RELIABILITY OF TRANSCALLOSAL CONDUCTION TIME MEASUREMENTS AT THE ABDUCTOR POLLICIS BREVIS

By

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RELIABILITY OF TRANSCALLOSAL

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Abstract: Transcallosal conduction time (TCT) can be measured using transcranial magnetic stimulation (TMS) during a submaximal voluntary contraction of a target muscle. By evaluating the time it takes for a potential to move across the corpus callosum (CC), we hope to see changes during phenomena such as cross-education. In the present study, we stimulated the contralateral and ipsilateral primary motor cortices during a 20% maximum voluntary contraction (MVC) of the abductor pollicis brevis (APB) of both hands in apparently healthy adults (n = 10). The motor evoked potential onset latency (MEPOL) that was obtained with the contralateral M1 stimulation was subtracted from the ipsilateral silent period onset latency (iSPOL) that was obtained through ipsilateral stimulation of the M1, which results in an approximate TCT. This was calculated using measurements at the participants' dominant and non-dominant hands and repeated again after more than 48 hours. Reliability measures of between the two visits showed that these measures were not reliable between visits. With further clarification on the definition of silent period onset latency (SPOL), and improvements in manual measuring techniques, we hope that measuring TCT can be a more accessible way to evaluate changes in interhemispheric interactions.

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CHAPTER I

INTRODUCTION

Transcranial magnetic stimulation (TMS) was introduced in 1985 and offered a pain-free method of stimulating the cortex, including primary motor cortex (M1) in order to elicit motor evoked potentials (MEPs), resulting from contraction of a target muscle (Barker, Jalinous & Freeston, 1985). TMS has since been used as a method of assessing the conduction of the corticospinal or corticobulbar tracts in both clinical and healthy populations. The action potentials generated by the magnetic force in TMS spreads across cortical axons transsynaptically to connected cortical and subcortical areas. This excitation generates action potentials that travel down the corticospinal tract to a target muscle where the electrical signal can be observed via electromyography (EMG) (Groppa et al., 2012).

The silent period (SP) is a cessation of EMG signal following TMS during a submaximal voluntary contraction, usually around 20% maximum voluntary contraction (MVC). This cessation of descending drive can be used as a measure of the inhibitory processes within the M1 when measured in muscles such as the first dorsal interosseous (FDI) or abductor pollicis brevis (APB), which are common in the area of study. The SP is often referred to as the cortical silent period (CSP) due to its origin being partly in GABAergic neurons within the cortex (Groppa, et al., 2012). Given that motor neurons decussate, the CSP is measured in a contralateral limb, which is termed the contralateral SP (cSP). Neurons within the corticospinal tract do not all decussate, however, and some innervate the ipsilateral muscle leading to the ability to measure the ipsilateral SP (iSP). Projections from the stimulated cortex may also cross the corpus callosum leading to the excitation of the homologous motor cortex that then continues down the contralaterally descending corticospinal tract (Deftereos et al., 2008; Jung & Ziemann, 2006).

Corticospinal control differs between the FDI and APB muscles in the hand. The iSP measured over the FDI is contaminated by a second phase of inhibition that has been proposed to be due to the non-decussating, ipsilateral corticospinal pathway that innervates the muscle. This second phase of inhibition is not present in EMG recordings of the iSP over the APB, and are thus less contaminated. In the FDI, iSPs preceded by a MEP had a significantly longer duration, though not a significantly longer onset latency, than those that were not preceded by a MEP (Jung & Ziemann, 2006). The cSP can be obtained without a preceding MEP at around 80% resting motor threshold (RMT). When looking at the APB, to obtain the cSP with a MEP, the percentage of RMT that is used varies slightly but a common method is to use 140% RMT (Groppa et al., 2012). The iSP without a preceding MEP is recommended to be measured using 160% RMT (Petitjean & Ko, 2013). Increasing the stimulus can change SP duration but does not affect the onset latencies of iSP, cSP, or MEPs (Petitjean & Ko, 2013).

Silent period and MEP onset latencies can be used to calculate an individual's transcallosal conduction time (TCT), often calculated by subtracting the MEP latency from the iSP latency. This method has been shown to overestimate TCT, so another method has been proposed where the cSP latency is subtracted from the iSP latency. Utilizing characteristics of both the iSP and cSP help account for this overestimation while not completely accounting for the additional time it would take to activate excitatory transcallosal neurons. This way of measuring TCT was also shown to be closer to interhemispheric conduction velocity (ICV) values seen in electron microscopic studies of the middle to posterior corpus callosum (CC) (Deftereos et al., 2008). Changes in IHI following unilateral resistance training as seen by Hortobágyi et al. (2011) and Hinder et al. (2010), along with changes seen in the ipsilateral homologous M1 by multiple researchers (Goodwill et al., 2012; Hortobágyi et al., 2011; Kidgell et al., 2011; Lee et al., 2010; Mason et al., 2018), suggests contribution from the ipsilateral M1 to the cross-education phenomenon with connections to the contralateral M1 via the CC.

Cross-education refers to the transfer of either skill or strength to a contralateral untrained limb, or homologous muscle, following unilateral training (Farthing et al., 2009; Manca et al., 2017; Manca et al., 2020a). A consensus of experts (Manca et al., 2020a) concluded that cross-education has clinical importance in orthopedic and sports injuries. Such as when a limb is immobilized, the contralateral limb may continue to undergo training in order to reduce strength loss in the immobilized limb (Farthing et al., 2009). Though a similar consensus could not be met on the use of cross-education in other clinical populations, some studies report positive findings in both stroke (Dragert &

Zehr, 2013; Urbin et al., 2015; Simpson et al., 2019; Sun et al., 2018) and multiple sclerosis (Manca et al., 2016; Manca et al., 2020b) patients.

Ipsilateral activity has been found to be greater in the left hemisphere of those who are right hand dominant and the hemispheric asymmetry of the ipsilateral M1 is not as consistent in left-handed individuals. In other words, symmetrical organization of the motor system in right-handed individuals has an important role in the dominance of hemispheres whereas left-handed people tend to have symmetrical functionality of both hemispheres (Reid & Serrien, 2014; Ziemann & Hallett, 2001). Unilateral eccentric training and stimulation of the target muscle provide the greatest cross-education of strength in the homologous muscle when compared to dynamic and isometric training, with transfer of motor skills occurring with each type of training (Manca, 2020a; Manca, 2017; Hortobágyi, 1997; Kidgell et al., 2015; Lepley, 2014; Frazer, 2018). The pace of training has also been presented as a possible avenue for future research in the cross-education of skill, but not in the cross-education of strength (Leung et al., 2018; Manca et al., 2020a). Cross-education of both skill and strength have been shown to favor a dominant to a non-dominant direction (Farthing, 2009). However, a consensus between experts does not exist for this preferential direction of transfer from a dominant, trained limb to a non-dominant, untrained limb (Manca et al., 2020a). To produce functionally meaningful transfer of strength to an untrained limb, the trained limb must undergo training at least 3 times per week for 4-6 weeks (Barss et al., 2018; Manca et al., 2020a). Consecutive daily training has also been shown to result in similar changes in strength in comparison to the 3 times/week model in half the time, in addition to the prospect of optimizing the recovery of strength within clinical populations by reducing days of rest (Barss, et al., 2018).

Though a consensus among experts for the direction of strength transfer in cross-education does not exist (Manca et al., 2020a), evidence suggests the preference of a dominant to non-dominant pathway (Farthing, 2009). A number of theoretical models to explain the contributions to cross-education have been proposed. These models include contributions from the mirror-neuron system (Manca et al. 2020; Zult et al., 2013), the ipsilateral primary motor cortex (M1) (Goodwill et al., 2012; Hortobágyi et al., 2011; Kidgell et al., 2011; Lee et al., 2010; Mason et al., 2018; Muellbacher, et al., 2000), bilateral access (aka callosal access) and cross activation (aka spillover) (Manca et al., 2020a). There is evidence to suggest that the pathways involved in the cross-transfer of motor function, which includes both strength and motor skills, differ from the ipsilateral motor pathway (Leung et al., 2018). This provides further evidence for one or more of the previously discussed models being responsible for the training specific adaptations that occur during the cross-education phenomenon. Interhemispheric inhibition (IHI) is used to describe the action of one hemisphere in suppressing its counterpart (Carson, 2020). A reduction of IHI at rest could indicate that the increased excitability of the ipsilateral M1 in comparison to the excitability prior to unilateral training could help facilitate the transfer of motor function to the ipsilateral, untrained homologous muscle (Hortobágyi et al., 2011). A few methodologies have been agreed upon by experts as promising tools to study the mechanisms of transfer of motor function. These include functional magnetic resonance imaging (fMRI), short intra-cortical inhibition (SICI), and IHI (Manca et al., 2020a). Previous research evaluating the cross-education of strength in the APB is lacking. There exist studies that view electrical signals in the APB in response to TMS, such as in the measurement of TCT (Deftereos et al., 2008; Jung & Ziemann, 2006; Petitjean & Ko, 2013), the evaluation of increased ipsilateral M1 excitability following activation of the APB (Meullbacher et al., 2000) and the effects of unilateral training on interhemispheric inhibition of the APB (Hinder et al., 2010), however. Other measurements of the pathways that have been proposed as mediators of the transfer of motor function may prove to be beneficial in either showing promise as direct measures of this phenomenon or by demonstrating further the importance of utilizing fMRI, SICI, and IHI.

This phenomenon may lead to or result from changes in conduction velocity across the CC, which can be calculated as TCT. By identifying the reliability of TCT and the corresponding latencies in SP or MEPs, use of a single-pulse TMS system may be able to identify changes in callosal conduction in relation to cross-education. By increasing the accessibility to these sorts of studies, labs that may have previously not been able to evaluate the cross-education phenomenon could take part in the evaluation of probably mechanisms and increase the body of literature in this area.

CHAPTER II

LITERATURE REVIEW

Barker, A. T., et al., Non-invasive magnetic stimulation of human motor cortex.

Introduction of the use of TMS. A note describing the novel method of directly stimulating the human motor cortex by a "contactless and non-invasive technique using a magnetic field." The coil used was flat and circular. Mention of the magnetic coil's use in the peripheral nervous system is mentioned, though use over the motor cortex requires a stronger stimulus and allows for more rapid stimuli of up to once every 3 seconds.

Barss, T. S., et al., Time course of interlimb strength transfer after unilateral handgrip training.

Unilateral handgrip training showed increases in strength in the trained arm after 9 sessions and the untrained arm after 12 sessions following a traditional training protocol of 3 sessions every week for 6 weeks. Daily training increased strength in the untrained limb in a similar number of total training sessions. The authors conclude that reducing rest days in clinical populations may optimize the recovery of strength.

Chen R., Yung, D., & Li, J., Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex.

Stimulation of the motor cortex leads to excitatory and inhibitory effects. Excitatory effects can be evaluating by eliciting ipsilateral MEPs (iMEPs) and inhibitory effects by evaluating the iSP. A reduction in corticospinal excitability can be seen following a conditioning stimulus. This IHI and iSP phenomena may be mediated by transcallosal pathways. Coil placement was determined to be optimal in the anterior lateral directions, with the handle of the coil pointed posterior and 45 degrees away from the central sulcus. This was optimal for the elicitation of an iSP with the highest threshold but no preference was shown for iMEP or IHI. Contralateral MEPs (cMEPs) had a preference for the anterior medial direction. This difference in prefence for direction between the cMEP and iMEP elicitation suggests that the ipsilateral effects, including IHI, are mediated by populations of cortical neurons that are different from those activating the corticospinal neurons. The authors also noted the importance of using iSP and IHI as complementary measures of ipsilateral inhibition, though the observations suggest similar circuits involved and may be related to transcallosal inhibition.

Daskalakis, Z. J., et al., An automated method to determine the transcallosal magnetic stimulation-induced contralateral silent period.

A contralateral silent period was evoked using TMS at 120% and 150% RMT. The SP duration was measured using two raters and an automated method developed by the researchers. The interclass correlation coefficient (ICC) between the two raters and the automated method were 0.99 (150% RMT) and 0.97 (120% RMT). The researchers conclude that this method provides a more objective approach to the measurement of SP duration.

Deftereos, S. N., et al., On the calculation of transcallosal conduction time using transcranial magnetic stimulation.

The authors suggest that the more widely used method for calculating transcallosal conduction time (TCT) overestimates the actual TCT. An alternate method for calculation of TCT is proposed. The previous equation subtracted contralateral MEP latency from iSP latency. The proposed equation subtracts cSP latency from iSP latency. This method was shown to overestimate to a significantly lesser extent and may provide an alternate method that results in less bias in group comparisons. This method would decrease the overestimation by taking into account the amount of time that it takes to activate the contralateral inhibitory interneurons within the cortex (cACT). This time is essentially taken from the amount of time it takes to activate transcallosal neurons that excite the contralateral inhibitory neurons (iACT). The previous equation would overestimate by iACT while the new equation would overestimate by iACT – cACT.

Dragert, K., & Zehr, E. P., High-intensity unilateral dorsiflexor resistance training results in bilateral neuromuscular plasticity after stroke.

Dorsiflexion torque in the affected, untrained limbs of stroke patients was increased following unilateral training of the unaffected limb. The training of the unaffected limb involved isometric dorsiflexion for 25 minutes per session, 3 sessions per week, for 6 weeks. The authors demonstrate residual plasticity many years post-stroke suggesting clinical applications for the cross-education phenomenon.

Farthing, J. P., Cross-Education of Strength Depends on Limb Dominance.

A review showing that the cross-education phenomenon has a preference for the dominant to non-dominant pathway, in other words, transfer of strength is greater when the dominant hand is trained in right-handed individuals. The review was limited to transfer in the upper limbs. The model presented in the review would suggest that adaptations are cortical in nature and are shared by both limbs. There is other evidence in the literature to suggest that cross-education occurs at multiple sites in the nervous system.

Farthing, J. P., Krentz, J. R., & Magnus, C. R. A., Strength training the free limb attenuates strength loss during unilateral immobilization.

During a 3-week immobilization period, unilateral training of the mobilized limb attenuated strength loss in the immobilized limb. Unilateral strength training may have also prevented muscle atrophy in the immobilized limb. There was no significant increase in strength of the untrained arm, though no decrease either. For the casted group that was not trained, there was a significant decrease in strength of the immobilized limb.

Giovannelli, F., et al., Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study.

A study of the ipsilateral silent period. Optimal positioning was found to be the same as for contralateral muscle activation using TMS. Anterio-lateral orientation with the handle pointed posteriorly and 45 degrees away from the central sulcus. TMS of the right M1 was given at 120% RMT in order to measure the ipsilateral SP. EMG was recorded over the right FDI. The researchers found the iSP to be subject to task-specific modulation. They conclude that their study reinforces the hypothesis that the M1 contralateral to a given voluntary movement contributes to the process of lateralization of voluntary movements by a late-stage inhibition of unwanted mirror motor output.

Goodwill, A. M., Pearce, A. J., & Kidgell, D. J., Corticomotor plasticity following unilateral strength training.

Study included the unilateral training of the participants' leg. Both a one legged squat and isometric MVC were used to evaluate strength in both legs. 3 training session for 3 weeks. Cross-education of strength was seen, though the training duration was shorter than seen in other studies. Along with the use of TMS and SICI, the researchers noted that the cross-education of strength may be modulated by intracortical inhibition within the iM1 (to the trained limb).

Green, L. A., & Gabriel, D. A., The effect of unilateral training on contralateral limb strength in young, older, and patient populations: a meta-analysis of cross education.

This meta-analysis of cross-education studies establishes a set of effect sizes in which future studies can base sample sizes from. Effect size of particular types of cross-education studies are established. The isometric contraction training group's effect size was 0.73 for the percent gain in strength of the contralateral limb, and 1.11 for the percent gain in strength of the trained limb. The lowest effect sizes found were for an "other" category with 0.46 and 0.53 along with Older adults with an effect size of 0.58 and 1.44 for the contralateral and trained limbs, respectively. The cross-education effect was accompanied by a significant moderate to large effect size in each population with an average transfer range of 48-77%. The study also presented evidence for the equivalence in cross-education between upper and lower limbs as well as in males and females.

Groppa S. et al., A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee.

This paper provides guidelines on the clinical use of TMS. Physiological aspects of TMS are discussed followed by safety issues. The authors discuss many variations in methodology such as the differing views on establishing a RMT. This is also a great source for drawing differences in similar terminology such as AMT and RMT or MEP onset and SP onset. Detailed descriptions of coil placement is also noted with images to display the correct coil orientation in order to induce the most effective stimulation.

Hinder, M. R., et al., Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb.

An investigation into the effect of voluntary contractions have on interhemispheric inhibition (IHI). The study focused on contractions of the APB, both tonic and ballistic contractions. MEP responses were also taken from the ADM and ECR in addition to the APB. Both tonic and ballistic contractions of the right APB resulted in an increase in IHI from the "active" to "passive" cortex. When testing the dominant APB this would be a dominant to non-dominant pathway, where the ipsilateral cortex's inhibitory neurons were excited by the contralateral cortex. The authors conclude that the evidence found in the study leads to the appearance that the mechanisms mediating the alteration in IHI affect an extended region of the cortex rather than being restricted to the networks controlling the homologous muscle.

Hortobágyi, T., Lambert, N. J., & Hill, J. P., Greater cross education following training with muscle lengthening than shortening.

Researchers tested the hypothesis that strength transfer following unilateral training differed based on whether the training involved concentric or eccentric contraction. The participants were split into three groups; concentric, eccentric and control. EMG was recorded for the vastus lateralis and the rectus femoris. The concentric group still saw cross-education of strength, but the effect was greater in the eccentrically trained group.

Hortobágyi, T., et al., Interhemispheric plasticity in humans.

This paper provides the first evidence for plasticity of the interhemispheric connections between the trained (contralateral) and untrained (ipsilateral) primary motor cortices following unimanual motor tasks. The training for this study focused on training of the dominant FDI. IHI decreased in the homologous untrained muscle following the unilateral training period which consisted of 3 sessions per week for 6 weeks. Hinder et al., 2010 saw increases in IHI of the homologous APB.

Julkunen et al., Feasibility of automated analysis and inter-examiner variability of cortical silent period induced by transcranial magnetic stimulation.

The authors of this paper outline the feasibility of automated methods in measuring SP characteristics. They were able to find that the inter-examiner reliability of measuring silent period duration was similar to the variability between the automated method and manual analysis.

Jung, P., & Ziemann, U. (2006). Differences of the ipsilateral silent period in small hand muscles.

Researchers compared the measurement of the ipsilateral silent period between the APB and FDI. They chose these muscles as they have been shown to have similar cortical placement of the TMS coil in order to elicit both a MEP and iSP. The authors propose that the FDI is subject to a second phase of inhibition in the ipsilateral corticospinal pathways and thus, callosal dysfunction should be analyzed using measurements from the APB since it is not subject to this second phase of inhibition. The second phase of inhibition is thought to arise from the same pathways which result in the more easily elicited iMEP of the FDI. This pathway would bypass callosal pathways that lead to iSP through cortical inhibition.

Kidgell, D. J., et al., Increased cross-education of muscle strength and reduced corticospinal inhibition following eccentric strength training.

Participants were split in concentric and eccentric training groups. The target muscles were the wrist flexors. Participants attended 3 sessions per week for four weeks. The researchers saw, as in previous studies, greater effect of cross-education of strength in the eccentric training group. This eccentric training was also seen to differentially modulate corticospinal inhibition and excitability. Decreases in cortical inhibition (SP duration; GABAB mediated pathways) are greater in eccentrically trained subjects. This is one possible way to explain the greater transfer of strength.

Kidgell, D. J., Stokes, M. A., & Pearce, A. J., Strength training of one limb increases Corticomotor excitability projecting to the contralateral homologous limb.

The target muscles for this study were the biceps brachii. Following unilateral training, researchers evaluated MEP amplitude and silent period durations at AMT, 20% AMT and MEPmax. Increases in the MEP amplitude and no change in the silent period led the researchers to the conclusion that the cross-education of strength may be mediated by the increase in excitation to the homologous muscle, while no change being seen in the silent period would indicate no changes in cortical inhibitory pathways. Increases in strength were also seen in the absence of hypertrophy. The researchers point out the limitation that their study does not account for changes elsewhere in the neural pathways involved with motor output not within the primary motor cortex and corticospinal pathway and that future research should investigate ipsilateral pathway excitability and inhibition.

Lee, M., et al., The ipsilateral motor cortex contributes to cross-limb transfer of performance gains after ballistic motor practice.

Participants in this study underwent unilateral training for the FDI and ADM. Changes in performance and corticospinal excitability were seen within the FDI in both hands for the training group and not for the control group. rTMS was used to induce a virtual lesion on both hemispheres and the impact on performance was noted. rTMS to both hemispheres resulted in detriments to performance. The authors drew the conclusion that since a virtual lesion in the untrained M1 led to performance decreases in the untrained hand (after seeing increases following unilateral training of the homologous muscle), that the ipsilateral M1 contributed to early retention of ballistic performance gains in the untrained FDI.

Lepley, L. K., & Palmieri-Smith, R. M., Cross-Education Strength and Activation After Eccentric Exercise.

This study focused on the cross-education of strength following eccentric training of the quadriceps on a dynamometer in comparison to a control group, no inclusion of a concentric training group. With a 90% training compliance (21/24 visits). This paper draws a distinction in the types of gains made following training. Participants showed gains that were both mode and speed-specific. The 6-week long eccentric training regimen led to consistently greater eccentric quadriceps strength in the unexercised limb. The participants attended 3 sessions per week and warmed up with concentric, isokinetic contractions prior to their training protocol each session.

Leung M., et al., The ipsilateral corticospinal responses to cross-education are dependent upon the motor-training intervention.

The focus of this study was to test the effect of different pacing in training on cross-education of strength and motor skills. The authors conclude that the cross-education of muscular strength and motor skills lead to specific patterns of corticospinal excitation and inhibition of the ipsilateral motor pathway. They find that these responses are mediated by the type of motor training. Whether that be changes in pacing or visuomotor training, with slow paced training and visuomotor training showing the greatest change is responses.

Lo, Y., & Fook-Chong, S., A transcranial magnetic stimulation study of the ipsilateral silent period in lower limb muscles.

This study analyzed the differences in iSP and TCT between age groups. The researchers focused on the abductor hallucis brevis. The subjects were separated into three different age groups; 20-40, 41-60, and 61-80. The researchers only included right-handed participants. The researchers did not find any statistically significant differences between the age groups for TCT, iSP duration, or cSP duration. The authors refer to the term "interhemispheric inhibition" as sometimes being considered the same as iSP. They point out that recent evidence suggests that iSP and interhemispheric inhibition may be mediated through different pathways within the corpus callosum (Chen, Yung, & Li, 2003).

Manca, A., et al., Effect of contralateral strength training on muscle weakness in people with multiple sclerosis: Proof-of-concept case series.

The authors of this paper refer to cross-education as "the contralateral strength training effect." This article highlights the clinical importance of the cross-education phenomenon. This study shows for the first time that the occurrence of cross-education on muscle performance (of ankle dorsiflexors) in people with MS. Cross-education may show promise as a rehabilitation approach to those with unilateral weakness that leads to inability to perform traditional methods of strength training on the affected side of the body.

Manca, A., et al., Cross-education of muscular strength following unilateral resistance training: a meta-analysis.

The aim of this meta-analysis was to evaluate the current literature (as of 2017) on cross-education of strength and determine the magnitude of its effect. The authors found among their sample that the "pooled" (all subtypes, including different contraction types and body regions) cross-education effect was a significant 11.9% increase in contralateral strength. Isometric, concentric, eccentric, and isotonic-dynamic training resulted in an 8.2%, 11.3%, 17.7%, and 15.9% increase in contralateral strength, respectively.

Manca, A., et al., Contralateral Effects of Unilateral Strength and Skill Training: Modified Delphi Consensus to Establish Key Aspects of Cross-Education.

This recent Delphi Consensus establishes opinions of key aspects in cross-education research from a cohort of experts. These aspects include basic terminology to refer to the phenomenon itself, to aims for future research that may provide much needed insight. An optimal training schedule is given with most experts stating that 13-18 sessions over 4-6 weeks is the shortest duration needed to induce contralateral strength gains. This consensus was not made for the transfer of motor skills. It is also noted that the distinction between strength and motor skill transfer and that both may involve differing pathways. Important tools for future investigation included fMRI and TMS, with SICI and IHI being important tools under the umbrella of "TMS." The consensus consisted of 61% of the qualified cross-education experts identified. It was also concluded that cross0-education could be considered an additional treatment for unilateral orthopedic conditions and sports injuries.

Manca, A., et al., Gait changes following direct versus contralateral strength training: A randomized controlled pilot study in individuals with multiple sclerosis.

Cross-education in this article is referenced as "contralateral strength training." This article covers a pilot study including 28 participants with MS that experience inter-side differences in strength of ankle dorsiflexors and moderate gait impairment. The groups were either allocated to train the less-affected dorsiflexors (cross-education) or the more-affected dorsiflexors. No differences in gait speed were seen in the experimental group. Though, both saw increases in strength of the affected limb, with no significant differences between interventions. The researchers conclude that the contralateral training should not be recommended right away if the main goal is to improve gait speed or other outcomes other than strength.

Mason, J., et al., Ipsilateral corticomotor responses are confined to the homologous muscle following cross-education of muscular strength.

This paper aimed to identify if unilateral training of an upper body muscle (biceps brachii) would lead to strength differences in another upper body muscle (flexor carpi radialis; FCR) not involved in the same actions. The researchers found that after training of the elbow flexors, an increase in strength was seen in other muscles as well. This is rationalized by the FCR's role as a synergist muscle in elbow flexion, though it is not directly responsible for that movement. They suggest that isotonic strength training be used in a rehabilitative environment in order to extend the cross-education of strength to as many muscles as possible, such as other synergist and stabilizers involved in the action that would not be used in the case of concentric or eccentric movements alone, or with isometric contractions.

Muellbacher, W., et al., Changes in motor cortex excitability during ipsilateral hand muscle activation in humans.

This study's aim was to analyze unilateral hand muscle activation and its effect on ipsilateral primary motor cortex (iM1) excitability. The researchers focused on the abductor pollicis brevis (APB). Excitability in the iM1 was seen to increase during unilateral hand muscle activation. This increase in excitability was also seen in the contralateral spinal cord. The authors provide contradicting evidence to the claim that this change in excitability is due to pathways involving the corpus callosum. They state that, though the involvement of the ipsilateral hemisphere would suggest use of a transcallosal pathway, a study by Meyer et al. (1995) found unattenuated MEP facilitation in patients with callosal agenesis. This provides evidence that this effect is not mediated by interhemispheric pathways.

Petitjean, M., & Ko, J. Y. L., An age-related change in the ipsilateral silent period of a small hand muscle.

This study focused on the differences in TCT in age groups found a significant effect of age on iSP parameters. They evaluated the iSP through measurements over the APB in accordance with recommendations from Jung and Ziemann (2006). The researchers in this study broke down their participants into two groups; ages 20-40 and ages 50-70. The authors mention that the small 20-year gap between participants in the study by Lo and Fook-Chung (2004) may have led to the inability to see differences in the iSP and TCT, which led to the 30-year difference in minimum and maximum cut-offs for their age groups. To ensure they were comparing a 30-year difference, the researchers controlled for height and gender and paired up young and old group members to compare their changes. They note that this decision may be arbitrary. Of the parameters measured, of both the left and right sides, (iSP onset latency, iSP offset latency, iSP duration, and TCT) only the right iSP duration did not show a statistical difference.

Reid, C., & Serrien, D., Primary motor cortex and ipsilateral control: A TMS study.

Researchers in this study assessed the motor cortex excitability in a resting hemisphere while the homologous hemisphere was active during a voluntary unilateral task. The researchers found that in right-handed individuals, the facilitation of MEPs was dependent upon hemisphere and that the left hemisphere in these individual's showed dominance. When the right hemisphere was active, facilitation was seen in the left, but not seen in the right when the left hemisphere was active. This hemispherical dominance was not seen in the left-handed participants.

Rossi S., et al., Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert guidelines.

This paper presents updates to TMS guidelines originally published in 2009. The guidelines outline TMS use in both healthy populations and patient populations, with safety considerations in each population and new devices. The paper includes safety measures to take with other tools such as MRI, electrical stimulation, non-removable implants, and certain drugs. Adverse effects are listed, such as seizures and transient increases in auditory thresholds. Hearing issues can be mediated by ear plugs and the risk for seizure is very low with only 3 reported seizures with use of single or double pulse, low-frequency TMS. For each possible adverse event, recommendations are given on how to reduce risk as much as possible.

Rossini, P., et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee.

This report provides an update to a previous report first published in 1994. It includes the physiology behind both magnetic and electrical stimulation along with descriptions of EMG characteristics recorded in the target muscle. The report also describes standard procedure for the collection and analysis of MEPs, silent periods, and central motor conduction time. Central motor conduction time requires simultaneous magnetic stimulation of the cortex and spinal cord along with peripheral nerve stimulation. Stimulation of spinal roots and peripheral nerves is also discussed.

Simpson, D., et al., Unilateral dorsiflexor strengthening with mirror therapy to improve motor function after stroke: A pilot randomized study.

Unilateral training with and without a mirror has been seen to increase strength in the homologous limb in healthy populations, but this study focuses on that transfer of strength within the clinical setting. This paper provides evidence for the practical use of cross-education in a clinical setting, specifically in clinical populations that suffer from unilateral weakness following a stroke. The mirror group in the study did not differ in strength gains but did have an increase in functionality (walking velocity).

Sun, Y., et al., Unilateral wrist extension training after stroke improves strength and neural plasticity in both arms.

This paper provides evidence for use of cross-education of strength within clinical populations of patients that suffer from unilateral weakness following a stroke. The target muscles for this study were the wrist extensors. The participants had 3 training sessions per week for 5 weeks. One session was in the lab and two were done at home. Researchers saw decreases in silent period and transcallosal inhibition from both hemispheres in the non-paretic limb and increases in strength in both limbs. This study shows that high intensity exercise of the non-paretic limb increases bilateral strength. It also provides evidence for cross-education's role in altering both spinal and cortical plasticity in clinical populations.

Urbin, M. A., et al., High-Intensity, Unilateral Resistance Training of a Non-Paretic Muscle Group Increases Active Range of Motion in a Severely Paretic Upper Extremity Muscle Group after Stroke.

This study focused on the cross-education of wrist extensor strength and range of motion in post-stroke patients. The results of the study concluded that high intensity resistance training of the non-paretic limb leads to increases in strength in the paretic limb. The wrist extensors were trained using dynamic contractions, which is functionally relevant to many of the goal-directed movements in the physical therapy of stroke patients. Along with strength, the active range of motion of the non-paretic arm was also increased. The authors note that future studies should evaluate the efficacy of different types of contractions.

Ziemann, U., & Hallett, M., Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance.

The aim of this study was to test the extent to which the increase in ipsilateral motor cortex excitability during unilateral motor tasks shows hemispheric asymmetry. During a unimanual complex task, the ipsilateral cortex was stimulated using TMS. The resulting effects on the task hand were noted. The motor task was more affected when the left hand (non-dominant in the sample population) was the task hand and the left hemisphere was being stimulated. The reverse resulted in a less affected motor task. The researchers demonstrate that hemispheric asymmetry of ipsilateral motor cortex excitation supports one of two ideas. The first idea is that the dominant motor cortex is more active during movements of the ipsilateral hand. The second idea is that the dominant motor cortex exerts more effective inhibitory control over the non-dominant hemisphere than vice versa. This was only looked at in right-handed individuals in the current study with a sample size of 6. The authors suggest that the asymmetry of ipsilateral motor cortex activation compromises another property of motor dominance in addition to being related to the hemisphere contralateral to the dominant hand.

Zult, T., et al., Role of the Mirror-Neuron System in Cross-Education.

This review proposes that cross education with a mirror would result in increased transfer of motor function to the limb contralateral to the trained limb. The review shows that the sensory neurons involved in the perception of an observed action connects to those involved in the motor output of that action. The unilateral mirror training involves setting up a mirror so that a unilateral task such as wrist flexion, appears to be bilateral. The visual stimuli being processed is as if the subject were flexing both wrists at once, though the motor output is unilateral. The authors state that this set-up could enhance the effects of cross-education. The pathways that could possibly be responsible for this effect on cross-education are presented in the paper and involve highly complex interactions between the motor cortices, occipital cortex, and areas within the temporal lobe. Figures displaying these pathways are shown in the paper in order to provide a more digestible presentation of the pathways involved.

CHAPTER III

METHODOLOGY

3.1 Subjects

Inclusion criteria for subjects include being age 18 - 64, apparently healthy, and without any contraindications to TMS. These contraindications include history of seizures, syncope, brain diseases or medications that may increase risk of seizure, the presence of implanted biomedical devices or pregnancy (Rossi et al., 2021). Participants completed an informed consent, COVID questionnaire, Par-Q, health history and a TMS safety-screening questionnaire (Rossi et al., 2011) before proceeding with the study. Participants were asked to sit in a chair with hands supinated on a table in front of them. The following TMS and peripheral nerve stimulation (PNS) protocol is administered while the participants were seated in the same chair.

3.2 Recording of EMG Activity

EMG surface electrodes were placed bilaterally on the APB with the ground placed over the styloid process of the ulna or dorsal aspect of the hand (Deftereos et al., 2008; Jung & Ziemann, 2006; Petitjean & Ko, 2013). The skin in the general area of electrode placement were prepared by abrading, wiping with isopropyl alcohol and shaving, if needed. A high pass filter was set at 50 Hz to remove movement artifacts. Cortical silent period (CSP) onset is defined as the MEP offset, or a return to zero following the MEP. CSP offset is the return of the background EMG signal. It is possible to automatically analyze the cSP and maintain accuracy. Some studies have found different ways that show either similar or even more variability between raters than between raters and automatic methods (Daskalakis et al., 2003; Julkunen et al., 2013). In the present study, EMG recordings were manually analyzed for the iSP onset, MEP onset, cSP onset, and SP durations.

3.3 Maximum Voluntary Contraction of APB

After the placement of electrodes, participants were asked to place one hand over a load cell located on a platform, as shown in Figure 1. Since silent period measurements are obtained during a 20% MVC of the target muscle, each participant was evaluated to find their MVC during each visit, and for each hand. In order to find each subject's MVC, participants completed two sets of an estimated 50% isometric MVC for 10 seconds. Participants were placed in front of a monitor so that they could see visual feedback of the force they were producing. These two warm ups were then followed by two attempts at a 100% isometric MVC of the APB. This same setup, with one APB contracting at 20% MVC and the other at rest, is used during the TMS protocol.

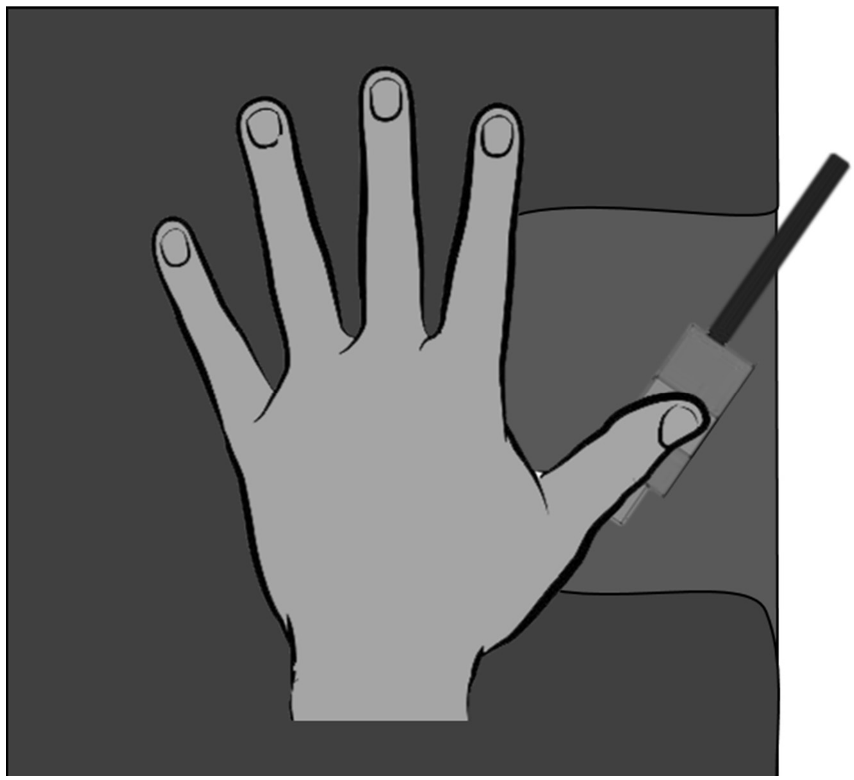

FIGURE 1: Participants' MVC for each APB was found by abducting the thumb (pressing down toward the table where the platform is placed) into the load cell. Participants were faced toward a monitor that provided visual feedback for force production.

3.4 Transcranial Magnetic Stimulation

Following a familiarization visit, TMS measurements were taken. Single-pulse TMS using a monophasic current waveform connected to a figure-eight coil was administered over the hand area of the M1. The coil was held at a 45-degree angle away from the midline, over the scalp. This orientation allows for the induced current to flow in an anterior-medial direction, perpendicular to the central sulcus. This orientation is optimal for producing transsynaptic activation of neurons in the corticospinal pathway

(Chen, Yung, & Li, 2003; Daskalakis et al., 2003; Giovannelli et al., 2009). The hot spot for the APB has been found to be around 6 cm lateral to the vertex and 1 cm anterior to the interaural line. Hot spot localization consisted of 3 stimulations at the reported hot spot in addition to 3 stimulations at: 1 cm anterior, 1 cm medial, 1 cm lateral, and 1 cm posterior to the reported hot spot. The individual's hot spot was the location that provided the largest MEP measured in the contralateral APB. RMT was found using an adaptive method where a relative frequency estimation algorithm, developed and made available by Awiszus and Borckhardt, was utilized (Awiszus & Borckhardt, 2011; Groppa et al., 2012; Rossini et al., 2015). After finding the RMT for the subject 120% RMT intensity was used to elicit a contralateral MEP and 140% RMT was used to elicit an iSP, without a preceding ipsilateral MEP (Petitjean & Ko, 2013). TMS was administered at a frequency of one stimulus every 3-5 seconds, in blocks of 10 with a 3-minute rest period between blocks. This method should reduce central and peripheral fatigue effects (Deftereos et al., 2008). Over the dominant hemisphere, a block of 10 stimulations at 120% RMT were given during contralateral 20% MVC of the APB, followed by another block of 10 stimulations at 140% RMT during 20% MVC of the ipsilateral APB. Hot spot localization, RMT identification and the two blocks of 10 stimulations during 20% MVC were repeated over the non-dominant hemisphere. Total stimulations, after identification of the hot spot and RMT, were 40 stimulations.

3.5 Data Analysis

In order to evaluate the test-retest, and intrarater, reliability, a few different measures were calculated including the $ICC_{3,1}$, standard error measurement (SEM), and minimal difference (MD). iSPOL and MEPOL were gathered from 10 trials for each of the 10 participants. Reliability tests were performed for mean MEPOL measured contralaterally to the stimulation site over both the dominant and non-dominant hemispheres and for iSPOL measured ipsilateral to the stimulated hemisphere. These tests were run following the removal of outliers. TCT was calculated in both directions, from the dominant to non- dominant hemisphere (D-nD) and from the non-dominant to dominant hemisphere (nD-D). Dominance was determined from self-reported handedness, where right-handers were left hemisphere dominant and the one left-handed participant was right hemisphere dominant. In order to calculate the D-nD TCT, the MEPOL measured contralateral to the dominant hemisphere was subtracted from the iSPOL measured ipsilateral to the non-dominant hemisphere. In order to calculate the nD-D pathway the MEPOL measured contralateral to the non-dominant hemisphere was subtracted from the iSPOL measured ipsilateral to the dominant hemisphere. This process is summarized in Figure 2.

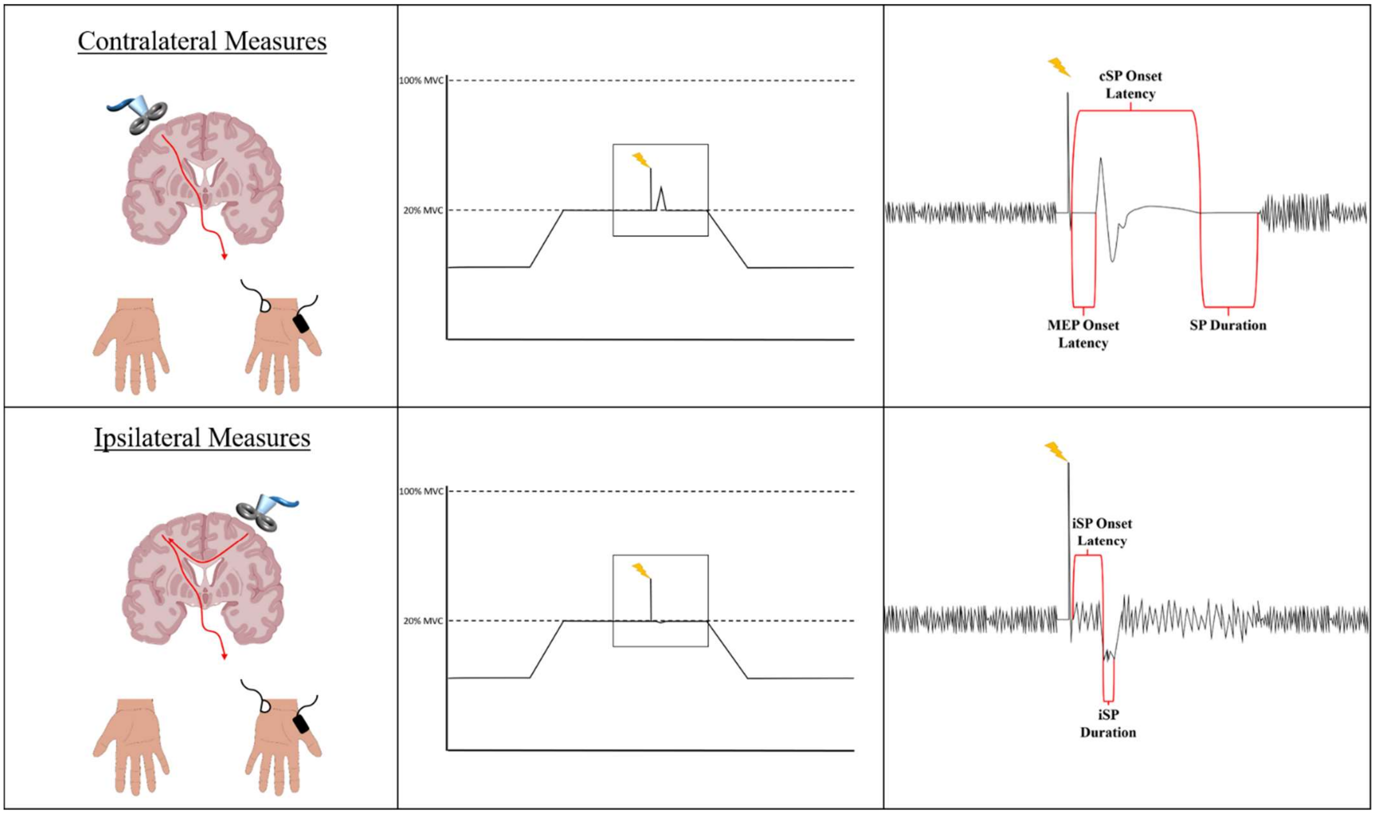

FIGURE 2: TCT is calculated by subtracting the MEPOL (contralateral measures) from the iSPOL (ipsilateral measures). Both are measured at the same target muscle. cSP = contralateral silent period; iSP = ipsilateral silent period; MEP = motor evoked potential; SP = silent period; MEPOL = motor evoked potential onset latency; iSPOL = ipsilateral silent period onset latency

CHAPTER IV

RESULTS

Results 4.1

Subject (n = 10) demographic information is summarized in Table 1. The subject pool consisted of equal numbers of male (n = 5) and female (n = 5) participants. The sample was relatively young with a mean age of 26.3 ± 5.6 years. For the D-nD pathway across the CC, the intraclass correlation coefficient (ICC) was found to be -0.062, with a standard error of measurement (SEM) of 4.347 ms. For the nD-D pathway, the ICC was found to be 0.337 with an SEM of 3.182 ms. The MEPOL measured contralateral to the dominant hemisphere had an ICC of 0.564 and SEM of 1.266 ms. The MEPOL measure contralateral to the non-dominant hemisphere had an ICC of -0.482 and SEM of 3.83 ms. The iSPOL measured ipsilateral to the dominant hemisphere was found to have an ICC of .603 and an SEM of 3.282 ms. The iSPOL measured ipsilateral to the non-dominant hemisphere had an ICC of -0.483 and an SEM of 3.83 seconds. Due to the inability to obtain some ipsilateral measures, the mean calculated for TCT in the D-nD direction included 9 participants and for the nD-D direction, 8 participants. iSPOL means were also calculated from 9 participants for the dominant hemisphere and 8 participants for the non-dominant hemisphere. When viewing the mean TCT data on a scatterplot, shown in

Figure 3, it can be seen that the points do not have close to a one-to-one relationship as would be expected when reliably taking measurements without intervention.

Subject	Age (yrs)	Sex (M/F/O)	Height (cm)	Weight (kg)
1	33	F	173	94.85
2	38	M	188	
3	28	M	175	86
4	27	M	171	80
5	25	M	180	93
6	22	F	158	53
7	25	F	162	82
8	21	F	155	59
9	24	F	175	69
10	20	M	175	81.81

TABLE 1: Subject demographic information. Height and weight were rounded to the nearest centimeter and kilogram, respectively. Yrs = years; M = male; F = female; O = other/not specified; cm = centimeters; kg = kilograms.

Measure	Hemisphere	$ICC_{3,1}$	SEM	MD	F Between	P
TCT	D-nD	-0.06	4.35	3.18	0.36	0.56
	nD-D	0.34	3.18	8.82	0.00	0.98
MEPOL	Dominant	0.56	1.27	3.51	0.01	0.92
	Non-dominant	0.78	1.04	2.89	1.87	0.21
iSPOL	Dominant	0.60	3.28	9.10	0.79	0.40
	Non-Dominant	-0.48	3.83	10.62	0.0	0.97

TABLE 2: Mean values in the reliability of measures used in the calculation of transcallosal conduction time between two visits separated by at least 48 hours. ICC = intraclass correlation coefficient; SEM = standard error of measurement; MD = minimal difference; MEPOL = motor evoked potential onset latency; iSPOL = ipsilateral silent period onset latency; D-nD = dominant to non-dominant pathway; nD-D = non-dominant to dominant pathway.

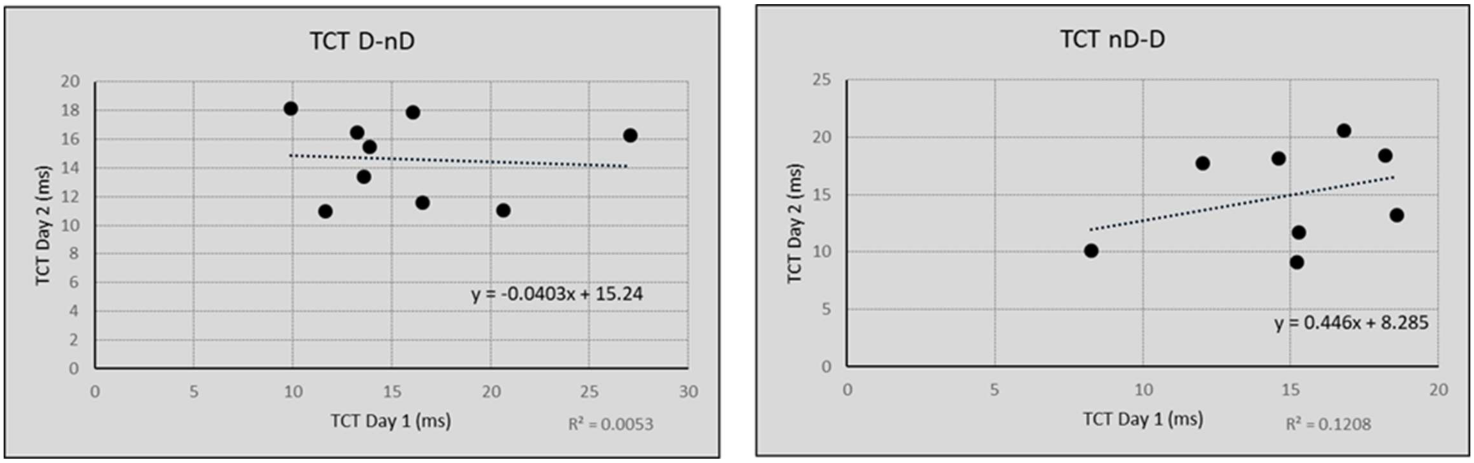

FIGURE 3: Scatterplots of mean TCT for each participant. The plot to the left shows mean TCT in the dominant to non-dominant direction (R^2 = .0053), while the plot to the right shows mean TCT in the non-dominant to dominant direction (R^2 = .1208). TCT = transcallosal conduction time; D-nD = dominant to non-dominant direction; nD-D = non-dominant to dominant direction.

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CHAPTER V

DISCUSSION

Discussion 5.1

It is apparent that the reliability of these measures is inadequate, with the tests suggesting that 66%, 45%, and 40% of the score variance being attributable to error in the measurements for the nD-D TCT, contralateral dominant MEPOL, and ipsilateral dominant iSPOL, respectively. The other measures resulted in a negative ICC. All of these results indicate unreliability in the measures. This may be due to a variety of factors such as poor intrarater reliability, equipment issues, or possibly physiological mechanisms that do not allow for reliable measurements. In order to identify the possible causes of error, future directions include reevaluating the data without any left-handed participants and while using an unfiltered EMG for measurements of the iSPOL. When measuring the ipsilateral measurements, the filtered EMG looked vastly different than other research demonstrates. For example, there was a lack of a ‘dip’ in the EMG signal and instead a silent period that resembled the cSP was visible. This could have led to issues in the measurements of the iSPOL.

Limitations of the study include variability of participants from day to day. Such as changes in the intake of caffeine or water, sleep quality or duration, or changes in motivation from one visit to the next. Another limitation to note would be the variations of the definition of silent period onset latency among researchers. More established definitions for these measurements might lead to improvements in the quality of research done in this area. Other measurements of interhemispheric interactions may be of use in future research in order to establish the correlations between measurements such as short intracortical inhibition (SICI) and long intracortical inhibition (LICI) along with TCT. Being able to reliably measure TCT with a single-pulse TMS is necessary in order to increase the accessibility of cross-education research among labs that do not have access to other equipment that may assist in the evaluation of interhemispheric interactions.

Conclusions 5.2

In conclusion, the findings in this particular study indicate that the measurements used in the calculation of TCT, and TCT itself, are unreliable within the confines of the current described protocol. With the introduction of better defined parameters for the measurements of iSP measures, and additional measures of interhemispheric interactions, this area of study can prove to be beneficial in the understanding of the physiological mechanisms underlying phenomena such as cross-education. With the ability to use TCT in order to evaluate interhemispheric interactions, labs with limitations to the equipment on hand may be able to contribute to the body of knowledge in this particular area.

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