked from high frequency vibrations and is an example of another unimodal ERP (Hamalainen et al., 1990; Bolton & Staines, 2014). Due to its bilateral nature, maximal peak amplitude is found most strongly at FCz (Adams et al., 2017). This waveform is attentional driven, shown by its attenuation in the presence of irrelevant stimuli post cTBS to the DLPFC (Bolton & Staines, 2014; Brown et al., 2015). Further, P100 was shown to

have greater activity when responding to a relevant tactile stimulus in an active and passive task, when the stimulus is presented alone compared to being presented in an oddball task (Adler et al., 2009). P100 is also sensitive to a crossmodal presentation of stimuli (Adams et al., 2017). When visual-tactile stimuli were presented in the SIM condition, P100 amplitude was increased, but decreased when the bimodal presentation was TVd or TT, suggesting that P100 is dependent on the attentional relevance of the stimulus for goal-oriented tasks (Popovich & Staines, 2014).

N140 (120-150 ms) waveform will follow P100, and like it, is generated in S2 with a bilateral nature and evoked by fast pulses or high frequency vibrations (Hamalainen et al., 1990). Similar to P100, its peak amplitude is seen greatest over FCz (Adams et al., 2017) and showed greater activity when responding to a relevant tactile stimulus alone, compared to an oddball task (Adler et al., 2009). It is suggested that N140 is important for the shift of attention since it appears to have a greater activation when evoked by a deviant-only stimulus in a silent background (Kida et al., 2004a, 2004b, 2006).

2.5 Visual-Tactile Enhancement

Each of the mentioned ERPs can be modulated by different factors, whether it be unimodal or bimodal stimuli presentation, relevance or irrelevance of stimuli for the task, or whether the task demands attention from the modality versus it being presented as a distractor. Focusing on the visual-tactile bimodal relationship, there is evidence suggesting the presence of a crossmodal enhancement phenomenon on tactile processing (P50) following a VTd stimulus onset (Dionne et al., 2013; Popovich & Staines, 2014). Salazar et al. (2023) have identified the optimal time window that best enhances tactile ERP P50 amplitude. Using the VTd condition time-locked to the onset of the tactile stimulus (vTd), times ranges of 0-100 ms, 100-200 ms,

200-300 ms and 300-400 ms were explored to identify which delay range best optimized this bimodal facilitation.

With a total of 35, young, healthy adults participating in 3 separate studies, Salazar et al. (2023) found that P50 upregulation was significant, and consistent among all participants within the 200-300 ms time window (Figure 1). Although no other time window showed any significance, it is important to mention that some participants in the 0-100 ms and 100-200 ms groups showed some upregulation in P50 amplitude. Though not significant, it is congruent with previous literature from the same group showing significant finding in VTd (0-100 ms) upregulation of P50 (Popovich & Staines, 2014). A likely explanation for this may be that individual physiology may account for some individuals experiencing upregulation in the smaller time frequencies, and the 200-300 ms accounts for a larger amount of the population experiencing this crossmodal enhancement.

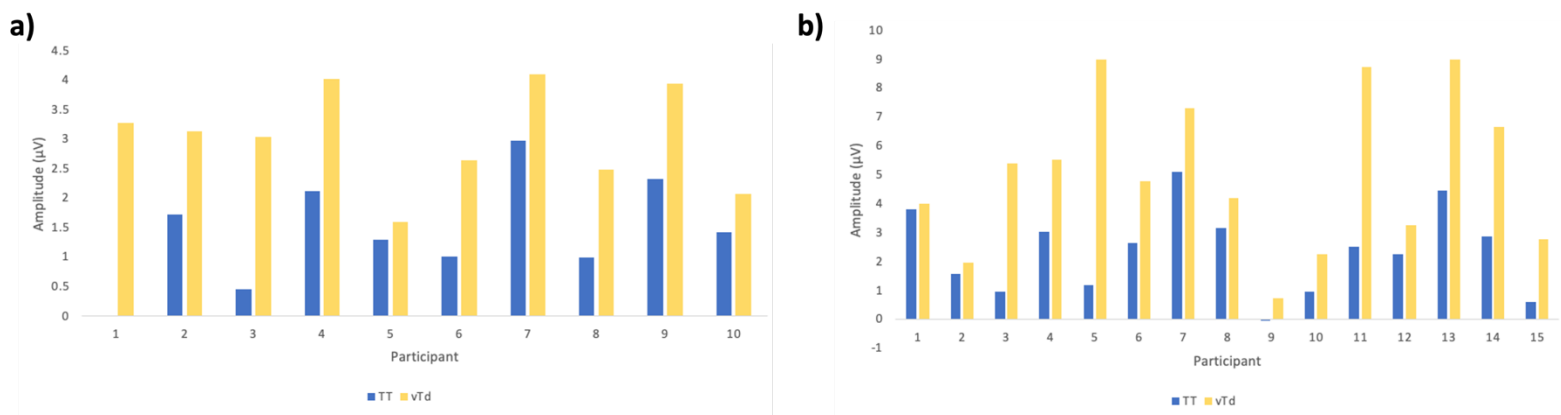


Figure 1: Bar graph averages of two separate data collections from electrode CP4 comparing somatosensory P50 amplitude evoked from TT (blue bar) stimuli and vTd (200-300 ms) (yellow bar) stimuli from Salazar et al., 2023.

2.6 Conclusion

We now have reasonable confidence to believe that this crossmodal enhancement phenomena on tactile information processing is a physiological adaptation resulting from a bimodal stimuli presentation. As well, confidence that the 200-300 ms time window optimises this response. The next step is to explore the driving factors behind this crossmodal upregulation. Literature has linked the PFC, within it the DLPFC as an area that subserves attentional resources (Bolton & Staines, 2011; Adams et al., 2019). We have seen modulation in S1 electrophysiology through the inhibition of DLPFC, as well as through the manipulation of attentional resources (Bolton & Staines, 2011; Popovich & Staines, 2014; Bolton & Staines, 2014). The purpose of this thesis is to attempt to understand whether the observed visual-tactile crossmodal enhancement is physiologically driven, by cortical projections from the visual cortex to the somatosensory cortex; and/or attentionally driven, with attention being a necessary precursor for the expression of crossmodal facilitation by the DLPFC. By using cTBS on the DLPFC, functionally inhibiting its neuronal populations and decreasing its effect on S1, if there is P50 crossmodal enhancement following a vTd (200-300 ms) condition, it would be suggestive that crossmodal enhancement is a physiologically driven phenomenon. If the inactivation of DLPFC eliminates the bimodal P50 enhancement relative to a TT control, it would suggest that DLPFC modulation on S1 is necessary and therefore is an attentionally driven phenomenon.

3.0 Aims & Hypothesis

The purpose of this study is to investigate the mechanistic cause for the observed crossmodal upregulation in tactile ERPs. DLPFC has been linked with afferent upregulation of relevant stimuli and afferent downregulation or suppression of irrelevant stimuli. By using cTBS to inhibit the neuronal population within the right (R.) DLPFC, linked to have some control over attentional regulation; attentional mechanisms to right S1 should be diminished. Comparing vibrotactile-evoked ERPs in right S1 from task-relevant vibrotactile stimulation to the left index finger both pre and post intervention to R. DLPFC, relevant stimulus facilitation by R. DLPFC will be diminished. Any conclusions made comparing pre and post intervention ERPs will have limited attentional interference, and therefore differences should be physiologically derived via direct or indirect pathways.

Post-intervention, if there is a decrease of P50 amplitude or complete eradication of crossmodal enhancements, it would be suggestive that the driving forces in a visual-tactile crossmodal enhancement result from attentional mechanisms. If there is a partial decrease in P50 amplitude, it would suggest that R. DLPFC plays a role in crossmodal upregulation, but other factors, like irrelevant stimulus suppression or corticocortical projections are also critical. If the P50 amplitude upregulation is completely eradicated, that would suggest that attention is the crucial factor in crossmodal upregulation.

Aim 1: Investigate R. DLPFC role in tactile ERP upregulation following a crossmodal, visual-tactile stimulation presentation with a 200-300 ms (vTd) delay onset following visual stimulus presentation.

Hypothesis 1: Inhibition of R. DLPFC neuronal activity during a goal-oriented task will eliminate selective attention crossmodal upregulation in tactile processing following vTd onset, observed via a decreased P50 amplitude.

Aim 2: To determine neural mechanisms that control crossmodal enhancement of early somatosensory cortical areas.

Hypothesis 2: A partial decrease in P50 amplitude following R. DLPFC neuron inhibition is resultant from the loss of attentional factors; upregulatory effects are still present due to direct or indirect somatosensory-visual cortical connections.

4.0 Methodology

4.1 Participants

EEG and behavioural data were collected from 36 healthy volunteers, aged 18-40. Four of the participants data was excluded. Three of the participants were excluded due to their resistance to TMS, where a threshold could not be found, therefore TBS could not be administered. One of the participants was excluded during the analysis of their data, where a clear P50 peak could not be identified. The analysis and interpretation for this study was based on the 32 participants data included (Table 1). Sample size was determined using a power calculation with alpha being 0.05, power 80% and a medium effect size. Participants were provided with an information and consent form outlining the experiment protocol as well as its risk. Consent was obtained through signage of the information consent letter. A transcranial magnetic stimulation (TMS) screening form was also administered to confirm TMS eligibility. All participants were neurologically healthy, with no previous or ongoing treatment for major neurological illnesses or experienced events such as seizures. Participants were also excluded if their English proficiency is not efficient enough to successfully understand experiment explanations. Participants had the option to withdraw from the study at any given point, without any consequence.

4.2 Questionnaires

A TMS screening form was administered for the participant to fill out once consent was obtained. The researcher handing out the questionnaire outlined the importance of the form and clarified any questions the participant had regarding the form and how to fill it out. Answering “yes” to any of the questions within the form (except the last two questions) resulted in the participant being excluded from the study unless the potential issue were remedied (i.e.,

providing earplugs for any ear ringing). The last two questions pertain to previous exposure to TMS or MRI, which were used to gauge a participants comfort level with the machinery, and as such, a “yes” was not considered an exclusion criterion.

4.3 Experimental Paradigm

This experiment used EEG; a method that non-invasively reads brain activity with an elasticized cap equipped with 32 surface electrodes. Conductive gel was injected into each of the electrodes to allow for electrical signals from the brain to conduct from the scalp to the electrode. The experimental task required participants to use a pressure-sensitive bulb to approximate the amplitude of discrete visual and tactile stimuli using a graded motor response. The stimuli were presented as two unimodal tactile (TT), a bimodal visual-tactile with a 200-300 ms delay (vTd (200-300 ms)), or bimodal visual-tactile with a 300-400 ms delay (vTd (300-400 ms)). Participants were seated comfortably in front of a computer screen with the palmar surface of the second digit of their left hand resting on a custom-made device that will deliver vibrotactile stimuli (Figure 2). They were asked to judge the amplitude of each stimulus type and combine them for a response. Their response to these judgments was made by gently applying force to a pressure sensitive bulb was held in their right hand (Figure 3).

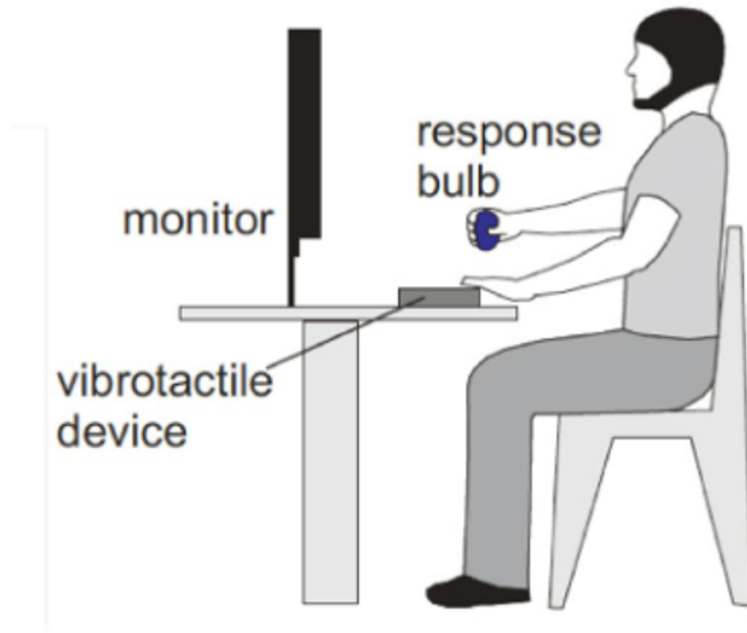


Figure 2: Depicted experimental setup for the positioning of the participant relative to placement of the monitor (visual input) and vibrotactile device (tactile input) (Popovich & Staines, 2014).

A custom LabVIEW (version 16.0; National Instruments) program was created to randomize the stimuli intensity, control stimuli presentation, and capture and measure force generated by the participant. The visual stimulus was presented as a yellow bar (6 cm wide) and shown in the center of a black computer screen in front of where the participants were seated. The bar was visible for 500 milliseconds and appeared at varying heights on the screen, representing different amplitudes that the participant judged and subsequently squeezed the pressure bulb. The vibrotactile stimuli were presented as 25 Hz vibrations of varying strengths to the index finger of the left hand for 500 milliseconds. White noise was delivered via headphones using STIM2 programming to cancel out any auditory stimuli resulting from the vibrating device.

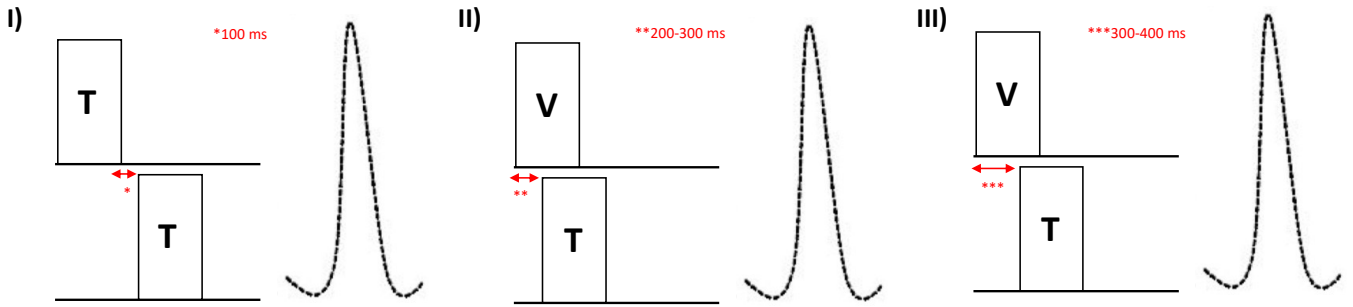


Figure 3: Illustration of sensory input and summation response. For each of the three stimulus presentations, a pair of stimuli will be presented. I) represents the coupled tactile-tactile stimuli presented about 100 ms apart. II) represents the coupled visual-tactile stimuli presented 200-300 ms apart. III) represents the coupled visual-tactile stimuli presented 300-400 ms apart. In each stimulus presentation participants will be required to produce an output response resembling the summated input amplitude using a pressure-sensitive bulb.

Ten blocks of 60 stimuli presented for 500 milliseconds with 3 seconds in between trials were performed following a training session. After 5 blocks, participants were set-up to undergo one of two modes of theta burst stimulation (TBS), either cTBS or intermittent TBS (iTBS) intervention on their R. DLPFC, found directly underneath F4 electrode using the 10-20 international system. CTBS intervention included thresholding to find 80% motor threshold (MT) for the participants abductor pollicis brevis (APB) using electromyography (EMG). Following the intervention, the last 5 blocks of trials were performed. Each block lasted for just under 3 minutes, making the task about 50-60 minutes long including intervention. The overall study duration was approximately 1.5-2 hours including set-up and breaks between blocks (Figure 4).

The experiment was preceded by a training session of approximately 3-5 minutes. The training session included a second, blue bar of varying heights in a proportional manner to the pressure created by the participant when they squeezed the bulb placed on their right hand. The blue bar was intended to provide visual feedback for the participant to understand the amplitude-pressure relationship between the visual stimuli and the bulb. At the same time, a vibrotactile stimulus of proportional amplitude to the pressure generated by squeezing the bulb will be presented on the second digit of the participants left hand; providing tactile feedback of the tactile-pressure relationship between tactile feedback and the bulb. It is important to note that no single stimulus required participants to exert maximal force output, making the physical nature of this task minimally taxing.

4.4 Stimulus

The stimulus used in the protocol were generated from a custom LabVIEW (version 16.0; National Instruments) program used to control for the amplitude and the timing, and randomized

stimuli order that made up the 60 trials per block. Each block consisted of 20 TT, 20 vTd (200-300 ms), and 20 vTd (300-400 ms) stimuli. There were five stimuli files to ensure randomization order of stimuli conditions being presented in each block. The files were used in their naming convention order (block one, file one, and so forth). The files were reused in block 6-10 after undergoing their groups TBS intervention following the same order used pre-TBS.

4.5 EEG

Electroencephalography data was recorded from 21 electrodes (32 channel Quik-Cap, Neuroscan, Compumedics, NC, USA) in accordance with the International 10-20 System for electrode placement and referenced to the linked mastoids. Impedance was maintained at or lower than 5 k Ω . EEG data was filtered (DC- 100 Hz) and digitized at 500 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC, USA). Data was saved, and epoched for subsequent analysis, followed by a baseline correction to the pre-stimulus interval. Epochs were created to be 600 ms in length, beginning 100 ms before stimulus onset (time-locked to tactile stimulus in vTd condition). Epochs were also be filtered to remove eye blinks and facial musculature contractions. The electrode of interest in this study is CP4, with additional electrodes used for analysis and comparisons where appropriate.

4.6 TMS

Either cTBS or iTBS was applied with a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure-8 coil. cTBS consists of a series of bursts of three pulses 20 ms apart, repeated every 200 ms for 40s while iTBS was applied for 190 s using a set of 3 stimuli at 50 Hz repeated at 5 Hz over 2 seconds with the pattern repeated every 10 seconds for a total of 600 pulses both at 80% of active motor threshold (AMT) for APB (Huang et al., 2005). AMT refers to the minimum single pulse intensity required to produce a motor-evoked potential

greater than 200 μ V in five out of ten consecutive trials while subjects hold approximately 10-20% of the maximum voluntary contraction of the APB. Electrode C4, placed according to the international 10-20 system, was used to guide the coil to the motor cortical area to establish AMT. 80% of AMT was used on electrode F4, overlaying the participants R. DLPFC. The center of the coil was placed over F4, and the current in the coil midline positioned with the coil positioned at 90 degrees angle from the mid-sagittal line (Grossheinrich et al., 2009; Brown et al., 2015; Adams et al., 2019).

These methods of stimulation are congruent with previous work done by Brown et al. (2015) and Adams et al. (2019) where cTBS was performed directly on R. DLPFC or PFC respectively. Both studies examined the effects of the aforementioned cortical regions on task-relevancy based modulation on gating systems. In both studies, task-relevancy modulation was abolished post-cTBS intervention. By using a similar process, it allows us to continue exploring the role of the PFC, especially the R. DLPFC on the attentional effects it may carry with information processing.

4.7 Data Analysis

For ERP analysis, amplitudes and latencies are reported as averages from peaks recorded by individual participants on each experimental trial. Potentials were calculated from peak-to-peak amplitudes between the peak of interest and the preceding potential of opposite polarity. For P50, amplitude was calculated by comparing the largest peak observed in a 40-70 ms time window and baseline.

Behavioural data was analysed by summing the amplitude of the two target stimuli per trial generated with the custom LabVIEW program and comparing the sum to the force applied by the participant for each trial. The percent different between the stimuli amplitude and the

force response was calculated and a two-way repeated measures ANOVA with stimulus condition (TT, vTd (200-300 ms), vTd (300-400 ms)), time (pre, post) was conducted for each intervention group to assess statistical differences across the experimental conditions.

To test the hypothesis of R. DLPFC contribution on attentional crossmodal upregulation, a three-way mixed model ANOVA was used with stimulus condition (TT, vTd (200-300 ms), vTd (300-400 ms)), cTBS intervention (pre, post) and intervention type (cTBS, iTBS) as the three factors. Likely underpowered, the three-way ANOVA was split into two-way models and each intervention group was analysed separately.

A two-way repeated ANOVA was used with stimulus condition (TT, vTd (200-300 ms), vTd (300-400 ms)) and cTBS intervention (pre, post) as the two factors. To compare the results of R. DLPFC contributions when upregulated, a two-way repeated ANOVA was used with stimulus condition (TT, vTd (200-300 ms), vTd (300-400 ms)) and iTBS intervention (pre, post) as the two factors. Lastly, a two-way mixed model ANOVA with stimulus (TT, vTd (200-300 ms), vTd (300-400 ms)) and condition type (cTBS, iTBS), with the dependent measure being a relative difference of post-pre amplitude was performed to compare if there were any significant differences between upregulating and downregulating R. DLPFC.

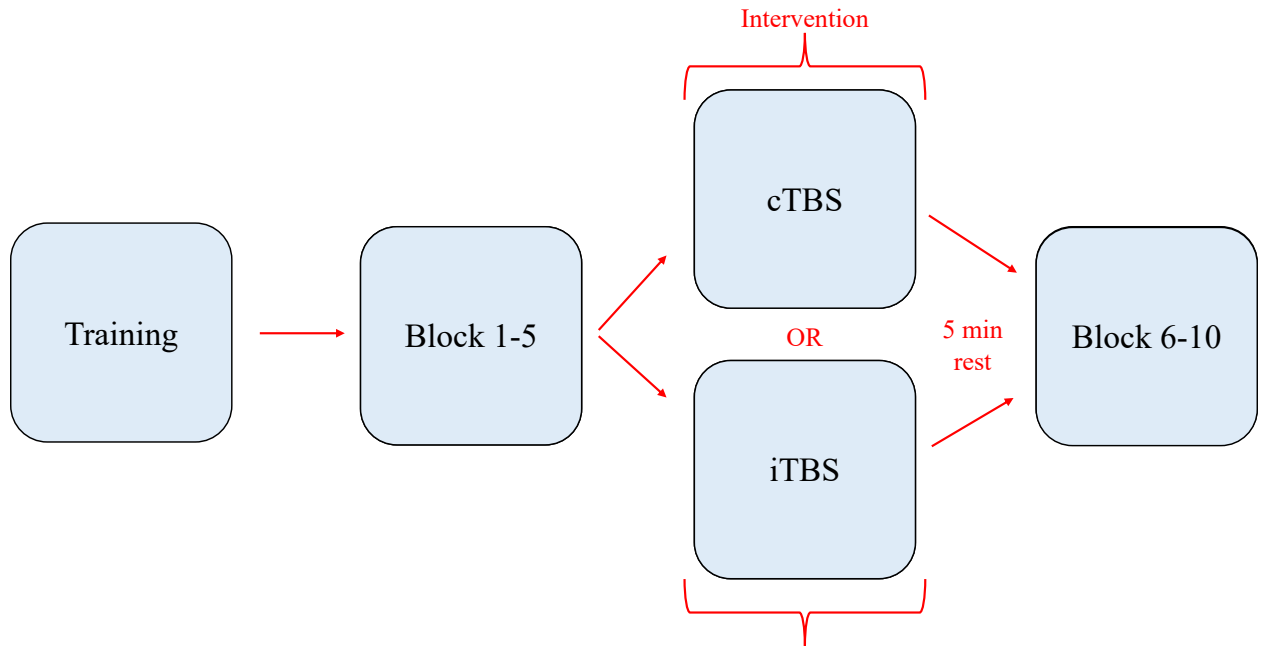


Figure 4: Schematic representation of experimental paradigm outlining the flow of time to get through the study session.

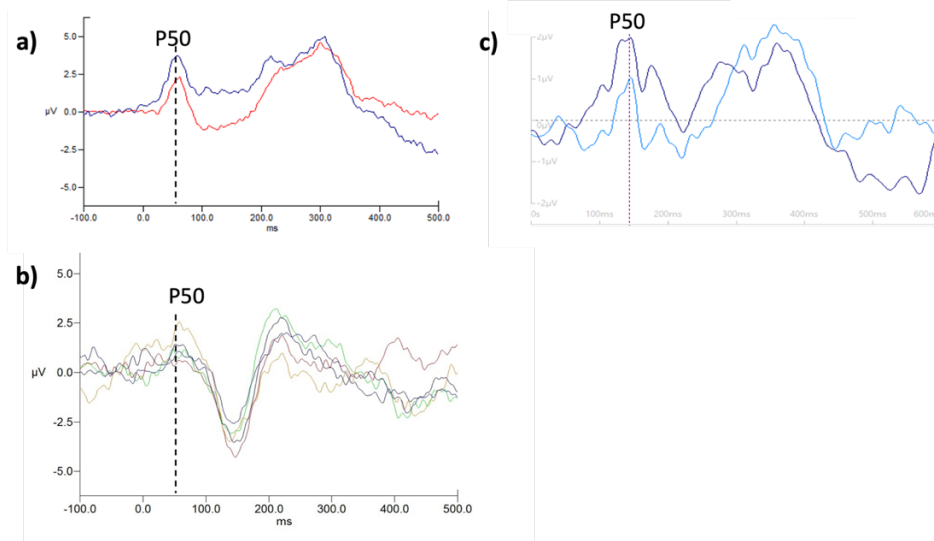


Figure 5: Somatosensory P50 ERPs extracted from Salazar et al. (2023) comparing TT vs vTd processing. A) CP3 traces compiled from an average of 9 participants (red line – TT, blue line – vTd (0-100 ms). B) CP4 traces compiled from an average of 10 participants (navy line – TT, yellow line – vTd (200-300 ms, other coloured lines represent different visual-tactile conditions in different temporal windows and order configuration). C) CP4 traces compiled from an average of 14 participants (light blue line – TT, dark blue line – vTd (200-300 ms).

5.0 Results

5.1 Behavioural

To understand any potential implications on behaviour relating to changes in R. DLPFC activity; a 2-way repeated measures ANOVA was conducted in the cTBS and iTBS group to assess for changes in accuracy while performing a motor graded response for a unimodal and bimodal response following intervention. For the iTBS group, one participant's data was removed due to it being an outlier. Both groups passed normality testing, following visual inspection of Q-Q plots, and Shapiro-Wilk normality testing. For the cTBS group, A significant main effect for condition and time were found ($F_{2,30} = 9.391$, $P = 0.001$, $\epsilon = 0.867$, $\eta_p^2 = 0.385$; $F_{1,15} = 4.642$, $P = 0.048000$, $\eta_p^2 = 0.236$, respectively). Post-hoc analysis revealed that accuracy in generating an accurate graded motor response was significantly lower in a unimodal response relative to both bimodal responses, vTd(200-300 ms) and vTd (300-400 ms) (44.0 ± 2.70 vs 40.0 ± 2.60 , 38.0 ± 2.33 ; $P = 0.01$, $P = 0.0000456$). Further, post-hoc analysis revealed that accuracy in generating an accurate graded motor response was significantly higher post-cTBS relative to pre-cTBS (37.7 ± 1.67 vs 43.6 ± 2.38 ; $P = 0.000804$).

5.2 Event-Related Potentials

P50

A 2-way repeated measures ANOVA was used to assess the changes in P50 amplitude following cTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A significant main effect for condition was found ($F_{2,30} = 5.899$, $P = 0.011$, $\epsilon = 0.844$, $\eta_p^2 = 0.282$)(Table 2). A significant condition x time interaction was found ($F_{2,30} = 5.078$,

$P=0.013$, $\varepsilon=0.973$, $\eta_p^2=0.253$)(Table 2). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that P50 amplitude generated by condition vTd (200-300 ms) following cTBS was significantly lower compared to P50 amplitude prior to cTBS (3.49 ± 0.378 vs 4.34 ± 0.32 ; $P=0.003$).

A 2-way repeated measures ANOVA was used to assess the changes in P50 amplitude following iTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,30}= 13.380$, $P= 8.87\times10^{-05}$, $\varepsilon=0.996$, $\eta_p^2=0.471$)(Table 3). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that P50 amplitude generated by condition vTd (200-300ms) was significantly larger than P50 amplitudes generated by vTd (300-400 ms) and TT (4.72 ± 0.339 vs 3.54 ± 0.314 , 2.35 ± 0.219 ; $P=0.013$, $P= 5.52\times10^{-7}$) and P50 amplitude generated by condition vTd (300-400 ms) was significantly larger than TT (3.54 ± 0.314 vs 2.35 ± 0.219 ; $P= 0.009$)

A 2-way mixed modal ANOVA was used to assess the relative change in P50 amplitude following cTBS/iTBS intervention in three stimuli delivery conditions. No significant effects were found.

N70

A 2-way repeated measures ANOVA was used to assess the changes in N70 amplitude following cTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,30}= 8.080$, $P= 0.003$, $\varepsilon= 0.872$, $\eta_p^2= 0.350$)(Table 2). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that N70 amplitude generated by condition vTd (200-300ms) was significantly larger

than N70 amplitudes generated by vTd (300-400 ms) and TT (0.743 ± 0.315 vs -0.788 ± 0.396 , -0.904 ± 0.295 ; $P = 0.001$, $P = 4.56 \times 10^{-4}$).

A 2-way repeated measures ANOVA was used to assess the changes in N70 amplitude following iTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition and time were found ($F_{2,28} = 16.736$, $P = 2.82 \times 10^{-5}$, $\epsilon = 0.936$, $\eta_p^2 = 0.545$; $F_{1,14} = 6.819$, $P = 0.021$, $\eta_p^2 = 0.328$)(Table 3). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that N70 amplitude generated by condition vTd (200-300ms) was significantly larger than N70 amplitudes generated by vTd (300-400 ms) and TT (1.96 ± 0.316 vs 0.421 ± 0.359 , -0.736 ± 0.291 ; $P = 0.003$, $P = 3.09 \times 10^{-8}$) and N70 amplitude generated by condition vTd (300-400 ms) was significantly larger than TT (0.421 ± 0.359 vs -0.736 ± 0.291 ; $P = 0.007$). It was also revealed that N70 amplitude was significantly larger following iTBS compared to baseline (0.904 ± 0.303 vs 0.192 ± 0.308 ; $P = 0.003$).

A 2-way mixed modal ANOVA was used to assess the relative change in N70 amplitude following cTBS/iTBS intervention in three stimuli delivery conditions. No significant effects were found.

P100

A 2-way repeated measures ANOVA was used to assess the changes in P100 amplitude following cTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,30} = 4.515$, $P = 0.030$, $\epsilon = 0.776$, $\eta_p^2 = 0.231$)(Table 2). Post-hoc analysis with Bonferroni adjusted P values, where applicable,

revealed that P100 amplitude generated by condition vTd (200-300ms) was significantly larger than P100 amplitudes generated by vTd (300-400 ms) and TT (3.17 ± 0.437 vs 1.74 ± 0.491 , 1.83 ± 0.398 ; $P = 0.008$, $P = 0.024$).

A 2-way repeated measures ANOVA was used to assess the changes in P100 amplitude following iTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,28} = 16.106$, $P = 4.15 \times 10^{-5}$, $\epsilon = 0.922$, $\eta_p^2 = 0.535$)(Table 3). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that P100 amplitude generated by condition vTd (200-300ms) was significantly larger than P100 amplitudes generated by vTd (300-400 ms) and TT (5.04 ± 0.488 vs 3.10 ± 0.39 , 2.42 ± 0.295 ; $P = 0.000432$, $P = 6.63 \times 10^{-7}$).

A 2-way mixed modal ANOVA was used to assess the relative change in P100 amplitude following cTBS/iTBS intervention in three stimuli delivery conditions. No significant effects were found.

N140

A 2-way repeated measures ANOVA was used to assess the changes in N140 amplitude following cTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,28} = 6.498$, $P = 0.005$, $\epsilon = 0.987$, $\eta_p^2 = 0.317$)(Table 2). A significant condition x time interaction was found ($F_{2,28} = 4.841$, $P = 0.027$, $\epsilon = 0.750$, $\eta_p^2 = 0.257$)(Table 2). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that N140 amplitude generated by condition vTd (300-400 ms)

following cTBS was significantly smaller compared to N140 amplitude prior to cTBS (-0.772 ± 0.765 vs -1.72 ± 0.8 ; $P = 0.003$).

A 2-way repeated measures ANOVA was used to assess the changes in N140 amplitude following iTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,28} = 20.029$, $P = 5.3 \times 10^{-6}$, $\epsilon = 0.970$, $\eta_p^2 = 0.589$)(Table 3). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that N140 amplitude generated by condition vTd (200-300ms) was significantly larger than N140 amplitudes generated by vTd (300-400 ms) and TT (2.45 ± 0.423 vs -0.157 ± 0.375 , -0.616 ± 0.268 ; $P = 1.45 \times 10^{-6}$, $P = 6.15 \times 10^{-8}$)

A 2-way mixed modal ANOVA was used to assess the relative change in N140 amplitude following cTBS/iTBS intervention in three stimuli delivery conditions. Data normality was assessed with a visual inspection of Q-Q plots and Shapiro-Wilk normality testing; normality conditions were met. A Significant main effect for condition was found ($F_{2,56} = 3.445$, $P = 0.046$, $\epsilon = 0.869$, $\eta_p^2 = 0.110$)(Table 4). Post-hoc analysis with Bonferroni adjusted P values, where applicable, revealed that N140 amplitude generated by condition vTd (200-300 ms) was significantly lower than N140 amplitude generated by condition vTd (300-400 ms) (-0.051 ± 0.301 vs 0.862 ± 0.236 ; $P = 3.62 \times 10^{-2}$).

Table 1: General Participant characteristics

	cTBS	iTBS
n	16	16
Age	24± 3	23± 2
Sex	7M, 9F	8M, 8F

Table 2: Results of two-way repeated measures ANOVA on cTBS group ERP amplitudes

Factors		P50	N70	P100	N140
Interaction effects	Condition x Time	$F_{2,30}=5.078, p=0.013, \eta_p^2=0.253$	$F_{2,30}=1.531, p=0.235, \eta_p^2=0.093$	$F_{2,30}=3.202, p=0.073, \eta_p^2=0.176$	$F_{2,28}=4.841, p=0.027, \eta_p^2=0.257$
Main effects	Condition	$F_{2,30}=5.899, p=0.011, \eta_p^2=0.282$	$F_{2,30}=8.080, p=0.003, \eta_p^2=0.350$	$F_{2,30}=4.515, p=0.030, \eta_p^2=0.231$	$F_{2,28}=6.498, p=0.005, \eta_p^2=0.317$
	Time	$F_{1,15}=4.285, p=0.056, \eta_p^2=0.222$	$F_{1,15}=1.209, p=0.289, \eta_p^2=0.075$	$F_{1,15}=0.789, p=0.388, \eta_p^2=0.050$	$F_{1,14}=3.696, p=0.075, \eta_p^2=0.209$

Table 3: Results of two-way repeated measures ANOVA on iTBS group ERP amplitudes

Factors		P50	N70	P100	N140
Interaction effects	Condition x Time	$F_{2,30}=0.440, p=0.635, \eta_p^2=0.028$	$F_{2,28}=0.114, p=0.865, \eta_p^2=0.008$	$F_{2,28}=0.630, p=0.513, \eta_p^2=0.043$	$F_{2,28}=0.752, p=0.463, \eta_p^2=0.051$
main effects	Condition	$F_{2,30}=13.380, p=8.87 \times 10^{-05}, \eta_p^2=0.471$	$F_{2,28}=16.736, p=2.82 \times 10^{-05}, \eta_p^2=0.545$	$F_{2,28}=16.106, p=4.15 \times 10^{-05}, \eta_p^2=0.535$	$F_{2,28}=20.029, p=5.30 \times 10^{-06}, \eta_p^2=0.589$
	Time	$F_{1,15}=0.156, p=0.698, \eta_p^2=0.010$	$F_{1,14}=6.819, p=2.10 \times 10^{-02}, \eta_p^2=0.328$	$F_{1,14}=3.915, p=6.80 \times 10^{-02}, \eta_p^2=0.219$	$F_{1,14}=2.117, p=0.168, \eta_p^2=0.131$

Table 4: Results of two-way mixed measures ANOVA on overall study ERP amplitudes

Factors		P50	N70	P100	N140
Interaction effects	Intervention x Condition	$F_{2,60}=2.046, p=0.140, \eta_p^2=0.058$	$F_{2,58}=0.350, p=0.683, \eta_p^2=0.012$	$F_{2,58}=0.142, p=0.846, \eta_p^2=0.005$	$F_{2,56}=1.216, p=0.301, \eta_p^2=0.042$
main effects	Intervention	$F_{1,30}=1.853, p=0.184, \eta_p^2=0.058$	$F_{1,29}=2.854, p=0.102, \eta_p^2=0.090$	$F_{1,29}=1.931, p=0.175, \eta_p^2=0.062$	$F_{1,28}=0.051, p=0.823, \eta_p^2=0.002$
	Condition	$F_{2,60}=1.721, p=0.189, \eta_p^2=0.054$	$F_{2,58}=1.037, p=0.355, \eta_p^2=0.035$	$F_{2,58}=2.796, p=0.076, \eta_p^2=0.088$	$F_{2,56}=3.445, p=0.046, \eta_p^2=0.110$

Table 5: Results of two-way mixed measures ANOVA for behavioural accuracy data

Factors		cTBS	iTBS
Interaction effects	Condition x Time	$F_{2,30}=0.548$, $p=0.561$, $\eta_p^2=0.035$	$F_{2,28}=0.044$, $p=0.937$, $\eta_p^2=0.003$
main effects	Condition	$F_{2,30}=9.391$, $p=0.001$, $\eta_p^2=0.385$	$F_{2,28}=1.584$, $p=0.139$, $\eta_p^2=0.102$
	Time	$F_{1,15}=4.642$, $p=0.048$, $\eta_p^2=0.236$	$F_{1,14}=1.362$, $p=0.263$, $\eta_p^2=0.089$

6.0 Discussions

This study sought to understand the relative contributions the right R. DLPFC has in the observed upregulation of P50 amplitude generated by a vibrotactile stimuli to the index finger when preceded by a task relevant visual cue. Average EEG traces can be seen in Figure 6. From our current understanding, R. DLPFC plays a role in upregulating the processing signal strength for task relevant stimuli, while depressing task irrelevant stimuli (Knight et al., 1999; Bolton et al., 2011; Bolton et al., 2014). If R. DLPFC is the crucial regulator in this crossmodal facilitation, downregulating its activity should abolish this visual-tactile bimodal phenomenon. Following cTBS on R. DLPFC, main findings suggest that diminished contributions from R. DLPFC result in a significant P50 amplitude decrease generated by the vTd (200-300 ms) condition (figure 7). This is suggestive that R. DLPFC is a main regulator in visual-tactile crossmodal facilitations, but not the only modulator, as facilitation is still present when comparing vTd (200-300 ms) post-cTBS relative to TT pre-cTBS.

6.1 Behavioural

The purpose of the behavioural analysis was to understand if there were any differences in accuracy controlled by changes in R. DLPFC activity. In the cTBS group, it was observed that there were significantly better accuracy scores when a graded motor response was generated following a bimodal paired stimulus, regardless of the time delay between the two stimuli in comparison to a unimodal tactile paired stimulus (Figure 8a, Table 5). Congruent with the observed physiological changes, seen with an increased P50 amplitude for bimodal stimuli presentation, a stronger processing signal will likely result in better accuracy performance. The implication of this relationship is not fully understood, but likely, the interactions from the visual and somatosensory cortex, as well as relevant association like the left posterior parietal lobule

(Gentile et al., 2008) may play a role. It was also observed that the through time, accuracy scores were better following cTBS, relative to pre-cTBS (Figure 8a, Table 5). With R.DLPFC being responsible for attentional mechanisms, it stands to reason that a decrease in R.DLPFC activity would result in a decrease accuracy performance. The opposite is observed in this case. With the experimental design being a repetition of the same task pre and post cTBS, likely participants were able to familiarize themselves with the intricacies of the task. Following the ending of each block, a percent accuracy score was provided for participants which determined how accurate they were. While the intended purpose for this feedback was to keep participants engaged and focused, it may have instead allowed participants to fine-tune the amount of pressure applied to the bulb, based on their own perception of over squeezing or under squeezing.

In the iTBS group, there were no significant changes observed in accuracy performance between condition, or through time (Table 5). No significant change through time is congruent with physiological changes in P50 amplitude following iTBS, where no significant increase in P50 amplitude was observed. Regarding the change in accuracy between conditions, it would make sense for there to be significant differences in accuracy comparing unimodal versus bimodal stimuli pairs, similar to that observed in the cTBS group. Future study designs should aim to address the inconsistency in accuracy changes, and further explore the role R. DLPFC plays.

6.2 Peaks

P50

The first objective in this experiment was to determine the modulatory effects in P50 amplitude when top-down processing from R. DLPFC were diminished. In the task used, attention is needed to integrate the intensity assigned to each stimulus modality and produce a

graded motor response. Previous work demonstrated the capacity for relevant bimodal stimuli to modulate P50 amplitude (Dione 2010, Dione 2013, Popovich & Staines, 2014). With the nature of both afferent modalities being task relevant, R. DLPFC will upregulate the processing capacities for both modalities. Based on previous work done in the lab, we know condition vTd (200-300 ms) is required for this P50 upregulation to be observed maximally (Salazar et al., 2023). To compare the differences of a bimodal response, a coupled tactile-tactile stimuli condition was also present, with only the first tactile P50 generated being used as the unimodal comparator. Previous research has explored this relationship with time delays ranging from 0-200 ms, with no consistent significant findings reported (Salazar et al., 2023). Beyond that, little exploration has been done with a longer time delay, which is why a vTd (300-400 ms) condition was also included to explore the potential effects of a longer time delay. Our primary hypothesis is that following cTBS on R. DLPFC, vTd (200-300 ms) P50 amplitude would be completely downregulated, mimicking P50 amplitude of unimodal tactile generation.

Not fully consistent but following a similar trend to our original hypothesis, following cTBS intervention on the R. DLPFC, there was a significant decrease in P50 amplitude to vTd (200-300 ms) (Figure 7, Figure 9a). This differs from our hypothesis where we believed the R. DLPFC downregulation would result in P50 peaks similar to one generated by a unimodal tactile stimulus. While a complete elimination of the crossmodal facilitation did not occur, a significant decrease in P50 amplitude is suggestive that R. DLPFC plays a crucial role in visual-tactile crossmodal facilitation, though it is not the only contributor.

The continued presence of this bimodal facilitation following R. DLPFC inhibition is suggestive that other, lesser-known mechanisms are significant contributors in this crossmodal phenomenon. These results align with our secondary hypothesis, which suggests direct or

indirect somatosensory-visual inter-cortical connections. Since the visual stimulus needs to precede the tactile stimulus for this facilitation to occur, an encoding period in the visual cortex is likely necessary, a sort of primer for S1 to receive the vibrotactile stimulus and generate a larger processing signal. Whether this priming occurs through direct cortico-cortico interactions between V1 and S1 or through indirect inter-cortico mechanisms is not yet clear.

With our current understanding of the R. DLPFC, we know it is involved in relevant mechanisms like motor control and attention (Knight et al., 1999). In this case, the downregulation of R. DLPFC resulting in any motor control deficiency would not be cause for concern due to the low physical difficulty and skill demand of the task. More likely, the influence of cTBS on neuron populations within R. DLPFC, resulted in a short-term depression, leading to a decrease of synapses of R. DLPFC interaction to S1. CTBS intervention would affect the influence R.DLPFC as a top-down processor with its projections to S1 being downregulated, preventing any state of facilitation generated by the preceding visual stimulus. By reducing the influence of said visual primer, it could explain why we are seeing a decrease in P50 upregulation following vTd (200-300 ms).

A potential contributor to the facilitation of tactile processing via the processing of a visual cue behaving like a primer could be the posterior parietal lobule. In a motion direction discrimination task, Nakashita et al. (2008) performed a T2 weighted fMRI neuroimaging to record brain activity in congruent and incongruent visual-tactile activity. It was found that when the congruent visual-tactile trials were performed, there was bimodal activation in the left posterior parietal lobule (LP). It was also observed that the left posterior LP was also activated in the visual-visual and tactile-tactile conditions for this study (Nakashita et al., 2008). With the left LP being a shared association area for both tactile and visual realms, it falls within reason that

this could be an integration region to allow for crossmodal interactions and upregulate tactile processing. Further, the receptor distribution of the left posterior PL is similar to that of the visual cortex (Scheperians et al., 2005) it would stand to reason that in a vTd (200-300 ms), when the visual stimulus is received at V1 for processing, the signal could then be shared to the left posterior PL, and then received by S1, as a primer for receiving the tactile input.

A 3T weighted fMRI study by Gentile et al. (2011) also linked the anterior intraparietal sulcus and inferior posterior parietal cortex as sites for visual-tactile convergence and integration for hand representation in space. While in our case it is less about the hand representation in space and more about the ability to integrate visual-tactile stimuli to generate a graded-motor response, understanding the placement of the hand relative to space is important to generate the squeezing. With the inferior parietal cortex being part of the circuit for sensory-guided hand postures (Lupino & Rizzolatti, 2000), it stands to reason that its role could be expansive and include aiding in perceiving tactile stimulus. The likelihood of one specific node being the sole contributor to this relationship is unlikely, it is most likely a contribution of multiple regions in this association area that help to with the upregulation in S1.

To control for the changes observed in the bimodal facilitation following R. DLPFC downregulation, 16 age-matched participants were recruited for a control group. The same experimental design was repeated with iTBS administered as the intervention instead of cTBS. In this case, no significant differences in P50 amplitude for condition vTd (200-300 ms) following R. DLPFC upregulation relative to pre-iTBS vTd (200-300 ms) was observed (Figure 10). This is likely indicative that the contributions R. DLPFC has in enhancing task relevant stimuli is already maximal, and a ceiling effect has already been achieved. The fact that R. DLPFC downregulation modulates the strength of the crossmodal facilitation for vTd (200-300

ms), but R. DLPFC upregulation incurs no change further supports the idea that the contributions from R. DLPFC to this bimodal facilitation phenomenon is already maximally efficient for the vTd (200-300 ms) condition.

Though iTBS has no notable effects on vTd (200-300 ms), increasing R. DLPFC activity did impact the pattern of activity in this bimodal facilitation for vTd (300-400 ms). While in the cTBS group, vTd (200-300 ms) significantly increased post-cTBS, P50 amplitudes generated by vTd (300-400 ms), and TT did not. P50 amplitudes by the two later conditions showed similar processing strengths. However, in the iTBS group, a separation between vTd (300-400 ms) and TT was found (Figure 11a). Condition vTd (200-300 ms) is presumably already optimal, where increased R. DLPFC activity would have no effect on the crossmodal upregulation. vTd (300-400 ms) on the other hand is not, as the additional 100 ms delay likely allows for the neuron populations in S1 to return to a baseline potential, no longer affected by the priming from V1. With increase R. DLPFC activity, it appears this priming period is sustained for a longer period of time, so in vTd (300-400 ms) there is still some upregulation to P50 amplitude, differentiating it from a standalone tactile stimulus.

N70

Current literature links N70 to be a peak more sensitive to selective attentional mechanisms (Adams et al., 2017; Adams et al., 2019). Based on this understanding, with all stimuli being task relevant, any modulation to N70 peaks would result from R. DLPFC downregulation since integrative attention is used continuously throughout the task. In the cTBS group, in the N70 peaks, there is a significant difference in P50 amplitude generated by vTd (200-300 ms) relative to both vTd (300-400 ms) and TT, where vTd (200-300 ms) generates the most positive amplitude, most downregulated signal (Figure 9b). Considering that this pattern is

generated regardless of intervention, it indicates that the strength pattern in N70 is occurring as a result of crossmodal interactions. Interestingly, following iTBS on R. DLPFC, the pattern of this relationship is altered. vTd (200-300 ms) remains significantly the most downregulated compared to vTd (300-400 ms) and TT, however, vTd (300-400 ms) is now also significantly downregulated compared to TT (Figure 11a).

For both the cTBS and iTBS group, this pattern of condition variation is likely carry-over effect from P50 peaks, where amplitude is largest to smallest in vTd (200-300 ms), vTd (300-400 ms) and TT, respectively. As the neuronal activity changes to generate N70, neuronal potential will change roughly the same amount, in this case an average drop of about 2.8-3.0 mV per peak, resulting in similar positive to negative amplitude trends, where the most positive signal is now the weakest, appearing to be an attenuated N70 peak. To confirm this is the case, peak-to-peak analysis was done looking at the relative amplitude difference between N70-P50 (Δ N70-P50) for both groups. A repeated-measures ANOVA was run, using Δ N70-P50 amplitude and the condition main effect was abolished, confirming that the enhanced positivity from P50 is responsible for this relationship.

The Δ N70-P50 ANOVA revealed a main effect in amplitude change pre-intervention compared to post-intervention. For both groups, following intervention, Δ N70-P50 amplitude is stronger in the pre-intervention group relative to post-intervention. Considering that analysis to N70 showed no significant main effect to time, this new time interaction must be influenced by P50 modulation through condition or intervention, influencing Δ N70-P50. Further research needs to be done to reveal whether this main effect observed is physiologically driven or relevant. Interestingly, there was a significant main effect on time in the iTBS group when the original repeated-measures ANOVA was run with the isolated N70 peaks (Figure 11b). The N70

amplitude generated post-iTBS were significantly larger than pre-iTBS, resulting in a downregulated signal. Again, increased R. DLPFC activity may be increasing the duration of a priming effect leading to the increased N70 amplitudes. Seeing an overall increased N70 post-iTBS, and a significant difference between bimodal generation compared to unimodal, it alludes to the fact that R. DLPFC is playing a critical role at priming S1 to receive tactile stimuli, but factors influenced by the visual cortex are also critical to this phenomenon.

P100

Similar to P50, this peak is modulated by crossmodal interactions whenever both stimuli are relevant for goal-oriented tasks (Popovich & Staines, 2014). In this case, the cTBS group only showed significant findings with condition as the main effect with P50 amplitude generated from vTd (200-300 ms) being significantly larger than vTd (300-400 ms) and TT (Figure 9b). This relationship being independent of cTBS intervention further suggests that inter-cortical interactions between tactile and visual realms are a significant contributor to crossmodal upregulation. With no significance found following cTBS, it can be inferred that integrative attentional mechanisms are not required to encode the signals in this later stage. With P100 being the first early cortical potential generated at the secondary somatosensory cortex (S2), inter-cortical connections from the visual cortex likely hold more weight in bimodal facilitation. This likely means that however the visual realm is creating this priming effect, it likely has direct input to both S1 and S2. Similarly, the iTBS group showed the same pattern as the cTBS group (Figure 11a). Different from P50 and N70, the significant amplitude changes are only observed in vTd (200-300 ms), meaning that the extended priming generated by an upregulated R. DLPFC only occur at the level of S1.

N140

N140 peak has been linked to attentional resources, and the quick shift of attention for relevant stimulus (Adler et al., 2009). In the cTBS group, there was a condition through time interaction for vTd (300-400 ms)(Figure 9c. Following cTBS, N140 amplitude is significantly smaller relative to pre-cTBS. This likely indicates that R. DLPFC influences the neuronal populations in S2 responsible for generating N140 peaks. Considering that N140 is linked to attentional mechanisms, downregulating R. DLPFC would influence this relationship. What is not yet clear is why the vTd (300-400 ms) condition is being affected rather than the vTd (200-300 ms). The differences between the bimodal conditions are their assigned time delay, where vTd (200-300 ms) has shown to have upregulatory effects, while vTd (300-400 ms) mimics a pattern similar to a unimodal tactile stimulus. There is a potential that following a visual primer, there is a short refractory period that leaves S1 more susceptible to downregulation, but R. DLPFC prevents that from happening. In a post-cTBS environment, the diminished neuronal activity in R. DLPFC would not prevent this, and vTd (300-400 ms) would elicit a weaker response.

Looking at the iTBS group, N140 amplitude for vTd (200-300 ms) is significantly smaller than N140 amplitudes generated by vTd (300-400 ms) and TT (Figure 11a). Similar to N70, this is likely carry-over effect from P100, where the maximal P100 amplitude is generated by vTd (200-300 ms) and the smallest by TT, resulting in what would appear to be an attenuated N140. Similar to P100, there is no significant difference in amplitudes generated by conditions vTd (300-400 ms) and TT, further supporting that the extended priming period observed in this group is exclusive to peaks generated at S1.

When the relative difference between pre and post in each group was subtracted (post-minus) and a comparison between the cTBS and iTBS groups were examined, a significant difference between vTd 200-300 ms and vTd 300-400 ms was observed. In this instance, vTd 300-400 ms amplitude was smaller than 200-300 ms, which is congruent with the upregulation of vTd (200-300 ms).

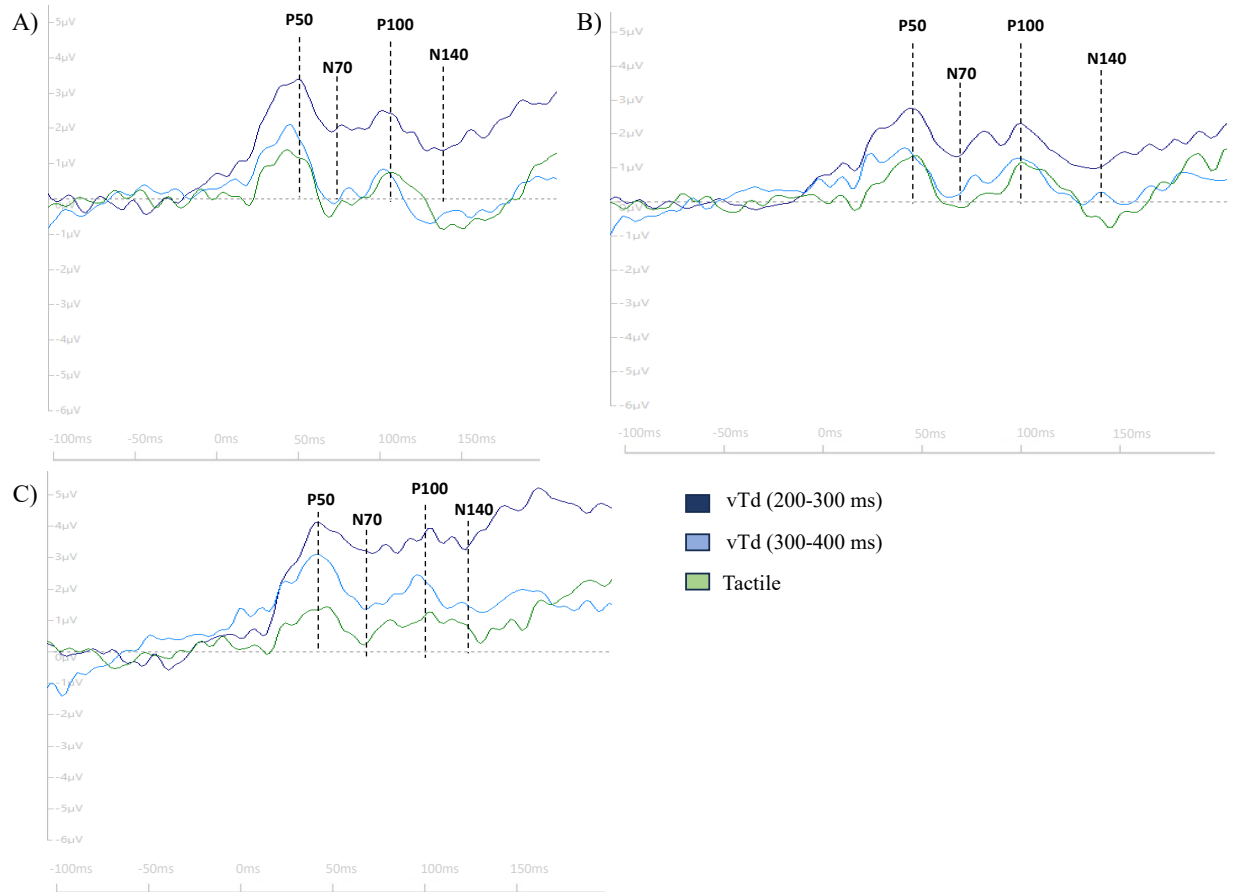


Figure 6: Grand Average EEG traces representing tactile P50, N70, P100 and N140 ERPS. A) Baseline ERP results generated by cTBS group (n=16), similar amplitude pattern generated by iTBS group, not shown. B) Post-cTBS ERP results generated by cTBS group (n=16). C) Post-iTBS ERP results generated by iTBS group (n=16).

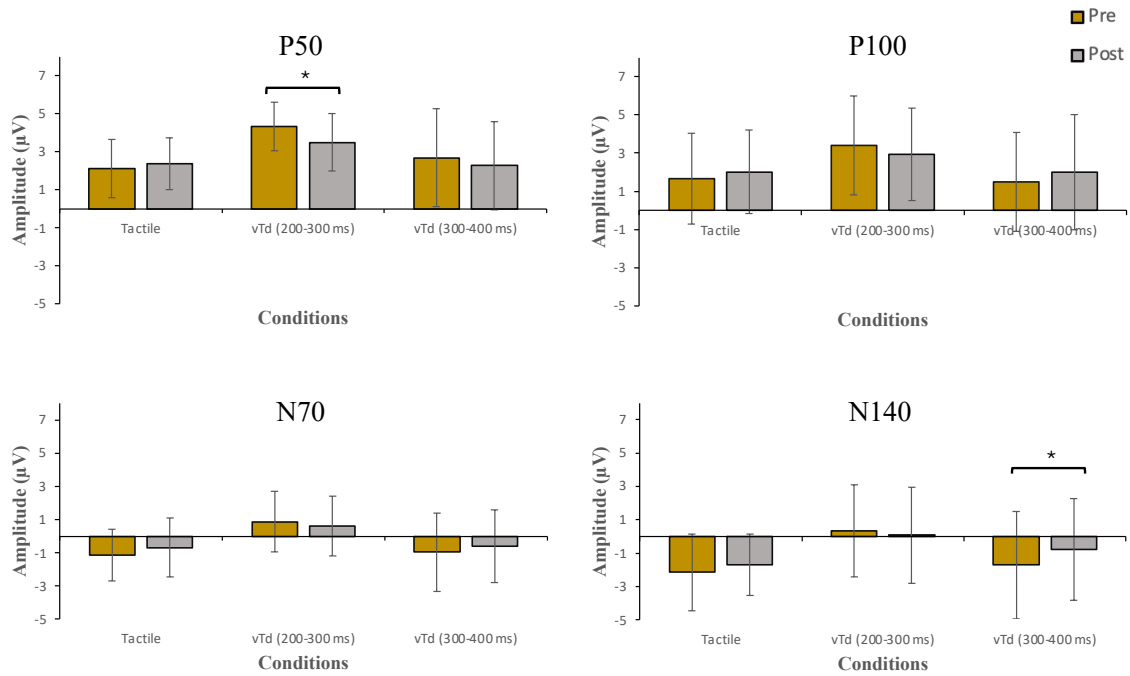


Figure 7: Participant ERPs mean average amplitude (extracted from electrode CP4) in cTBS group pre and post cTBS intervention depicting amplitude change within condition.

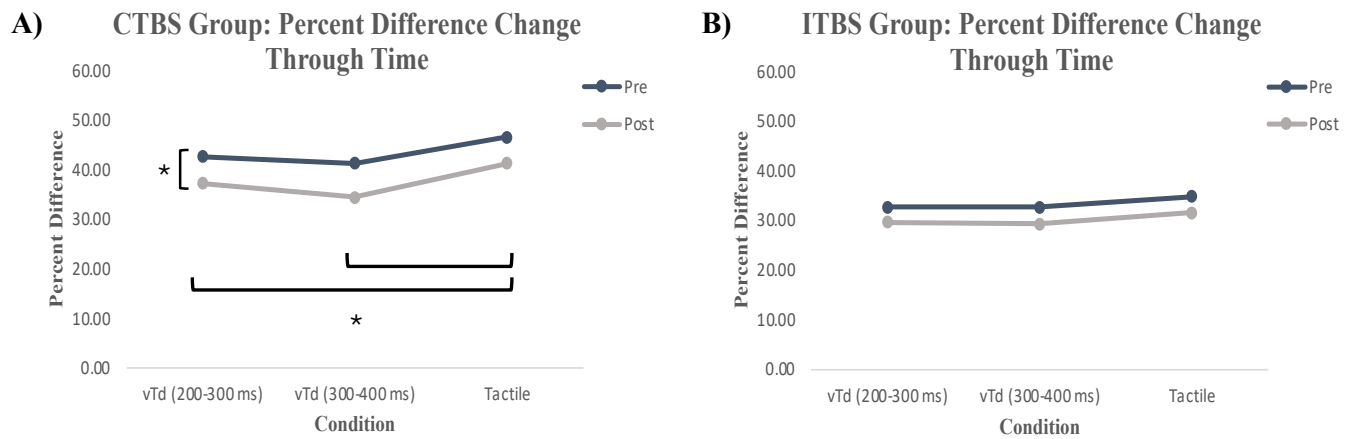


Figure 8: Line graphs depicting differences in percent difference (accuracy) between conditions, separated by time. A) Depicts differences in accuracy between conditions pre-cTBS and post-cTBS. Analysis revealed accuracy to be improved for bimodal conditions relative to unimodal ($p < 0.05$), and post-cTBS relative to pre-cTBS ($p < 0.05$). B) Depicts difference in accuracy between conditions pre-iTBS and post-iTBS.

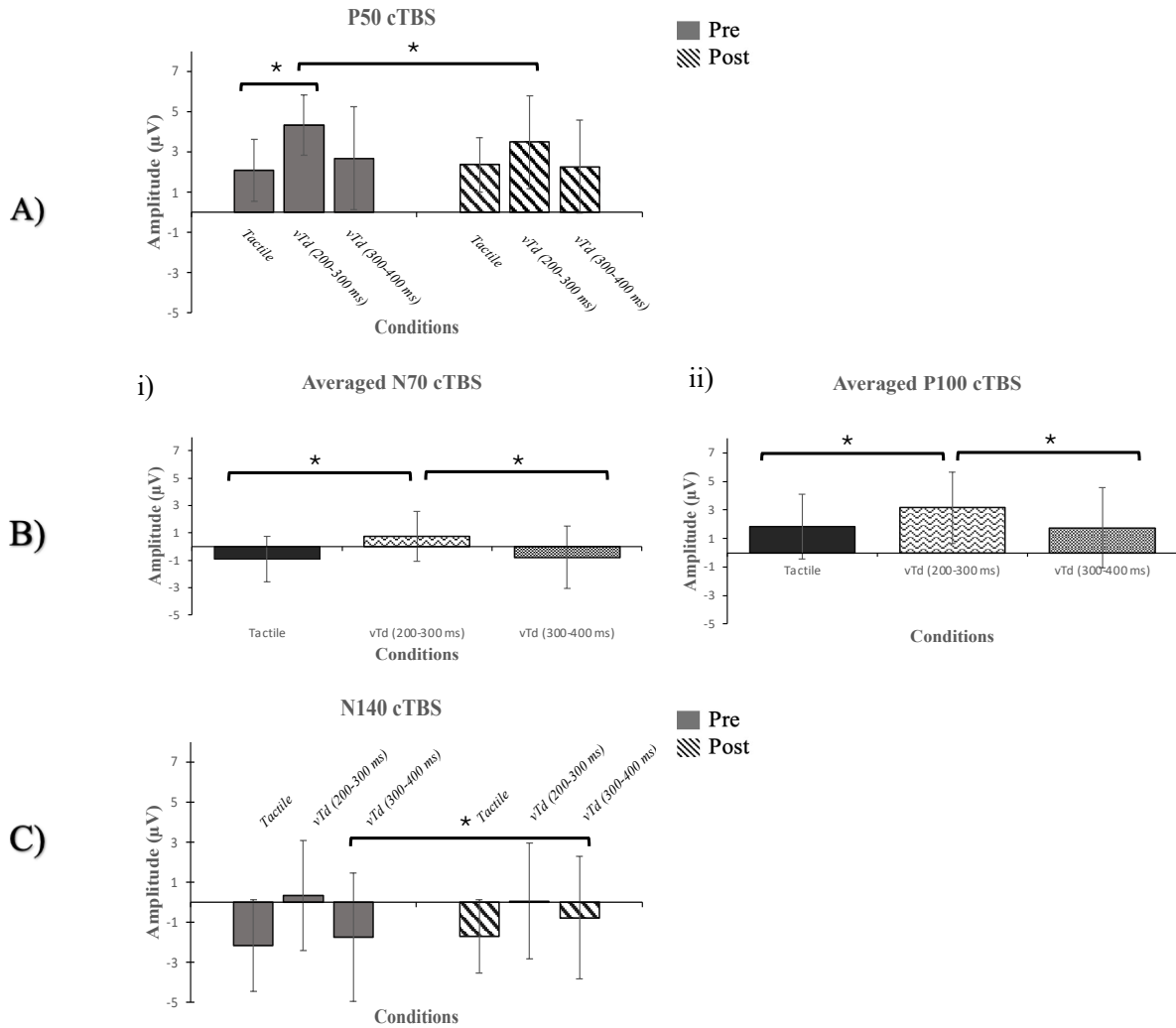


Figure 9: Participant ERPs mean average amplitude (extracted from electrode CP4) in CTBS group. A) Bar graph depicting P50 amplitude changes within conditions and following cTBS intervention. B) Bar graphs comparing (i) N70 and (ii)P100 amplitude differences within condition. C) Bar graph depicting N140 amplitude changes within conditions and following cTBS intervention.

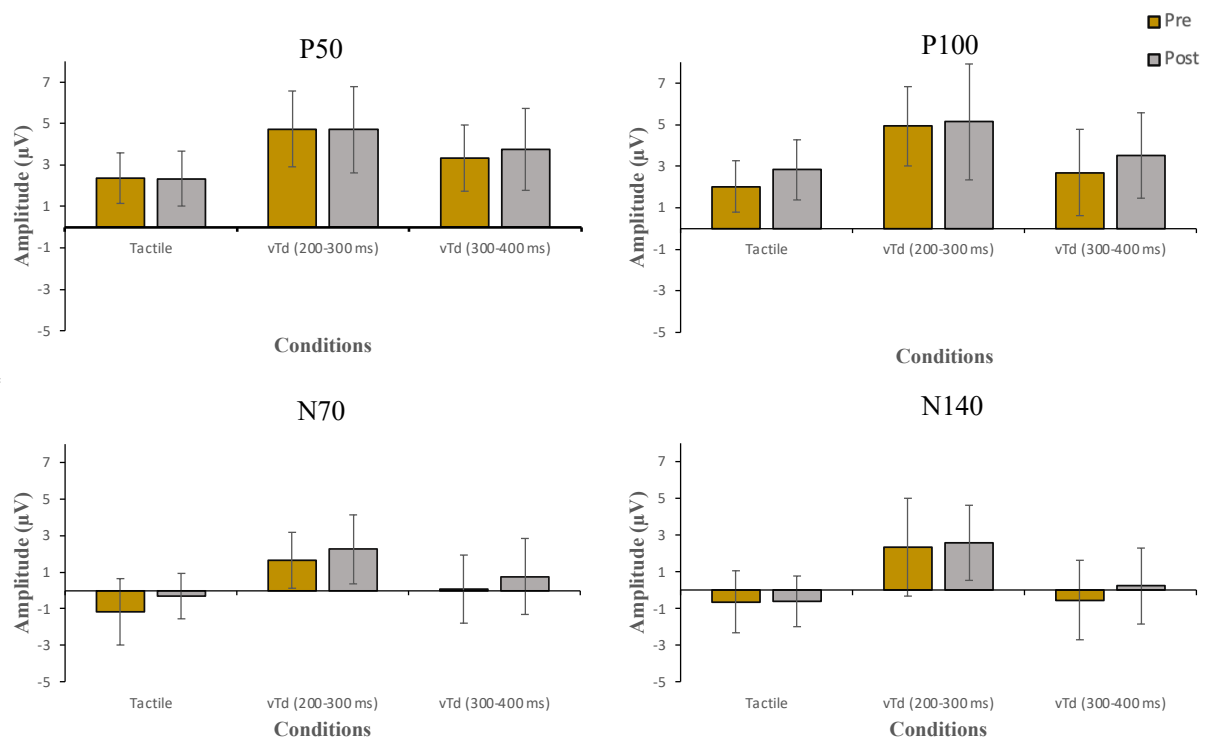


Figure 10: Participant ERPs mean average amplitude (extracted from electrode CP4) in iTBS group pre and post iTBS intervention depicting amplitude change within condition.

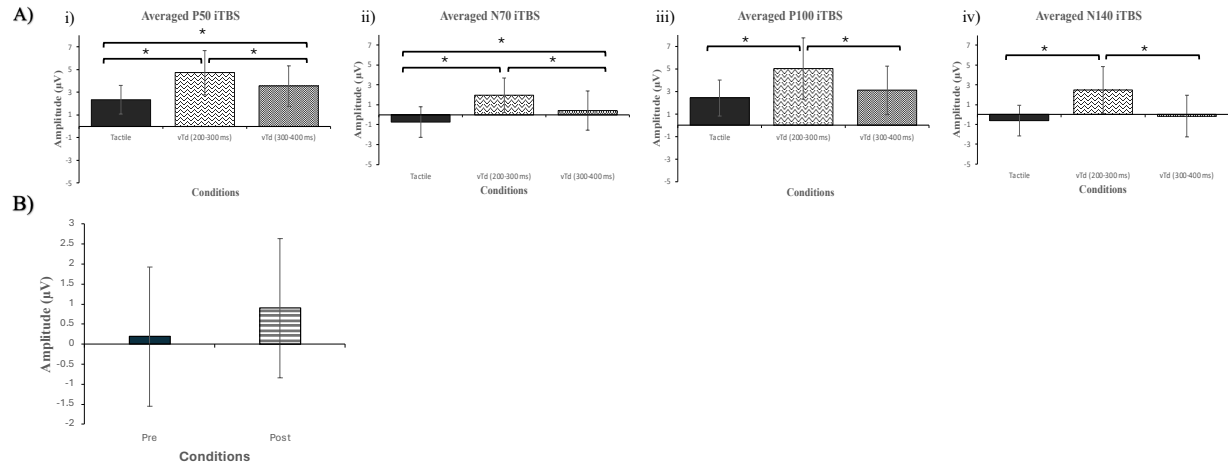


Figure 11: Participant ERPs mean average amplitude (extracted from electrode CP4) in iTBS group. A) Bar graphs comparing (i)P50, (ii)N70, (iii)P100 and (iv)N140 amplitude differences within condition. B) Bar graph comparing N70 amplitudes pre- and post- iTBS and C) Bar graph comparing conditions for relative differences between cTBS and iTBS groups.

6.3 Limitations

This study presented with some limitations that need to be addressed. The first limitation is the potential projections of top-down processing arising from the left (L.) DLPFC. Much of the current literature focuses on the effects R. DLPFC has on crossmodal interactions due to its connection to attentional and cognitive processes. That being said, while the effects R. DLPFC may be more prominent, L. DLPFC would have some influence in top-down processing for attention as well. These projections could still be present and modulating the facilitation of visual priming for bimodal upregulation.

A second study limitation present is the difficulty in assigning changes in behavioural outcomes following changes observed in EEG. While behaviour is modulated based on physiological changes, changes to a single physiological marker is not likely enough to elicit an entirely new behaviour. In this study, P50 modulation is altered by cTBS intervention, but subsequent cortical peaks are not modulated to the same extent. The ability to accurately assign relative intensities to each stimulus, then generate a graded motor response will be influenced by multiple downstream factors that cannot be controlled by with the current study design.

Lastly, the horizontal bar used to stimulate the visual realm is a limitation to the study. There are 6 known characteristics that can influence the way V1 processes information: colour, contrast, motion, line orientation and brightness. While the height of the bar changed, linked to an increase or decrease in relative amplitude made familiar by the training session, none of the characteristics that would modulate V1 activity were altered. To understand the extent of contribution arriving from the visual system, it will be important to learn how to optimize the stimulus type.

6.4 Implications

Multisensory interactions and integration are required for every-day tasks like crossing a street, walking through a park, or grabbing your house keys. Our nervous system is constantly receiving sensory stimuli from all modalities, where task relevant signals need to be hierarchically attended to. By furthering our understanding of crossmodal interactions, and how signals from two different modalities can enhance the way our nervous system attends to said information, it opens possibilities for future therapies of bimodal paired stimuli presentation as a means to prime or modulate brain regions, rather than solely relying on TMS techniques. As well, it could potentially be used to stimulate regions with decreased cortical activity resulting from lesions or other forms of brain trauma.

6.5 Future Directions

With our increased understanding of how visual-tactile bimodal upregulation is being controlled by different contributors, a shift in focus to understand the effects and mechanisms for these contributors is necessary. There are inter-cortical connection between the visual cortex and the tactile cortex like the left posterior LP and anterior intraparietal sulcus that may aid to prime S1 and generate larger potentials. These networks need investigating to understand the specific roles they play, and what type of conditions need to be met for optimization of function. One way of exploring these potential neuroanatomical connections can be to modulate the characteristics of the visual stimulus to identify if any specific stimulus traits most enhances this priming effect observed. Alternatively, by downregulating neuronal activity to the left posterior LP and observing any changes to this crossmodal upregulation, we can start to explore the neuroanatomical regions that guide this relationship.

While the peak of interest in this study was P50, this study revealed some changes to later potentials like N70 and N140. While N70 is presently linked to selective attentional modulation (Adams et al., 2017; Adams et al., 2019), and N140 is relevant in attentional shifts (Adler et al., 2009; Kida et al., 2004a, 2004b, 2006) changes to R. DLPFC activity have shown modulation on these respective peaks. It would be wise to start exploring how a change in selective attention is modulating how selective and attentive attention are linked.

7.0 Conclusion

The aim of this study was to further the understanding of the contributions the R. DLPFC has on the crossmodal facilitation observed in tactile processing in a visual-tactile paired stimuli with a 200-300 ms delay. Following R. DLPFC downregulation, achieved via cTBS, a decrease to P50 amplitude is suggestive that R. DLPFC is a significant contributor in this phenomenon, while simultaneously highlighting the existence of other significant contributors. Following R. DLPFC upregulation, achieved via iTBS, resulted in an extended priming period, optimizing crossmodal interactions in a longer delay range. Future directions should be to continue to expand our understanding on how the visual cortex can prime the somatosensory cortex, likely through inter-cortical connections to the left posterior LP. While some early cortical components are not yet fully understood, like N140, having an increased understanding of the influences R. DLPFC has on P50 is critical to our overall understanding of visual-tactile crossmodal facilitations.

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Appendices

Appendix A



TRANSCRANIAL MAGNETIC STIMULATION (TMS) SCREENING FORM

Below is a questionnaire used to exclude participants considered not suitable for transcranial magnetic stimulation (TMS). This information, as well as your identity, will be kept confidential in all future publications.

PLEASE COMPLETE FORM BELOW:

Participant's Name: _____ Age: _____

Please **CIRCLE ONE**:

Do you have epilepsy or have you ever had a convulsion or a seizure?	YES	NO
Have you ever had a fainting spell or syncope? If yes, please describe in which occasion(s)	YES	NO
Have you ever had severe (i.e., followed by loss of consciousness) head trauma?	YES	NO
Do you have any hearing problems or ringing in your ears?	YES	NO
Are you pregnant or is there any chance that you might be?	YES	NO
Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)	YES	NO
Do you have cochlear implants?	YES	NO
Do you have an implanted neurostimulator? (e.g., DBS, epidural/ subdural, VNS)	YES	NO
Do you have a cardiac pacemaker or intracardiac lines or metal in your body?	YES	NO
Do you have a medication infusion device?	YES	NO
Are you taking any medications? (Please list)	YES	NO
Did you ever have a surgical procedure to your spinal cord?	YES	NO
Did you ever undergo TMS in the past?	YES	NO
Did you ever undergo MRI in the past?	YES	NO

I hereby declare that all information given on this TMS screening form is true and complete in every respect.

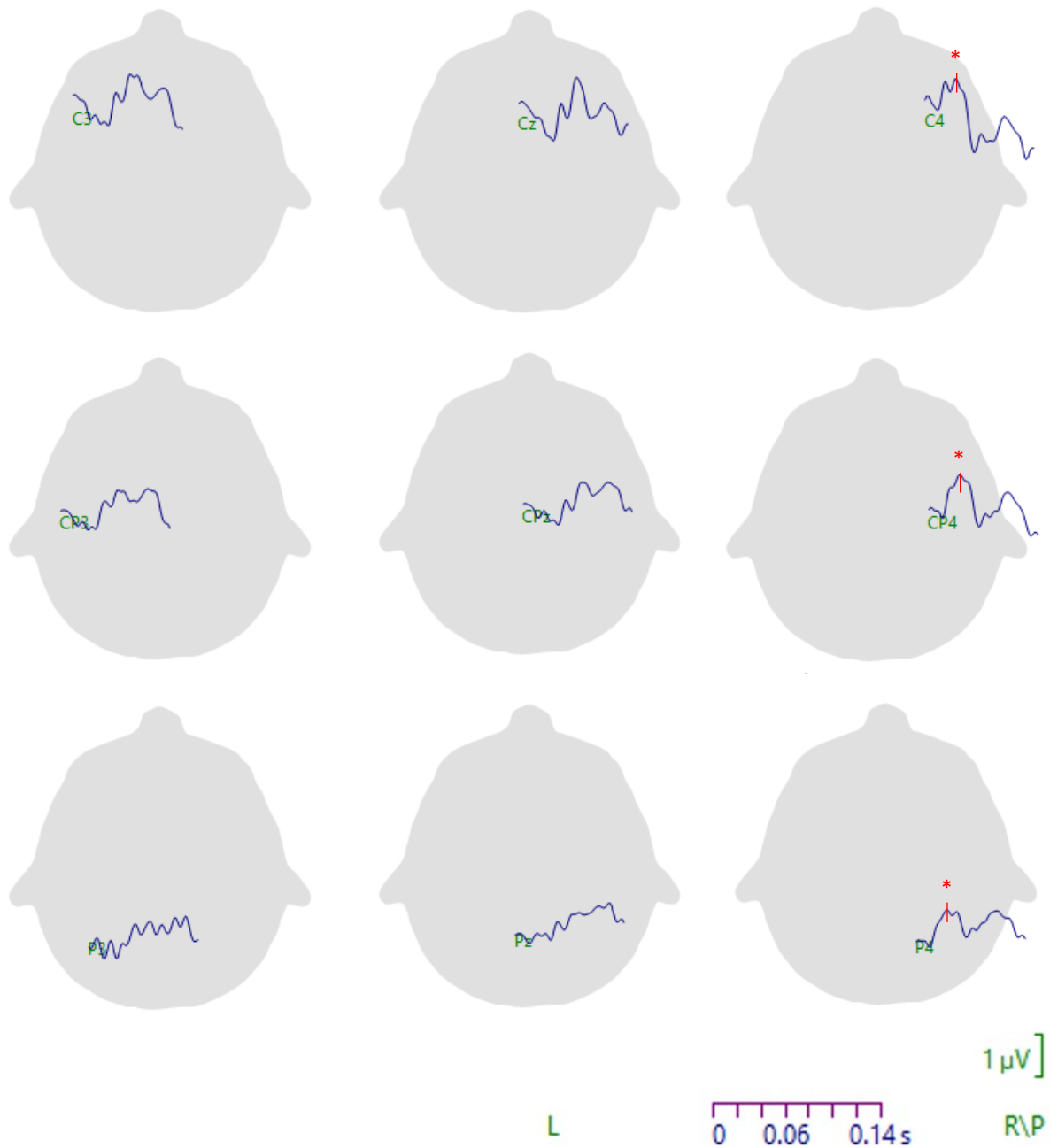
Signature of Participant

Date

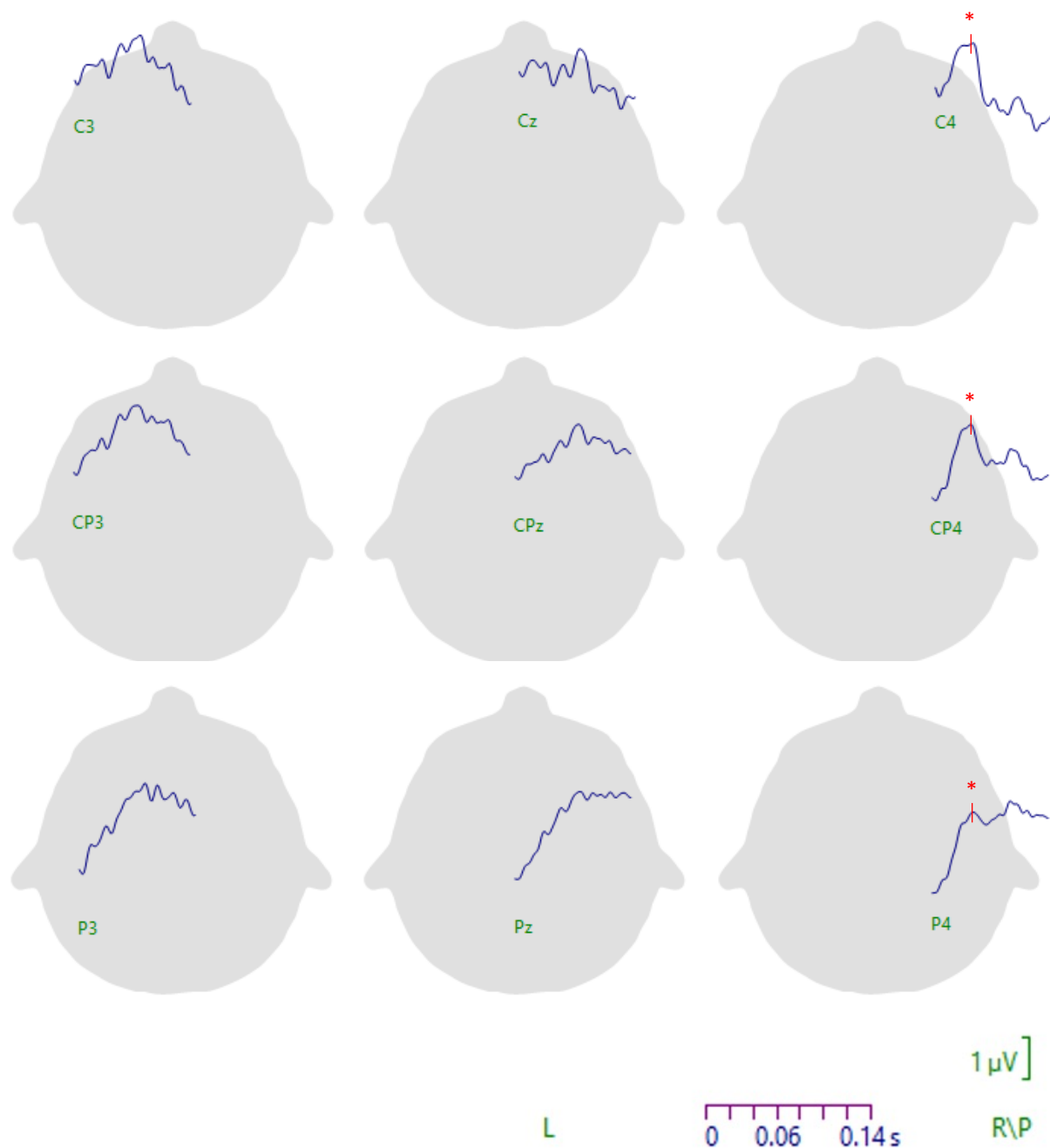
Signature of Witness

Date

Appendix B

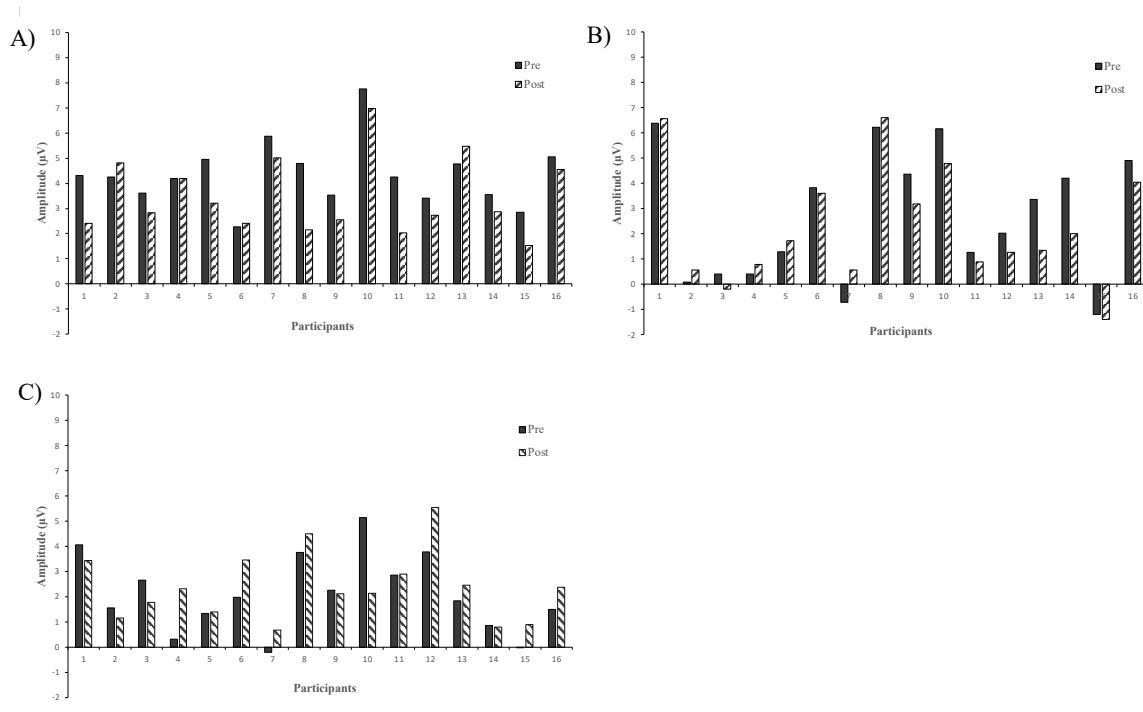


Grand Average topographic traces extracted from cTBS group (n=16) generated by unimodal tactile stimulation to the left index finger. Traces extracted from 9 electrodes: C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4 demonstrating ERP signal recorded. *P50 peak tagged in electrodes C4, CP4 and P4 to highlight the electrodes where P50 and other relevant ERPS peaks will be most clearly recorded. Electrode CP4 elicited the maximal peak amplitude across all four relevant peaks.

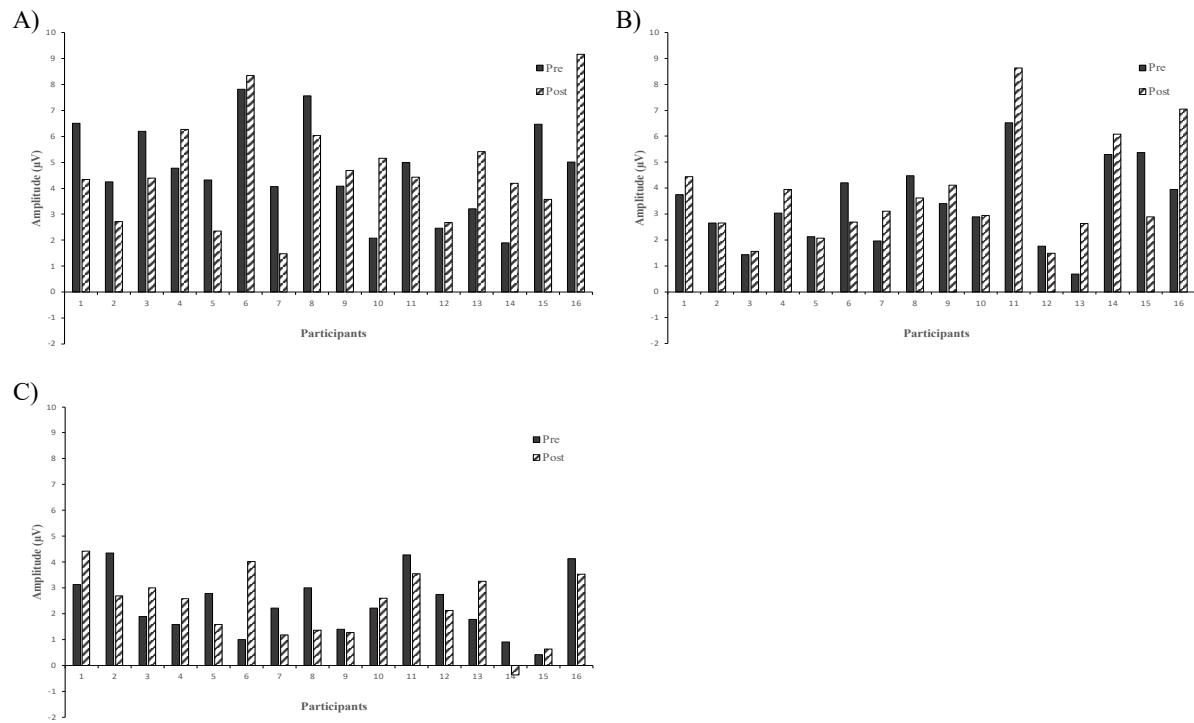


Grand Average topographic traces extracted from cTBS group (n=16) generated by bimodal visual-tactile (200-300 ms) stimulation to the left index finger. Traces extracted from 9 electrodes: C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4 demonstrating ERP signal recorded. *P50 peak tagged in electrodes C4, CP4 and P4 to highlight the electrodes where P50 and other relevant ERPS peaks will be most clearly recorded. Electrode CP4 elicited the maximal peak amplitude across all four relevant peaks.

Appendix C



Participant average P50 amplitude (extracted from electrode CP4) in cTBS group pre and post cTBS intervention. (A) condition vTd (200-300 ms), (B) Condition vTd (300-400 ms) and (C) tactile condition



Participant average P50 amplitude (extracted from electrode CP4) in iTBS group pre and post cTBS intervention. (A) condition vTd (200-300 ms), (B) Condition vTd (300-400 ms) and (C) tactile condition