No hemispheric asymmetries in long-acting cortical inhibition in young adults using TMS-EEG

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Declaration

I declare that this thesis is my own account of my research and contains as its main content work that has not previously been submitted for a degree at any tertiary educational institution.

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Table of Contents

General Acknowledgments

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Abstract

It is well established that fine motor control is asymmetrical: this is known as handedness. Handedness is controlled by cortical motor processes, including long-acting inhibition. Long-acting cortical inhibition is asymmetric between the left and right hemispheres. Therefore, asymmetries of handedness may be attributable to asymmetries in long-acting inhibition. Asymmetries of long-acting inhibition have previously been tested using a measure of corticospinal excitability, but have not been previously investigated using combined transcranial magnetic stimulation (TMS) and electroencephalography (TMS-EEG), a measure of cortical inhibition not influenced by spinal excitability. This study aimed to determine if long-acting cortical inhibition is asymmetrical using TMS-EEG and to investigate any associations of asymmetrical inhibition with fine motor control. In young adults (n = 14) fine motor control was measured using the Purdue Pegboard task. EEG was used to record the cortical responses to paired-pulse, single-pulse and sham TMS. Results showed no asymmetry in fine motor control using the Purdue Pegboard task and no asymmetries of long-acting inhibition between the left and right hemispheres using TMS-EEG. There was no significant difference between the response to sham and single-pulse stimulation, suggesting that the cortical response to TMS was influenced by auditory or physiological artefacts. There were no associations between TEPs of long-acting inhibition and fine motor control. Overall, there were no conclusive results whether asymmetries of long-acting inhibition are replicable using TMS-EEG. Further investigation of the importance of LICI as a neural underpinning of handedness is important to better understanding the workings of handedness and fine motor control.

Keywords: fine motor control, transcranial magnetic stimulation, electroencephalography, long-interval intracortical inhibition, handedness

Investigating hemispheric asymmetries in long-interval intracortical inhibition in young adults using TMS-EEG

Human hands are used daily to interact with our environment; skilled motor control of the hands is critical for actions such as eating, writing, and opening a jar. The asymmetry in the way we use our hands (known as handedness) is well characterised: many hand functions require fine motor control in which the two hands are specialised for different aspects of movement. For example, when opening a jar, the dominant hand is used to manipulate and open the lid, whilst the non-dominant hand is used in a stabilising role to steady the jar (Duff & Sainburg, 2007; Hammond, 2002; Mutha, Haaland & Sainburg, 2013; Sainburg, 2005). Though such functional asymmetries are well documented, the underlying neural controls of asymmetrical motor control are not well understood (Opie, Rogasch, Goldsworthy, Ridding & Semmler, 2017).

The primary motor cortex (M1) is responsible for the execution of voluntary movements. M1 is located in the frontal lobes of the brain and has somatotopically arranged representations within it. A large area of M1 is devoted to hand representation because it requires complex movement patterns (Scheiber, 2001). There is evidence to suggest that asymmetries of motor functioning, such as handedness, may be mediated by neural mechanisms in M1 (Aoki, Rivlis & Scheiber, 2016; Civardi, Cavalli, Naldi, Varrasi & Cantello, 2000).

Cortical inhibition is an essential function by which neural excitatory processes are suppressed or reduced (Premoli, Castellanos, et al., 2014). The inhibitory process is mediated by the receptors of the neurotransmitter gamma-amino butyric acid (GABA) in the brain (Rogasch, Daskalakis & Fitzgerald, 2013). Cortical inhibition in M1 is a means by which the brain is able to regulate controlled movements (Hammond & Vallence, 2007; Sinclair & Hammond, 2007; Ridding, Taylor & Rothwell, 1995).

Because there is evidence that motor control is mediated by neural inhibition, it is a possibility that there are also asymmetries of inhibition, and that these asymmetries might be a mechanism mediating handedness.

Cortical inhibition can be measured using transcranial magnetic stimulation (TMS). Single-pulse TMS is a non-invasive procedure in which a brief, high intensity electrical pulse generates a magnetic field. This magnetic field passes through a coil and travels through the scalp and skull and induces a current in the underlying tissue. If the intensity of the pulse is sufficient, the induced current flow will depolarise interneurons in the brain (Barker, Jalinous & Freeston, 1985; Hallett, 2007). The result of a TMS pulse over the hand area of M1 is a motor evoked potential (MEP) in the corresponding hand, which is measured using electromyography from the belly of the muscle (Hallett, 2007). The amplitude of the MEP is a measure of excitability of the pathway from the stimulation point (M1) to the muscle, i.e. the corticospinal pathway, known as corticospinal excitability (Hallett, 2007; Di Lazzaro, Ziemann & Lemon, 2008).

Paired-pulse TMS can be used to measure cortical inhibition (Valls-Solé, Pascual-Leone, Wassermann & Hallett, 1992; Wasserman, et al., 1996). When a conditioning pulse is delivered prior to a test pulse 50-200ms apart, inhibitory neurons are activated by the initial conditioning pulse, which in turn moderate the amplitude of the MEP in response to the test pulse (Valls-Solé et al., 1992; Wasserman, et al., 1996). The MEP evoked from paired-pulse TMS is reduced in comparison to the MEP evoked from single-pulse TMS. This reduction, identified as inhibition, of the paired-pulse MEP is known as long-interval intracortical inhibition (LICI; Valls-Solé et al., 1992; Wasserman et al., 1996). LICI is a long-acting inhibitory process, thought to be mediated by the neurotransmitter $GABA_B$. LICI is consistently enhanced and

suppressed by a known $GABA_B$ agonist and antagonist, respectively (Premoli, Castellanos, et al., 2014; Premoli, Rivolta et al., 2014; Sanger, Garg & Chen, 2001).

There is evidence that LICI is an important mechanism of motor control. Studies of the dominant left hemisphere have shown that LICI is reduced during and prior to muscle contractions compared to resting state (Buccolieri, Abbruzzese & Rothwell, 2004; Hammond & Vallence, 2007; Zoghi, Pearce & Nordstrom, 2003). This reduction of LICI during muscle contraction is greater during precision grasping than finger abduction (Kouchtir-Devanne, Capaday, Cassim, Derambure & Devanne, 2012).

Two recent studies have investigated hemispheric asymmetries of LICI in young people and found evidence that LICI is asymmetrical across hemispheres in young adults. Hammond and Garvey (2006) aimed to measure LICI in the M1 of each hemisphere using paired-pulse TMS to determine if there were asymmetries of LICI. Over the course of three TMS studies, results showed that LICI was greater in the relaxed dominant right hand than the non-dominant left hand and that there was evidence that the threshold for LICI activation was lower in the dominant hemisphere than the non-dominant hemisphere (Hammond & Garvey, 2006).

A second study, by Vallence, Smalley, Drummond and Hammond (2017) aimed to replicate the asymmetry in LICI demonstrated by Hammond and Garvey (2006). They also aimed to test whether there is a difference in LICI asymmetry between young and older adults, as LICI has been linked to manual dexterity and manual dexterity is known to decline with age (Opie, Sidhu, Rogasch, Ridding & Semmler, 2018; Raw, Kountouriotis, Mon-Williams, & Wilkie, 2012). Participants' manual dexterity was tested using the Purdue Pegboard task and paired-pulse TMS was used on both hemispheres. Hemispheric differences were tested using a range of control stimulus intensities and intervals between the control and test pulse, known as interstimulus

intervals (ISIs). The study found that manual dexterity was asymmetrical in young adults, with the dominant right hand placing more pegs than the non-dominant left hand. The study also found that the dominant hemisphere demonstrated more LICI at the 100ms ISI than the nondominant hemisphere and no differences in LICI at the 150ms ISI. Vallence et al. (2017) found that the results of Hammond and Garvey (2006) were replicated and that LICI circuits in the dominant hemisphere were more sensitive and powerful than those in the non-dominant hemisphere of young adults. The study also provided evidence that LICI processes are time dependent, as the LICI asymmetry in young adults was only evident at 100ms ISI.

Whilst paired-pulse TMS can be used as a reliable measure of inhibition (Valls-Solé et al., 1992; Wasserman et al., 1996), it is limited by the fact that it can only provide indirect information about cortical output, as TMS MEPs are a measure of combined cortical and spinal output (Premoli, Rivolta, et al., 2014; Rogasch et al., 2013). One method to overcome this problem is by combining TMS with electroencephalography (EEG). EEG is a commonly used technique used to record and measure electrical activity of the cortex from a number of electrodes placed in standardised positions (Rogasch et al., 2013). The use of EEG enables direct measurement of cortical electrical activity, which is thought to reflect neural processes. By combining TMS and EEG (TMS-EEG) it is possible to measure neural responses to TMS using the cortical electrical activity recorded by the EEG.

When TMS is applied over M1 it results in a series of positive and negative peaks in the EEG output, known as components, the sum of which are known as the TMS evoked potential (TEP; Premoli, Castellanos et al., 2014). The time from the TMS test pulse to the cortical response, known as latency, of TEP component peaks after the test stimulus is not dependent on stimulus intensity (Komssi, Kähkönen, & Ilmoniemi,

2004). Each of these components are thought to have differing underlying mechanisms (Komssi et al., 2004). The primary TEP components are P30, N45, P60, N00 and P180 (see *Figure 1*). The early TEP component P30 is related to general excitation of the cortex (Rogasch et al., 2013). The N45 component is related to short-acting inhibition mediated by the neurotransmitter $GABA_A$ (Komssi et al., 2004). P60 is a component which has unclear origins and function. It is consistently found in studies of LICI and it has been suggested that it is related to short-acting inhibition (Cash et al., 2017) and may have an auditory component, as it is reduced after sound masking (ter Braack, de Vos, & van Putten, 2015). The N100 component has been linked to long-acting inhibition (Farzan et al., 2013; Rogasch et al., 2013). There is evidence that the final TEP component, P180, is related to global cortical TMS responses (Komssi et al., 2004; Premoli, Castelanos et al., 2014).

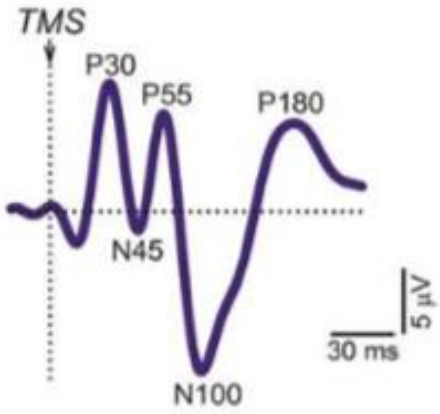

Figure 1. Example TEP highlighting positive and negative peaks at 30, 45, 55, 100 and 180 seconds post TMS test pulse (A.-M. Vallence, personal communication, March 14, 2018).

Of particular interest to the study of LICI is the N100, which is a highly reproducible long-latency negative peak that occurs approximately 100 ms after the test stimulus (Nikulin, Kičić, Kähkönen & Ilmoniemi, 2003; Yamanaka, Kadota & Nozaki,

2013). Larger amplitude of N100 from the TEP of a single TMS pulse is indicative of greater inhibition (Rogasch et al., 2014). Pharmaceutical studies of LICI and $GABA_B$ have shown that N100 is enhanced by a known $GAGA_B$ agonist and suppressed by a known $GABA_B$ antagonist (Komssi et al., 2004; Premoli, Rivolta et al., 2014), providing evidence that N100 is closely related to LICI .

The TMS component of LICI measured paired-pulse TMS-EEG is conducted in the same way as paired-pulse TMS, in which a control stimulus precedes a test stimulus by 50-200ms and the test stimulus response is inhibited compared to the control stimulus response when LICI is present (Opie et al., 2017; Rogasch et al., 2013; Valls-Solé et al., 1992; Wasserman, et al., 1996). The response of the N100 component of the LICI TEP is particularly important to note, as it differs from the N100 of single-pulse TMS TEPs. At 100ms ISI, the N100 component of the paired-pulse LICI TEP has a smaller amplitude when greater levels of inhibition are present (Opie et al., 2017), compared to the single-pulse TEP, in which the N100 increases with inhibition.

Whilst previous research has provided insights into the asymmetrical functioning of LICI in young adults, thus far asymmetries of LICI have only been investigated using paired-pulse TMS to measure the inhibition of the MEP. Though MEPs are a reliable measurement of LICI, the MEP is recorded from a peripheral muscle, and as such, the data gained from MEPs may be subject to subcortical or spinal interference (McNeil, Martin, Gandevia, & Taylor, 2011; Rogasch et al., 2013). This makes it difficult to reliably ascertain whether or not LICI and the previously exhibited asymmetries of LICI in young adults (Hammond & Garvey, 2006; Vallence et al., 2017) are purely cortical in nature or have a corticospinal component. By using combined TMS-EEG it is possible to measure the cortical-only response to TMS in with single-pulse and paired-pulse TEPs. Thus, by using TMS-EEG to measure cortical-only

responses using TEPs this study aimed to replicate the asymmetries in long-acting inhibition demonstrated in previous research (Hammond & Garvey, 2006; Vallence et al., 2017) and to determine whether or not these asymmetries of inhibition are purely cortical or corticospinal in nature. This study also aimed to determine if asymmetries of fine motor control are associated with asymmetries of long-acting inhibition.

To address these aims, paired-pulse, single-pulse and sham TEPs were recorded from the left and right hemisphere using TMS-EEG. The sham condition was included to ensure that the TEPs were not merely an artefact evoked by the TMS (Massimini et al., 2005). As a measure of fine motor control, the Purdue Pegboard task was administered to participants using both the left and right hands. In accordance with the aims of this study, it was hypothesised that:

- Participants would place more pegs with the dominant right hand than non-dominant left hand during the Purdue Pegboard task measuring fine motor control.
- Single-pulse TMS would elicit greater TEP amplitude than sham TMS.
- The dominant hemisphere would exhibit greater TEP amplitude than the non-dominant hemisphere evoked from single-pulse TMS.
- The dominant hemisphere would exhibit smaller LICI TEP amplitude than the non-dominant hemisphere evoked from paired-pulse TMS,.
- There would be a positive correlation between LICI TEPs of the dominant left hemisphere with the Purdue Pegboard performance of the dominant right hand and this positive correlation would also be evident between the LICI TEPs of the non-dominant right hemisphere with the Purdue Pegboard performance of the non-dominant left hand.

Method

Subjects

A total of 55 participants were recruited for this study. To address the current research question, data from 14 right-handed young adults were included in the analyses (9 women, 5 men, *M* = 24 years, range: 19-31 years). More participants were recruited than were included in the current analyses as this study was part of a larger research project investigating age-related changes in long-acting cortical inhibition. Of the 55 participants recruited, 26 were young adults. 12 of those were excluded due to not meeting eligibility criteria or handedness requirements, high RMT on one or both hemispheres, abnormal MEP, and equipment malfunction (described in detail below).

Participants were recruited from the Murdoch University research portal, the wider community via advertisements placed online and on community notice boards, and by word-of-mouth from previous participants. Undergraduate psychology students from Murdoch University received credit points for their participation and community members received a Woolworths voucher and a parking was arranged for the duration of the session. The research procedures were approved by the Murdoch University Human Research Ethics Committee (approval number 2018/019).

Screening. All participants provided written informed consent and were screened for contraindications to TMS (Rossi, Hallett, Rossini & Pascual-Leone 2009; 2011) before their inclusion. One potential participant was unable to participate after initial screening due to a history of regular cluster headaches. The Edinburgh Handedness Inventory (EHI; Oldfield, 1971) was used to confirm the handedness of participants (median = 85; range 60-100). Scores of ≥ 40 on the EHI are considered to indicate right-handedness, therefore only participants with scores of ≥ 40 could participate. The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was

used to screen all participants for cognitive impairment. Scores ≥ 26 are suggested to reflect no cognitive impairment, therefore only participants with scores of ≥ 26 were accepted for inclusion.

Exclusions. Twelve study recruits were excluded from further participation due to participant history of cluster headaches (n = 1), participants not meeting handedness requirements on the EHI (n = 2); equipment malfunction of the EEG (n = 2); abnormal delayed MEP (n = 1); and RMT over 85% terminated in order to avoid the machine overheating (n = 6).

Fine Motor Control

The Purdue Pegboard task (Lafayette Instruments, Lafayette, IN) was used to measure fine motor control in both hands using standardised testing procedures. The peg insertion subtest was used. Participants were instructed to take pegs from a well in the top right-hand corner of the board and then to place pegs individually in a vertical row of holes on the right side of the board with the right hand. Participants were required to place as many pegs as possible in 30 seconds first with the one hand and then the process was repeated with the other on the left side of the board; the order of hands tested was counterbalanced across participants.

Electromyography

Throughout the experiment participants were seated in a comfortable chair with their hands placed on a pillow on their lap and their eyes open with their gaze fixed on the wall. Surface electromyography (EMG) was recorded from the relaxed first dorsal interosseous (FDI) muscle of the right (dominant) and left (non-dominant) hands by two surface electrodes placed in a belly-tendon montage with a grounding electrode placed on the wrist bone. The EMG signal was amplified (1000x) using a CED1902 amplifier (Cambridge Electronic Design, Cambridge, UK) and band-pass filtered (20-1000 Hz)

before being digitised at 2 kHz using a CED 1401 analogue to digital converter (Cambridge Electronic Design, Cambridge, UK).

Electroencephalography

EEG data were recorded with 128 electrode HydroCel Geodesic Sensor Nets (Electrical Geodesics, Inc.) using HydroGel GSN 128 10 Montage and Net Station (4.5.6) software. The data were collected using a Net Amps 300 amplifier and signals were amplified (10,000x), filtered (0.1 – 500 Hz) and digitised at a sampling rate of 1000 Hz before being recorded for offline analysis. Impedance was checked consistently throughout the experiment and adjusted when necessary to below 50 kΩ.

Transcranial Magnetic Stimulation

All TMS occurred with the EEG cap in place. Using a Magstim BiStim 200^2 stimulator (Magstim, Whitland, UK) single- and paired-pulse stimuli were delivered through a figure-of-eight- coil (90mm diameter). The coil was placed over the EEG cap tangentially to the scalp with the handle at a 45° from the midline, which is the optimal angle for eliciting a posterior-anterior current in the cortex (Cirillo & Byblow, 2016). The coil was then moved systematically over the motor cortex to identify the best location for eliciting MEPs in the relaxed FDI muscle, usually over the C1 and C3 electrodes on the dominant left hemisphere and over C2 and C4 electrodes on the right non-dominant hemisphere. The optimal location was marked in permanent marker on a sheet of plastic attached to the EEG net for easy reference and checked continuously throughout the experiment. The resting motor threshold (RMT) of the resting FDI muscle was then obtained. RMT was defined as the lowest stimulus intensity to elicit a MEP of at least 50 μV in three out of five consecutive trials (Hammond & Garvey, 2006; Opie et al., 2018); RMT was expressed as a percentage of maximum stimulator output (MSO). Both the optimal site for eliciting MEPs in the FDI muscle and the RMT

were obtained for the dominant and non-dominant hemisphere, counterbalancing the order across participants.

Sham stimulation. Sham stimulation was administered with the TMS coil held at a perpendicular to the scalp with the wing of the coil resting over the site of optimal stimulation. Pulses were administered at RMT but did not penetrate the scalp to elicit a response. This technique ensures that the TMS click of the coil is still the same as the single-pulse stimulation and vibrations of the stimulation can still be felt (Rogasch et al., 2013).

Experimental Procedure

The entire experimental protocol took approximately two and a half to three hours to complete. TMS was applied in blocks of sham, single and paired-pulse stimulation. Single-pulse blocks comprised of 50 stimuli with an inter-trial interval of 5 seconds (=/-20% jitter). Blocks of paired-pulse stimuli comprised of 50 stimuli and were administered at 100ms ISI, as this interval elicits reliable LICI and has been shown to be asymmetric in young adults (Hammond & Garvey, 2006; Vallence et al., 2017). Sham stimulation blocks comprised of 50 stimuli with an inter-trial interval of 5 seconds (=/-20% jitter). All TMS stimuli were administered at RMT to minimise TMS artefact in the EEG signal (Rogasch et al., 2014). EEG data was recorded throughout the duration of the blocks of TMS, with each block taking approximately four minutes to complete. TMS was applied in two single-pulse blocks, two paired-pulse, blocks and one sham stimulation block delivered to each hemisphere, with the order of testing counterbalanced and randomised across participants. All blocks were administered at rest in order to avoid TEP interference from other movement activated intracortical processes. Participants were also required to listen to white noise through inserted

headphones for the duration of each block in order to minimise auditory evoked potentials resulting from the click of the TMS coil (Massimini, et al., 2005).

Data Analysis

TMS-EEG.

Data were analysed using various software including the MATLAB platform (R2015b, The Mathworks, USA); EEGLAB (Delorme & Makeig, 2004); and a TMS-EEG signal analyser (Rogasch et al., 2017). Data from all left hemisphere blocks were merged into a single file and the same was done for data from all right hemisphere blocks. Epochs of data 1000 ms pre and post each TMS pulse were selected for analysis and baseline corrected from -650 to -200 ms before the TMS pulse.

TEPs can be influenced by TMS artefacts. Data was removed at -1.5 to 20 ms around the TMS pulse from single-pulse trials in order to compensate for these artefacts. For paired-pulse trials data was removed at -1.5 to 20 ms and -110 to -50 ms around the test stimulus. The removal of the data at -110 to -50 ms around the test stimulus of the paired-pulse data removed the artefact from the conditioning pulse. Removed data was replaced using cubic interpolation. This removal of the large artefact in the data was necessary for effective decomposition by independent components analysis (ICA) (Hernandez-Pavon et al., 2012; Rogasch et al., 2017) (which was subsequently used for data pre-processing). The data were also band-pass filtered at 1-100 Hz; notch 50 Hz to remove interference from the main power supply. The ICA identified and removed components relating to TMS pulse decay, muscle activity, blinks and eye movement (Rogasch et al., 2014).

Global Mean Field Amplitude. Global mean field amplitude, an index of global cortical excitability (Komssi, et al., 2004), was calculated to ensure that any specific differences in TEPs between hemispheres was not resultant of global differences in

cortical excitability. GMFA was quantified by the area under the GMFA curve at 0-300 ms following the test stimulus (Opie et al., 2018).

TMS-evoked potentials. In paired-pulse trials, the first (conditioning) stimulus generates a TEP (because the stimulation intensity of the first (conditioning) stimulus is the same as the second (test) stimulus, which also generates a TEP). Therefore, for paired-pulse trials, a correction procedure was used to remove the TEP generated by the control stimulus from the TEP generated by the test stimulus. This was achieved via 'time-shifting' the TEP generated by the test stimulus alone to coincide with the control stimulus, which was subtracted from the paired-pulse data. The corrected paired-pulse TEP was then compared to the single-pulse generated TEP.

The primary dependent variable is N100, identified as the maximum negative TEP peak between 70 – 145 ms. Several secondary dependent variables were identified from other TEP components of P30, N45 and P180. These were the maximum positive peaks between 20 – 30 ms (P30), 50 – 70 ms (P60) and 160 – 270 ms (P180) and the maximum negative peaks between 40 – 60 ms (N45) (Opie et al., 2018). TEPs were taken from known electrodes over motor regions of interest on both left and right hemispheres – left hemisphere: C1, C3, FC1, FC3; right hemisphere C2, C4, FC2, FC4. TEP amplitude was calculated from the largest positive peak minus the largest negative peak from 25 – 300 ms following the test stimulus (Opie et al., 2018). Paired-pulse TEP amplitude was subsequently expressed as a percentage of single-pulse TEP amplitude (Opie et al., 2017; Opie et al., 2018; Rogasch et al., 2013; Rogasch et al., 2015). The equations used to determine the positive LICI peaks and negative LICI peaks are presented below:

LICI Positive Peaks = ((PeakSingle - PeakPaired) / (TEPMax - TEPMin)) X 100

Equation 1.

LICI Negative Peaks = ((PeakSingle - PeakPaired) / (TEPMin - TEPMax)) X 100

Equation 2.

Asymmetry Ratios. Right hand performance was expressed as a ratio of left hand performance: ratios greater than one indicated that the right hand performed better than the left hand and ratios less than one indicated that the right hand performed worse than the left hand. Asymmetry ratios between the corrected LICI TEP components of the left and right hemisphere were also calculated, with left hemisphere TEP components expressed as a ratio of right hemisphere TEP components. Ratios more than one indicated more LICI in the dominant left hemisphere than non-dominant right hemisphere and ratios less than one indicated more LICI in the non-dominant right hemisphere than the dominant left hemisphere.

Statistical Analyses

Two-tailed paired samples *t*-tests were used to determine if there were any statistically significant differences between the performance of participants left and right hands in the Purdue Pegboard peg insertion task. A two-tailed paired samples *t*-test was used to test for differences between the RMT of the left hemisphere and the right hemisphere.

The TMS-EEG data of two participants was removed from analysis as it contained too much 50Hz interference from the main power supply. However, their Purdue Pegboard and RMT data were retained for *t*-test analysis. These data were excluded from further correlational analyses.

Paired-samples *t*-tests were run between the global mean field amplitudes of the single-pulse and sham stimulation conditions in order to test for global hemispheric differences between the two conditions. Separate *t*-tests were performed on the data for left and right hemispheres.

To test for differences between the single-pulse and sham stimulation, within-subjects repeated measures ANOVAs were performed on the single-pulse and sham stimulation data with factors of Condition (2 levels: single-pulse and sham) and Component (5 levels: N100, N45, P30, P60, P180). Separate ANOVAs were performed on the data for left and right hemispheres. Conditional on a significant main effect of interaction, post-hoc paired t-tests were conducted on the data from the single-pulse and sham stimulation.

To test for hemispheric asymmetries of all components of single-pulse stimulation, a within-subjects repeated measures ANOVA was conducted on the single-pulse data of the left and right hemispheres with factors of Hemisphere (2 levels: left hemisphere and right hemisphere) and Component (5 levels: N100, N45, P30, P60, P180).

A within subjects repeated measures ANOVA was performed on the normalised LICI TEP data with factors Hemisphere (2 levels: left hemisphere and right hemisphere) and Component (5 levels: N100, N45, P30, P60, P180) in order to test for hemispheric asymmetries of all components of paired-pulse stimulation

Pearson correlations were performed between corrected LICI TEP component data from both hemispheres and Purdue Pegboard data from both hands to test for associations between TEPs and fine motor control. Specifically, corrected LICI TEP data from the dominant left hemisphere were correlated with Purdue Pegboard data

from the dominant right hand and corrected LICI TEP data from the non-dominant right hemisphere were correlated with the non-dominant left hand.

In order to test for any associations between asymmetry of the Purdue Pegboard task and asymmetry of the corrected TEP data, Pearson correlations were performed between the asymmetry ratios of each TEP component and the asymmetry ratio of the Purdue Pegboard task.

Results

Fine Motor Control Results

Figure 2 shows participant performance on the Purdue Pegboard peg placement task. The right hand showed a higher number of pegs placed than the left hand; however, this trend did not reach statistical significance based on the results of a two-tailed paired samples *t*-test (t (13) = 1.81, p = 0.09, two-tailed, d = 0.48). The assumptions of normality and normality of difference were not violated based on the Shapiro-Wilk test of normality and inspection of the stem-and-leaf plots of the data.

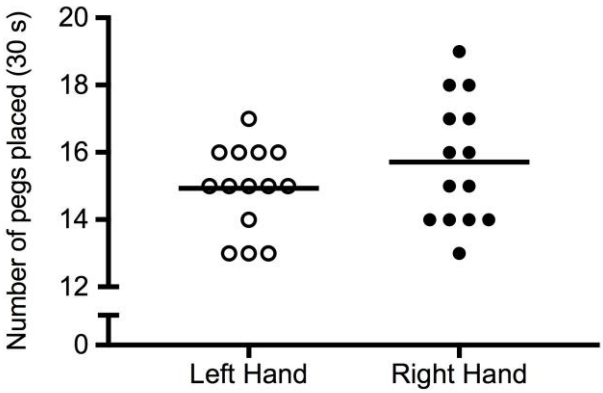

Figure 2. Column scatterplot showing performance of left and right hands on the Purdue Pegboard peg insertion task. Each symbol is representative of data from individual participants and the lines through the data are representative of the group mean.

Resting motor threshold

Figure 3 shows RMT from both hemispheres. RMT was similar in the non-dominant right hemisphere and dominant left hemisphere based on the results of a paired-samples *t*-test (t (13) = 2.00, p = 0.07, two-tailed, d = 0.54). The assumptions of normality and normality of difference were not violated based on the Shapiro-Wilk test of normality and inspection of the stem-and-leaf plots of the data.

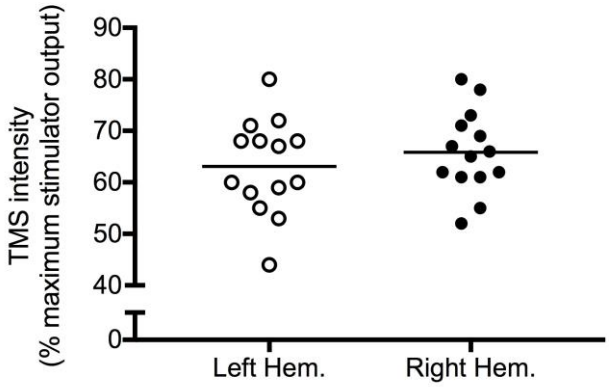

Figure 3. Comparison of resting motor thresholds between left and right hemispheres expressed as a percentage of maximum stimulator output. Each symbol is representative of data from individual participants and the lines through the data are representative of the group mean.

Global Mean Field Amplitude

The left hemisphere global mean field amplitude TEPs from single-pulse and sham stimulation exhibited a larger global mean field amplitude from single-pulse stimulation than sham stimulation. Descriptive statistics showed that the single-pulse stimulation exhibited a larger mean and standard deviation (M = 341.72, SD = 171.55) of global mean field amplitude scores than the sham condition (M = 223.39, SD = 84.76). A paired-samples *t*-test showed that the difference between the single-pulse and sham stimulation was significant (t (11) = -3.25, p = 0.01, two-tailed, d = 0.94) and Cohen's d is indicative of a large effect (Cohen, 1992). The assumptions of normality

and normality of difference were not violated based on the Shapiro-Wilk test of normality and inspection of the stem-and-leaf plots of the data.

The right hemisphere global mean field amplitude TEPs from single-pulse and sham stimulation exhibited a larger global mean field amplitude from single-pulse stimulation than sham stimulation. Descriptive statistics showed that the single-pulse stimulation exhibited a lager mean and standard deviation (M = 429.80, SD = 276.89) of global mean field amplitude than the sham stimulation (M = 229.97, SD = 93.52). A paired-samples t-test showed that the difference between the single-pulse and sham stimulation was significant (t (11) = -2.89, p = 0.02, two-tailed, d = 0.84), with the large Cohen's d indicative of a large effect (Cohen, 1992). The assumptions of normality and normality of difference were not violated based on the Shapiro-Wilk test of normality and inspection of the stem-and-leaf plots of the data.

TEPs

Two-way within-subjects repeated measures ANOVAs were calculated using single-pulse; sham; and corrected paired-pulse TEP data from the left and right hemispheres. Mauchly's Test of Sphericity was violated across all ANOVAs, so the more conservative Huynh Feldt correction was applied to all ANOVA calculations. The Bonferroni correction was used to adjust for multiple comparisons across all ANOVAs. Some ANOVAs demonstrated violations of normality, however ANOVAs are robust even to large violations of data and as such were considered to be appropriate for use in this context (Blanca, Alarcón, Arnau, Bono & Bendayan, 2017)

Single-pulse versus sham stimulation. The single-pulse and sham stimulation of the left hemisphere showed similar responses between the two conditions. Descriptive statistics showed only small mean differences between single-pulse and sham condition TEP components (see Table 1). The results of a two-way within-

subjects ANOVA of the single-pulse versus sham stimulation TEP components showed no main effect of condition (F (1, 11) = 0.08, p = 0.78, η_p^2 = 0.01), a significant main effect of component (F (2.06, 22.64) = 19.19, p = 0.00, η_p^2 = 0.64), and a significant interaction between component and condition (F (3.67, 40.35) = 4.30, p = 0.01, η_p^2 = 0.28). Stem-and-leaf plots and the Shapiro-Wilk test indicated that the assumption of normality was violated. F_{max} was 5.04 for the sham stimulation data and 4.21 for the single-pulse data, demonstrating homogeneity of variances.

Table 1

Means (SD) for single-pulse and sham stimulation TEP component amplitudes from left (LH) and right hemispheres (RH)

	Single-pulse LH	Sham LH	Single-pulse RH	Sham RH
N100	-2.53 (2.12)	-1.59 (1.00)	-3.41 (3.97)	-1.50 (0.99)
P30	1.15 (1.55)	0.08 (0.60)	0.65 (1.11)	0.34 (0.45)
N45	-0.86 (1.51)	-0.13 (0.67)	-0.36 (1.20)	-0.02 (0.49)
P60	-0.06 (1.17)	0.16 (1.02)	0.39 (1.70)	0.30 (0.52)
P180	2.90 (2.40)	1.81 (1.34)	2.53 (1.89)	1.44 (0.92)

Post-hoc paired samples t-tests were used to investigate the condition by component interaction. Significant positive differences, indicating larger single-pulse components compared to sham in the left hemisphere were found in P30: t (11) = 2.21, p = 0.05, two-tailed, d = 0.64; and P180 t (11) = 2.75, p = 0.02, two-tailed, d = 0.79.

There were no significant differences between N100, N45 and P60 between sham and single pulse conditions (all t (11) = < 2.10, all p = > 0.05).

The single-pulse and sham stimulation of the right hemisphere showed similar responses for the two conditions. Descriptive statistics showed only small mean differences between single-pulse and sham condition TEP components (see Table 1). The results of the two-way within subjects ANOVA of the single-pulse versus sham stimulation TEP components of the right hemisphere showed no effect of condition (F (1, 11) = 0.70, p = 0.42, η_p^2 = 0.06), a main effect of component (F (2.203, 24.23) = 16.50, p = 0.00, η_p^2 = 0.60) and no condition by component interaction (F (1.48, 16.26) = 2.79, p = 0.10, η_p^2 = 0.20). Shapiro Wilk statistics and stem-and-leaf plots indicated a violation of the assumption of normality. F_{max} was 4.90 for the sham condition TEPs, indicating homogeneity of variance for these data. Homogeneity of variance was violated for the single-pulse condition, exhibiting an F_{max} of 12.81.

Left hemisphere versus right hemisphere single-pulse TEPs. *Figure 4* shows the single-pulse TEPs for the left and right hemispheres, which demonstrate similar responses for both hemispheres. Descriptive statistics show only small differences between the means and standard deviations of the single-pulse data from the left and right hemispheres (see Table 1). The two-way within-subjects ANOVA testing for differences between the single-pulse TEP components of the left and right hemispheres found a main effect of component (F (2.51, 27.58) = 24.49, p = 0.00, η_p^2 = 0.69), no main effect of hemisphere (F (1, 11) = 0.63, p = 0.45, η_p^2 = 0.05) and no interaction of hemisphere and component (F (2.29, 25.13) = 0.41, p = 0.70, η_p^2 = 0.04). The assumption of normality was shown to be violated by Shapiro-Wilk statistics and stem-and-leaf plots. Homogeneity of variance was satisfied in the data from the dominant left

hemisphere (F_{max} = 4.21) and violated in the non-dominant right hemisphere (F_{max} = 12.70).

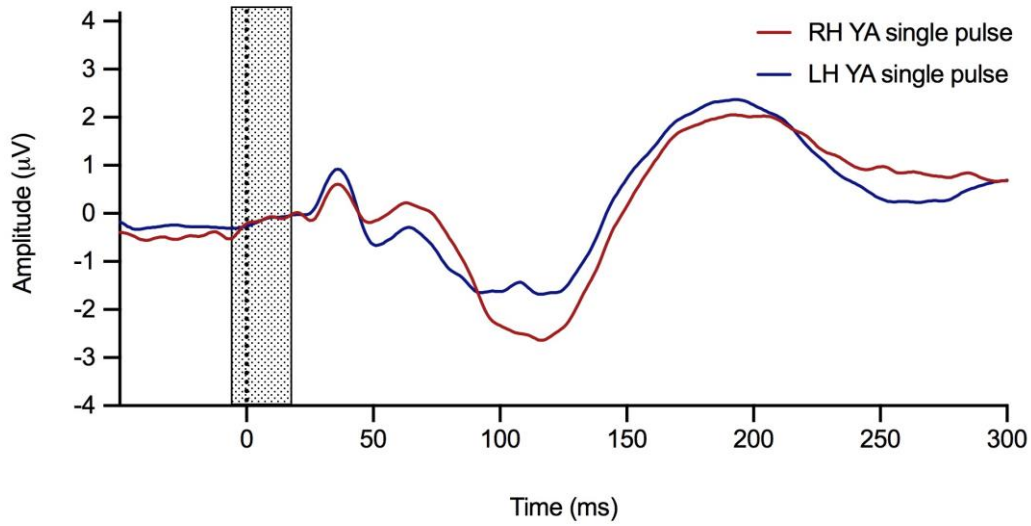

Figure 4. Single-pulse TEPs for left (blue line) and right hemispheres (red line). The shaded area represents the area the TMS artefact was removed from.

Corrected paired-pulse TEPs. The corrected paired-pulse LICI TEPs did not exhibit any statistically significant asymmetries between the left and right hemisphere. Descriptive statistics (see Table 2 below) showed moderate mean differences between the corrected LICI TEP amplitudes. Standard deviations were large, however, indicating a great deal of variation in the data. The two-way within subjects ANOVA testing for hemispheric differences in paired-pulse LICI TEP components between the left and right hemispheres found no significant main effects of hemisphere (F (1, 11) = 1.44, p = 0.26, η_p^2 = 0.12) or component (F (2.17, 23.85) = 2.46, p = 0.18, η_p^2 = 0.18) and no significant interaction between hemisphere and component factors (F (2.06, 22.64) = 1.62, p = 0.22, η_p^2 = 0.13). Boxplots, Shapiro-Wilk statistics, z-skew and z-kurtosis scores indicated large violations of the assumption of normality. F_{max} was 3.07 for the

left hemisphere and 30.76 for the right hemisphere, indicating homogeneity of variances in the left hemisphere and violated homogeneity of variance in the right hemisphere.

Table 2

Means (SD) for corrected LICI TEP component amplitudes of the left and right hemispheres.

	Left hemisphere	Right hemisphere
N100	2.00 (22.92)	-40.85 (112.31)
P30	6.72 (34.62)	-36.52 (105.07)
N45	-12.00 (30.92)	14.48 (62.06)
P60	3.08 (25.72)	20.47 (57.80)
P180	31.86 (19.76)	27.32 (20.25)

No Associations Between LICI and Fine Motor Control

Correlations between corrected LICI TEP components and Purdue Pegboard data. An outlier was removed from the left hemisphere P60 data before correlation as it skewed otherwise non-significant data to a significant result. *Figure 5* below demonstrates the relationships between the corrected LICI TEP component data of the dominant left hemisphere with the Purdue Pegboard data from the dominant right hand, and the corrected LICI TEP components of the non-dominant right hemisphere with the non-dominant left hand. The Pearson correlations conducted to test for significant associations between the dominant left hemisphere LICI TEP components and dominant right hand Purdue Pegboard performance showed no significant correlations between the component and Purdue Pegboard data of the N100 (r (10) =

0.21, p = 0.51); N45 (r (10) = 0.06, p = 0.86); P30 (r (10) = -0.06, p = 0.86); P60 (r (10) = -0.07, p = 0.84); and P180 (r (10) = 0.56, p = 0.06).

Pearson correlations conducted to test for significant associations between the non-dominant right hemisphere LICI TEP components and non-dominant left hand Purdue Pegboard performance showed no significant correlations between the components and Purdue Pegboard data: N100 (r (10) = -0.4, p = 0.20); N45 (r (10) = 0.10, p = 0.75); P30 (r (10) = -0.26, p = 0.41); P60 (r (10) = 0.19, p = 0.55); P180 (r (10) = 0.30, p = 0.34).

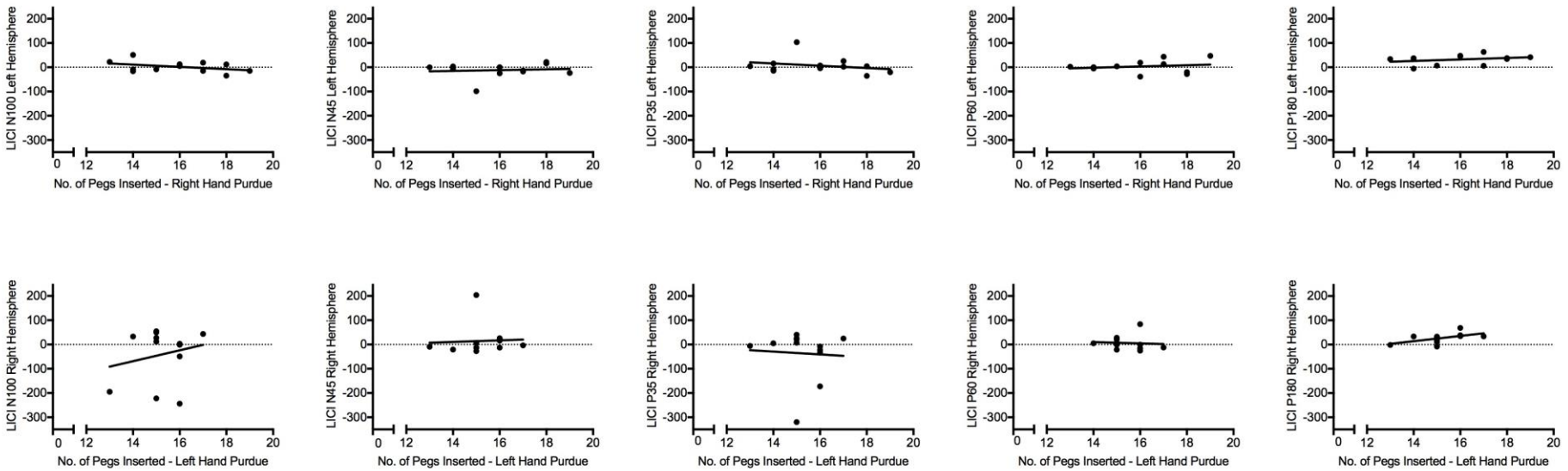

Figure 5. Associations between corrected LICI TEP components N100, N45, P30, P60, and P180. The top row depicts correlations of corrected LICI TEP components of the left hemisphere and Purdue Pegboard results from the right hand. The bottom row depicts correlations of corrected LICI TEP components of the right hemisphere and Purdue Pegboard results from the left hand.

Asymmetry ratios. An outlier was removed from the left hemisphere P60 data before correlation as it skewed otherwise non-significant data to a significant result. *Figure 6* below depicts the associations between the asymmetry ratios of the results of the left and right handed performance on the Purdue Pegboard task and the asymmetry ratios of each individual component of the corrected LICI TEP data. The five Pearson correlations conducted on this data to examine associations between each LICI TEP component asymmetry ratio and Purdue Pegboard performance asymmetries. All correlations demonstrated negligible non-significant associations accounting for less than ten percent of shared variance between the asymmetry ratios of each TEP component and the Purdue Pegboard asymmetry ratios: N100: r (10) = -0.19, p = 0.55, R^2 = 0.04; N45: r (10)= 0.07, p = 0.82, R^2 = 0.01; P30: r (10) = 7.662e-005, p = 1.0, R^2 = 5.87e-009; P60: r (10) = -0.26, p = 0.43, R^2 = 0.07; P180: r (10) = 0.05, p = 0.88, R^2 = 0.00.

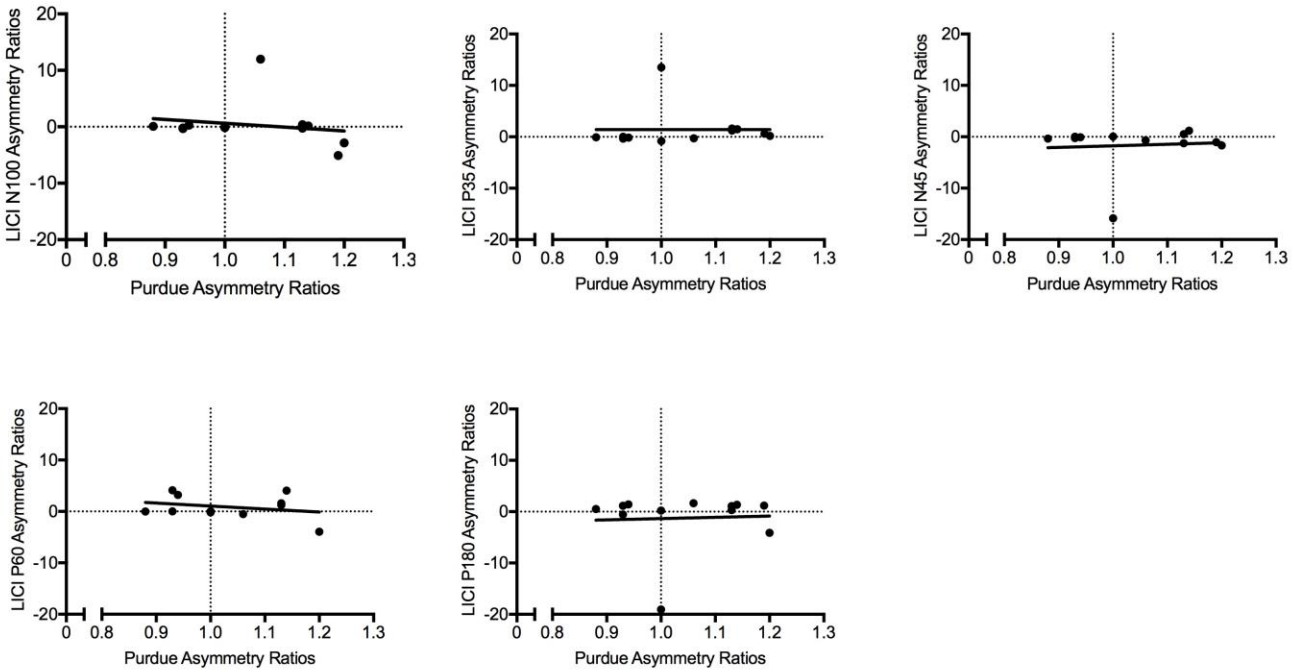

Figure 6. Associations between asymmetry ratios of the corrected TEP components P30, N45, P60, N100 and P180 between hemispheres and asymmetry ratios of Purdue Pegboard performance between hands. *X-axis*: Ratios > 1 indicate superior dominant right hand performance (compared to the non-dominant left) and ratios <1 indicate superior non-dominant left hand performance (compared to the dominant). *Y-axis*: Ratios > 0 indicate greater asymmetry in the dominant left hemisphere (compared to the non-dominant right) and ratios < 0 indicate greater asymmetry in the non-dominant right hemisphere (compared to the dominant left).

Discussion

The current study aimed to determine if long-acting cortical inhibition measured by TMS-EEG is asymmetric. It was hypothesised that the LICI TEP results would show more inhibition in the dominant than non-dominant hemisphere. There were four main findings of the current study. First, the Purdue Pegboard fine motor control data did not show any asymmetries of performance between the left and right hands. Second, there was no difference between the data of the sham and single-pulse conditions. Third, neither single-pulse TEP or corrected paired-pulse LICI TEP data showed hemispheric asymmetries of inhibition. Fourth, there were no significant associations between fine motor control and long-acting inhibition.

No Asymmetries in Fine Motor Control

The results of the Purdue Pegboard task showed a numerical difference in favour of the dominant right hand placing more pegs than the non-dominant left hand. However, this difference did not show a statistically significant asymmetry between the fine motor control of the left and right hands (see *Figure 2*). This non-significant result is inconsistent with the findings of previous studies, which demonstrated a significant functional asymmetry in which the dominant right hand was better at placing pegs than the non-dominant left hand (Brouwer, Sale & Nordstrom, 2001; Garry, Kamen & Nordstrom, 2003; Noguchi, Demura, Nagasawa & Uchiyama, 2006; Vallence et al., 2017). The Vallence et al. (2017) study had a higher median and range of Edinburgh Handedness Inventory laterality quotient scores (minimum score = 75; median = 100) than the present study (minimum score = 60; median = 85). This increased laterality quotient may underlie the lack of asymmetry found in the current study, as there is evidence showing statistically significant associations between fine motor task performance on the Purdue Pegboard and EHI score (Annett, 1985; Brouwer, Sale, &

Nordstrom, 2001). Brouwer et al. (2001) found that people who demonstrate a more overt degree of handedness on the EHI show more asymmetries of motor performance and score higher on the Purdue Pegboard task than those with a less overt degree of EHI determined handedness (Annett, 1985; Brouwer et al., 2001). It is pertinent to note, however, that the initial norms of the Purdue Pegboard task did not show any statistically significant differences of left and right handed performance in the peg insertion task (Tiffin & Asher, 1948), though their sample may also have been less overtly right handed as they used very large numbers of participants. The original Purdue Pegboard norms do not measure the handedness of their participants (Tiffin & Asher, 1948), which makes it difficult to compare the data from this study to them in a meaningful way.

A second potential explanation for the lack of statistically significant differences between the left and right hand fine motor function on the Purdue Pegboard is that the Purdue Pegboard task is not a sensitive measure of asymmetries of fine motor control between the left and right hands. Though in some previous research the Purdue Pegboard has been shown to be sufficiently sensitive to measure differences in hand performance (Brouwer, Sale & Nordstrom, 2001; Garry, Kamen & Nordstrom, 2003; Noguchi, Demura, Nagasawa & Uchiyama, 2006; Vallence et al., 2017), there is substantial evidence that each hand serves a different functional purpose and that as such the dominant hand is movement-based and the non-dominant hand is used in a stabilising role (Duff & Sainburg, 2007; Hammond, 2002; Mutha, Haaland & Sainburg, 2013; Sainburg, 2005). This kind of asymmetry is not measured by the Purdue Pegboard, which tests both hands exactly the same way (Tiffin & Asher, 1948; Vallence et al., 2017). A recent study by Woytowicz et al. (2018) found evidence of functional differences of handedness using a new stabilising and reaching test. Specifically, using

a brace that immobilised the upper arms and restricting the movement of the upper body, participants held a spring in both hands, stabilising it with one hand and simultaneously conducting a reaching motion with the other. The study found that the left hand of right handed participants demonstrated superior stabilising capabilities compared to the right hand and the right hand showed straighter reaching and movement than the left hand (Woytowicz et al., 2018). Such measures may provide a more accurate way than the Purdue Pegboard task of measuring fine motor control and asymmetries of handedness. Further research in using these techniques should be used to further explore the lack to of association between asymmetries of the Purdue Pegboard task and asymmetries of corrected LICI TEPs.

No Difference Between Single-Pulse and Sham TEPs

The global mean field amplitude of single-pulse stimulation was significantly larger than the global mean field amplitude of sham stimulation between the left and right hemispheres, which suggests that the single-pulse stimulation had a larger neural contribution than the sham stimulation. Given that single-pulse stimulation elicited similar global mean field amplitudes in both the left and right hemispheres, it is unlikely that any differences in the single-pulse TEPs are due to differences of general excitability between the hemispheres. As this was the first study to measure TEPs following the stimulation of M1 in both hemispheres, this finding is a novel one and should be explored further in relation to hemispheric asymmetries of general excitability.

Despite greater global cortical excitability in the single-pulse than sham stimulation conditions in both the left and right hemispheres measured by global mean field amplitude, there were a number of TEP components that showed no difference between single-pulse and sham stimulation. ANOVAs showed significant differences

between only two components of the dominant left hemisphere TEPs: the P30 and the P180, which were larger in the single-pulse condition than the sham condition. There were no significant differences between paired-pulse and sham TEP components of the non-dominant right hemisphere. This result was unexpected, as it was hypothesised that single-pulse stimulation would have a larger TEP amplitude than sham stimulation. This non-significant difference between the sham and single-pulse stimulation means that it is not possible to be sure that the N45, P60 and N100 single-pulse components are not the product of TMS artefacts in the data.

TMS-EEG data is vulnerable to several kinds of artefacts, including auditory and somatosensory evoked potentials from the click of the TMS coil, electrode movement, activity in cranial muscles, TMS pulse decay, and eye movements (ter Braack et al., 2015; Conde et al., 2018; Ilmoniemi & Kičić, 2010; Nikulin et al., 2003, Rogasch et al., 2014). Several measures were used throughout the experiment to minimise the likelihood of such artefacts and all TEP data was processed using band-pass filtering and ICA to remove known artefacts (Rogasch et al., 2014). It is important to note, however, that TMS-EEG is an emerging field of research and protocols to minimise, identify and remove artefacts from the EEG data and protocols are continually being improved upon. Given that there are no differences between the sham and single-pulse conditions, it is possible that the data are contaminated by unknown artefacts that were not removed.

Artefacts from the TMS click are particularly hard to suppress, as both auditory and somatosensory processes are engaged (Conde et al., 2018). Throughout this experiment, participants wore headphones playing white noise in order to minimise the auditory evoked potentials (Massimini et al., 2005), as TEP components such as P60 and N100 are known to be influenced by sound (ter Braack et al., 2015; Komssi et al.,

2004). However, it is only possible to turn up the sound of the white noise to a level that participants are comfortable listening to, which means that complete suppression is not always possible (Conde et al., 2018). Even with consistent white noise loud enough to cover the majority of sound from the TMS click being administered, auditory evoked potentials can be evoked reliably by very short noise stimulation gaps. Because of this, small modulations of sound such as the ongoing presence and then absence of sound from the TMS click may still evoke auditory evoked potentials (Conde et al., 2018). This may create larger than expected artefacts in the data and influence individual TEP components (ter Braack et al., 2015; Komssi et al., 2004).

Even with suppression of the auditory component of the TMS click, some sound will still be conducted through the bones of the skull and there will be somatosensory responses to the sensation of TMS on the scalp (ter Braack et al., 2015; Conde et al., 2018; Ilmoniemi & Kičić, 2010). These responses can be suppressed to an extent via the use of foam padding on the TMS coil to attenuate the somatosensory evoked potentials, but recent research has shown that this is an imperfect method of artefact suppression (Conde et al., 2018). Therefore, whilst this is a method that should be employed in future studies to minimise somatosensory artefacts, future research should also include a sham condition that measures any remaining artefact.

The use of a sham TMS condition in a TMS-EEG study allows non-transcranial aspects of TMS-EEG to be measured and thus removed from the TEPs generated in the test conditions (Gordon, Desideri, Belardinelli, Zrenner & Ziemann, 2018; Ilmoniemi & Kičić, 2010). This study used a commonly employed sham condition (Rogasch et al., 2013) in which the coil was held perpendicular to the scalp with the wing touching the head, preserving the TMS click but removing stimulation and the majority of somatosensory stimulation (Conde et al., 2018; Rogasch et al., 2013). Given the fact

that it is not currently possible to completely suppress somatosensory artefacts from the TMS click (Ilmoniemi & Kičić, 2010), this kind of sham stimulation may be too different to normal TMS stimulation to reliably indicate artefacts that must be removed from the data (Conde et al., 2018). This is supported by the fact that there were no significant differences between the sham and single-pulse stimulation data, particularly those components such as N100 which are sensitive to auditory evoked potentials (ter Braack et al., 2015). Because of this, it is recommended that future research should incorporate a realistic sham condition that matches with the test condition as realistically as possible in order to generate a realistic comparison between the two conditions.

No Hemispheric Asymmetries of Single- or Paired-Pulse TEPs

The latency and amplitude of the single-pulse TEP components in this experiment were similar to those found in previous research (Rogasch et al., 2013; Vallence et al., 2017). Based on the results of research by Hammond and Garvey (2006) and Vallence et al. (2017) it was hypothesised that the dominant left hemisphere would exhibit greater single-pulse TEP amplitude than the non-dominant right hemisphere, indicating more inhibition. However, this was the first study to investigate whether or not there are hemispheric differences in single-pulse TEPs and results showed that there were no statistically significant differences between the two hemispheres both overall and at any of the individual TEP components.

The N100 component of MEPs and TEPs has been related to $GABA_B$ modulated long-acting inhibition (Farzan et al., 2013; Rogasch et al., 2013). In single-pulse paradigms N100 larger in amplitude when more inhibition is present and in paired-pulse paradigms N100 decreases in amplitude when more inhibition is present (Rogasch et al., 2014). The slope of the N100 after a conditioning pulse in LICI research shows a

significant relationship between increased N100 slope and an increase in size of the corresponding MEP, which is thought to reflect increased inhibition (Hammond & Garvey, 2006; Rogasch et al., 2013). As MEPs are measures of corticospinal output, it is possible that large increases in MEP amplitude after TMS stimulation are indicative of spikes in spinal output reacting to the stimulation. If this is the case, hemispheric differences between single-pulse MEPs that have been observed in previous studies (Hammond & Garvey, 2006; Vallence et al., 2017) may not be observable using TEPs because they do not measure spinal output.

Keeping in mind the possible spinal input to previously found asymmetries of single-pulse MEPs, it is possible that the P30, N45, P60 and P180 TEP components showed no hemispheric differences because the processes that they represent are cortical in nature. The P30 and P180 TEP components are thought to be related to general global mechanisms of excitation in the cortex in reaction to the TMS pulse (Komssi et al., 2004; Premoli, Castelanos et al., 2014; Rogasch et al., 2013). A lack of hemispheric asymmetry of these components suggests that on a global level, the cortex does not react differently to stimulation of each hemisphere.

The N45 component is thought to be related to short-acting inhibition, known as the paired-pulse protocol short-interval intracortical inhibition (SICI; Sanger et al., 2001). When a conditioning stimulus is delivered at a very short ISI (1 – 6 ms) before a test stimulus and the response to the test stimulus is inhibited then SICI is engaged. This short-acting inhibition has been associated with $GABA_A$ related inhibition, as SICI is enhanced by a known $GABA_A$ agonist and inhibited by a known $GABA_A$ antagonist (Premoli, Castelanos et al., 2014; Premoli et al., 2018). SICI is known to be asymmetric between the left and right hemispheres, with an enhanced presence in the dominant left hemisphere (Hammond et al., 2004). As the N45 component is thought to be related to

$GABA_A$, it is possible that there were no differences between the single-pulse components of the left and right hemisphere because there were no asymmetries of $GABA_A$ inhibition evoked by single-pulse TEPs in this experiment.

The component P60 is not well understood, but there is evidence to show that it may be related to short-acting inhibition (Cash et al., 2017) or auditory stimuli (ter Braack et al., 2015). If P60 is related to short-acting inhibition, which is modulated by $GABA_A$ (Hammond et al., 2004), then it may show similar characteristics to the N45 component and it is possible that there were no asymmetries of P60 in this experiment because there may have been no asymmetries of $GABA_A$ evoked in this study. If P60 has an auditory component, however, it is possible that there were no differences between the two hemispheres because of auditory evoked potentials in the data (Conde et al., 2018; ter Braack et al., 2015).

The ANOVA conducted between the normalised paired-pulse LICI TEP data from both hemispheres showed that there were no significant differences in any of the TEP components between the hemispheres. This non-significant difference does not support the hypothesis that the dominant left hemisphere would exhibit greater inhibition than the non-dominant right hemisphere elicited from paired-pulse stimulation. This was unexpected based on previous findings by Vallence et al. (2017) and Hammond and Garvey (2006), which found stronger LICI in the dominant hemisphere than the non-dominant hemisphere. A possible explanation for this is that the current study used RMT for both control stimulus and test stimulus intensities because RMT has shown to be sufficient to elicit a TEP and in order to minimise TMS artefacts in the EEG data (Premoli, Rivolta, et al., 2014).

Whilst there are studies available investigating the role of different test stimulus intensities and how this affects LICI (Opie & Semmler, 2014), much less is known

about the effect of different intensities of control stimulus intensity on LICI, particularly in the context of TMS-EEG and TEPs. In the Vallence et al. (2017) TMS study of LICI asymmetry, asymmetries of LICI at the 100ms ISI were found to occur at control stimulus intensities as low as 100% RMT in the dominant left hemisphere than the non-dominant right hemisphere. LICI also increased across both hemispheres as control stimulus intensity increased. Studies have shown that clear TMS responses can be evoked by single-pulse stimulations at as little as 60% of RMT (Komssi et al., 2004) and that LICI is increased at test stimulus intensities 110 % of RMT of compared to RMTs over 130%, with a control stimulus of 120% RMT (Opie & Semmler, 2014). Considering this evidence, it appears that control stimulus RMTs reflect test stimulus RMTs in that the lower the intensity the more likely large levels of LICI are likely to be evoked. However, given that the threshold needed to elicit RMT in this study was higher than that shown in other paired-pulse research (Farzan et al., 2013; Opie et al., 2017; Opie et al., 2018; Premoli, Castellanos, et al., 2014; Premoli, Rivolta et al., 2014; Rogasch et al., 2013) and that this is the first study examining hemispheric asymmetries of LICI using TEPs, there are two explanations for our results. First, the control stimulus intensity used was too high to elicit reliable LICI and thus needs to be lowered to below 100% RMT for future studies. Second, due to the distance from the head that the TMS coil had to be held because of the height of the EEG electrodes and the dispersion of the TMS pulse this may have caused (Hallett, 2007), the control stimulus RMT may not have been high enough to elicit LICI reliably.

There is also a possibility that the test stimulus intensity used in this study may not have been strong enough to evoke hemispheric asymmetries of LICI. This is supported by the fact that Hammond and Garvey (2006) used 110% RMT MSO for their test stimulus and Vallence et al. (2017) used 120%. This approach to the test

stimulus is also evidenced in a number of TMS-EEG studies examining LICI, none of which used a TS intensity of less than 105% of RMT (Opie et al., 2017; Rogasch et al., 2013; Rogasch et al., 2014; Rogasch et al., 2015). Research has shown that RMT is a sufficient level of stimulation to elicit TEPs (Premoli, Rivolta, et al., 2014), therefore it was expected that this intensity would also be sufficient to observe TEP inhibition. It was also not possible to test different control and test stimulus intensities as a part of the current research because of the large number of trials needed for each condition on each hemisphere and due to the paired-pulse correction procedure used. Future research should investigate these possibilities further using combinations of varied control stimulus intensities paired with the same test stimulus intensities as well as control stimulus intensities paired with a number of test stimulus intensities to determine if control or test stimulus intensity is a factor affecting whether or not asymmetries of LICI are exhibited.

No Relationship Between LICI TEPs and Fine Motor Control

Correlations. Correlations between LICI TEP components of each hemisphere and results of the Purdue Pegboard task for the corresponding contralateral hand showed no significant associations between long-acting inhibition and fine motor control. There are several explanations for this lack of association. Firstly, the process of long-acting $GABA_B$ mediated inhibition is not the only process that is used in fine motor control. Other inhibitory processes such as SICI (Sanger et al., 2001) or excitatory processes such as neural facilitation (Kujirai et al., 1993) may also be important for fine motor control and may play a bigger role than LICI, hence the lack of association.

Another explanation for the lack of association between LICI and fine motor control is that the Purdue Pegboard task is not sensitive enough to pick up distinct

differences of functioning between the two hands (Hammond, 2002; Sainburg, 2005; Tiffin & Asher, 1948). Because of this, further exploration of the results would be unable to accurately compare the associations between this data and other associated TEP data. Since hand functions are distinct from one another (Duff & Sainburg, 2007; Hammond, 2002; Mutha et al., 2013; Sainburg, 2005), it is reasonable to surmise that there may also be different neural substrates of handedness as well. In this case, the formerly mentioned test employed by Woytowicz et al. (2018) might be a better test to compare hemispheric data to in order to determine if there are associations with fine motor control and long-acting inhibition. As discussed above, there is a possibility that there are artefacts that have not been identified in this data (Gordon et al., 2017). This may be another reason for no associations between LICI and fine motor control, as the data may be skewed by auditory and somatosensory artefacts.

Asymmetry ratios. Correlations of asymmetry ratios of the Purdue Pegboard and the asymmetry ratios of corrected LICI TEP components did not show a significant association, which suggests that asymmetries of LICI may be unrelated to asymmetries of fine motor control. This is consistent with Vallence et al.'s (2017) study in which significant asymmetries were documented in both the Purdue Pegboard task and in LICI between the hemispheres but no relationship was found between the two. This lack of association could also be attributed to the Purdue Pegboard task, which, as previously noted, is sensitive enough to detect asymmetries in hand function (Brouwer et al., 2001), but does not consider the differing roles of each hand (Hammond, 2002; Sainburg, 2005; Tiffin & Asher, 1948). Given the possible lack of sensitivity of the Purdue Pegboard task for measuring the stabilising and reaching asymmetries of handedness, further research should investigate the correlates of a different measure of handedness with TMS-EEG. As such, this provides further incentive to investigate

alternative measures of asymmetry of fine motor control to determine if asymmetries of LICI and fine motor control are related or not.

Limitations and Future Research

The EEG data were collected with HydroCel sensor nets, which have not been used to measure TEPs in TMS-EEG literature previously. Whilst the nets provided advantages of ease of use and application and a large number of electrodes, the height of the electrodes was approximately 1cm above the head, which meant that the TMS coil was a minimum of 1cm from the scalp, as the coil had to be held over the electrodes of the net. This meant that the electromagnetic pulse had to travel further to stimulate the cortex and may have dispersed over a wider area, making it less effective than TMS applied directly from the scalp as the intensity of TMS stimulation varies as a function of distance (Hallett, 2007). This distance from the skull also meant that overall mean RMT levels were higher than those of previous TMS-EEG studies that used EEG caps with electrodes closer to the scalp (Farzan et al., 2013; Opie et al., 2017; Opie et al., 2018; Premoli, Castellanos, et al., 2014; Premoli, Rivolta et al., 2014; Rogasch et al., 2013). High RMTs also mean that the noise and physiological intensity of the TMS pulse would increase the risk of auditory and somatosensory evoked artefacts in the data (ter Braack et al., 2015; Conde et al., 2018). In light of this, future research should replicate this study using electrodes more commonly used in TMS-EEG studies (Hammond & Garvey, 2006; Rogasch et al., 2013; Vallence et al., 2017) that allow the TMS coil to be closer to the skull to determine if the higher RMT required in this study was a confounding factor.

Measuring participant RMT before and after the EEG cap is placed on the head in future research may provide further insight into how different EEG electrodes influence participants' RMT levels (Farzan et al., 2013). It may also give some

indication of which participants are most likely to exhibit high RMT once the TMS cap has been placed on their head. Given that it is advisable to keep stimulus levels as low as possible to avoid large cortical muscle response artefacts (Ilmoniemi & Kičić, 2010), being able to explore the possibility of charting how high the RMT of a participant is likely to increase dependent on the electrode type may be valuable for future research.

Only 36% of the participant population of this study was male, therefore it is important to note the gender imbalance in this study. Given that there is evidence to suggest that the menstrual cycle can be a confound to TMS studies due to its effect on cortical excitability (Smith, et al., 1999), it would be worthwhile to do further research with comparable samples of men and women.

One of the benefits of TMS-EEG is that it provides information from a number of electrodes, not just those of the region of interest. Further research using TMS-EEG to investigate asymmetries of LICI should investigate cortical responses to TMS from a wide range of electrodes in order better understand how long-acting inhibition works in a wider cortical area. This may be particularly useful for further understanding of TEP components such as P60, which has unclear functioning (ter Braack et al., 2015; Cash et al., 2017); and P180 which is thought to be related to wider cortical responses (Komssi et al., 2004; Premoli, Castelanos et al., 2014).

Conclusion

This study aimed to determine if long- acting inhibition is asymmetric in young adults using TMS-EEG. Based on previous results from TMS literature (Hammond & Garvey, 2006; Vallence et al., 2017) it was expected that the dominant left hemisphere would demonstrate more LICI than the non-dominant right hemisphere; however, the results of the study did not reflect this. There were four main findings. First, fine motor control between the hands was not asymmetrical. Second, single-pulse TMS stimulation

did not display a statistically larger TEP amplitude than sham stimulation. Third, the dominant hemisphere did not show greater inhibition than the non-dominant hemisphere after single-pulse stimulation or, crucially, after paired-pulse stimulation. Fourth, there were no associations between long-acting inhibition and fine motor control. Though replication of previous asymmetries were not achieved due to several factors, the results of this study are inconclusive as to whether asymmetries of LICI can be replicated using TMS-EEG. Future studies should replicate this research using different EEG equipment and more realistic sham conditions and further research should be conducted using different control stimulus and test stimulus intensities to determine baseline control and test stimuli for eliciting LICI asymmetries in TMS and TMS-EEG studies. Further investigation of the importance of LICI as a neural underpinning of handedness is important to better understanding the workings of handedness and fine motor control.

References

Annett, M. (1985). *Left, Right, Hand and Brain: the right shift theory*. London: Lawrence Erlbaum Associates.

Aoki, T., Rivlis, G., & Scheiber, M. H. (2016). Handedness and index finger movements performed on a small touchscreen. *Journal of Neurophysiology, 115*, 858-867. doi: 10.1152/jn.00256.2015

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*(8437), 1106-1107.

Blanca, M. J., Alarcón, R., Arnau, J., Bono, R., & Bendayan, R. (2017). Non-normal data: Is ANOVA still a valid option? *Psicothema, 29*(4), 552-557. doi: 10.7334/psicothema2016.383

ter Braack, E. M., de Vos, C. C., van Putten, M. J. A. M. (2015). Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. *Brain Topography, 28*, 520-528. doi: 10.1007/s10548-013-0312-z

Brouwer, B., Sale, M. V., & Nordstrom, M. A. (2001). Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance. Experimental Brain Research, 138, 467-476. doi: 10.1007/s002210100730

Buccolieri, A., Abbruzzese, G., & Rothwell, J. C. (2004). Relaxation from a voluntary contraction is preceded by increased excitability of motor cortical inhibitory circuits. *Journal of Physiology, 558*(2), 685-695. doi:10.1113/jphysiol.2004.064774

Cash, R. F. H., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T. K., … Blumberger, D. M. (2017). Characterization of glutamatergic and $GABA_A$-mediated neurotransmission in motor and dorsolateral prefrontal cortex using

paired-pulse TMS-EEG. *Neuropsychopharmacology*, *42*, 502-511. doi: 10.1101/337782

Cirillo, J. & Byblow, W. D. (2016). Threshold tracking primary motor cortex inhibition: the influence of current direction. *European Journal of Neuroscience*, *44*, 2614-2621. doi: 10.1111/ejn.13369

Civardi, C., Cavalli, A., Naldi, P., Varrasi, C., & Cantello, R. (2000). Hemispheric asymmetries of cortico-cortical connections in human hand motor areas. *Clinical Neurophysiology*, *111*, 624-629. doi: 10.1016/S1388-2457(99)00301-6

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*, 155-159. doi: 10.1037/003-2909.112.1.115

Conde, V., Tomasevic, L., Akopian, I., Stanek, K., Saturnino, G. B., Thielscher, A., … Siebner, H. R. (2018). The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. *bioRxiv*. doi:10.1101/337782

Dassonville, P., Z, X.-H., Uğurbil, K., Kim, S.-G., & Ashe, J. (1997). Functional activation in motor cortex reflects the direction and the degree of handedness. *Proceedings of the National Academy of Sciences in the United States of America*, *94*(25), 14015-14018. Retrieved from https://www.jstor.org/stable/43851

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9-21. doi:10.1016/j.jneumeth.2003.10.009

Di Lazzaro, V., Ziemann, U., & Lemon, R. N. (2008). State of the art: Physiology of transcranial motor cortex stimulation. *Brain Stimulation*, *1*(4), 345-362. doi: 10.1016/j.brs.2008.07.004

Duff, S. V., & Sainburg, R. L. (2007). Lateralization of motor adaptation reveals independence in control of trajectory and steady-state position. *Experimental Brain Research*, *179*(4), 551-561. doi: 10.1007/s00221-006-0811-1

Farzan, F., Barr, M. S., Hoppenbrouwers, S. S., Fitzgerald, P. B., Chen, R., Pascual-Leone, A., & Daskalakis, Z. J. (2013). The EEG correlates of the TMS-induced EMG silent period in humans. *NeruoImage*, *83*, 120-134. doi: 10.1016/j.neuroimage.2013.06.059

Garry, M. I., Kamen, G., & Nordstrom, M. A. (2003). Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. *Journal of Neurophysiology*, *91*, 1570-1578. doi: 10.1152/jn.00595.2003

Gordon, P. C., Desideri, D., Belardinelli, P., Zrenner, C., & Ziemann, U. (2018). Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. *Brain Stimulation*. doi: 10.1016/j.brs.2018.08.003

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron*, *55*, 187-199. doi: 10.1016/j.neuron.2007.06.026

Hammond, G., Faulkner, D., Byrnes, M., Mastaglia, F., & Thickbroom, G. (2004). Transcranial magnetic stimulation reveals asymmetrical efficacy of intracortical circuits in primary motor cortex. *Experimental Brain Research*, *155*, 19-23. doi: 10.1007/s00221-003-1696-x

Hammond, G. R., & Garvey, C.-A. (2006). Asymmetries of long-latency intracortical inhibition in motor cortex and handedness. *Experimental Brain Research, 172*, 449-453. doi: 10/1007/s00221-006-0349-2

Hammond, G.R., & Vallence, A.-M. (2007). Modulation of long-interval intracortical inhibition and the silent period by voluntary contraction. *Brain Research, 1158*, 63-70. doi: 10.1016/j.brainres.2007.05.2017

Hernandez-Pavon, J. C., Metsomaa, J., Mutanen, T., Stenroos, M., Mäki, H., Ilmoniemi, R. J., & Sarvas, J. (2012). Uncovering neural independent components from highly artifactual TMS-evoked EEG data. *Journal of Neuroscience Methods, 209*(1), 144-157. doi:10.1016/j.jneumeth.2012.05.029

Ilmoniemi, R. J. & Kičić, D. (2010). Methodology for combined TMS & EEG. *Brain Topography*, *22*, 233-248. doi: 10.1007/s10548-009-0123-4

Komssi, S., Kähkönen, S., & Ilmoniemi, R. J. (2004). The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. *Human Brain Mapping, 21*(3), 154-164. doi:10.1002/hbm.10159

Kouchtir-Devanne, N., Capaday, C., Cassim, F., Derambure, P., & Devanne, H. (2012). Task-dependent changes of motor cortical network excitability during precision grip compared to isolated finger contraction. *Journal of Neurophysiology, 107*, 1522-1529. doi: 10.1152/jn.00786.2011

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., … Marsden, C. D. (1993). Corticocortical inhibition in human motor cortex. *Journal of Physiology, 471*, 501-519. doi: 10.1113/jphysiol.1993.sp019912

Levine, M., & Ensom, M. H. (2001). Post hoc power analysis: An idea whose time has passed? *Pharmacotherapy, 21*(4), 405-409. doi:10.1592/phco.21.5.405.34503

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science, 309*(5744), 2228-2232. doi:10.1126/science.1117256

McNeil, C. J., Martin, P. G., Gandevia, S. C., Taylor, J. L. (2011). Long-interval intracortical inhibition in a human hand muscle. *Experimental Brain Research, 209*, 287-297. doi: 10.1007/s00221-011-2552-z

Mutha, P. K., Haaland, K. Y., & Sainburg, R. L. (2013). Rethinking motor lateralization: specialized but complementary mechanisms for motor control of each arm. *PLoS ONE, 8*(3), e58582. doi: 10.1371/journal.pone.0058582

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699. doi: 10.1111/j.1532- 5415.2005.53221.x

Nikulin, V. V., Kičić, D., Kähkönen, S., & Ilmoniemi, R. J. (2003). Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *European Journal of Neuroscience, 18*(5), 1206-1212. doi: 10.1046/j.1460-9568.2003.02858.x

Noguchi, T., Demura, S., Nagasawa, Y., & Uchiyama, M. (2006). An examination of practice and laterality effects on the Purdue Pegboard and moving beans with tweezers. *Perceptual and Motor Skills, 102*(1), 265-274. doi: 10.2466/pms.102.1.265-274

O'Keefe, D. J. (2007). Brief report: Post hoc power, observed power, A priori power, retrospective power, prospective power, achieved power: Sorting out appropriate uses of statistical power analyses. *Communication Methods and Measures, 1*(4), 291-299. doi:10.1080/19312450701641375

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113. doi: 10.1016/0028- 3932(71)90067-4

Opie, G. M., Rogasch, N. C., Goldsworthy, M. R., Ridding, M. C., & Semmler, J. C. (2017). Investigating TMS-EEG indices of long-interval intracortical inhibition at different interstimulus intervals. *Brain Stimulation*, *10*, 65-74. doi: 10.1016/j.brs.2016.08.004

Opie, G. M. & Semmler, J. G. (2014). Modulation of short- and long-interval intracortical inhibition with increasing motor evoked potential amplitude in a human hand muscle. *Clinical Neurophysiology, 125*, 1440-1450. doi: 10.1016/j.clinph.2013.11.015

Opie, G. M., Sidhu, S. K., Rogasch, N. C., Ridding, M. C., & Semmler, J. G. (2018). Cortical inhibition assessed using paired-pulse TMS-EEG is increased in older adults. *Brain Stimulation, 11*(3), 545-557. doi:10.1016/j.brs.2017.12.013

Premoli, I, Castellanos, N., Rivolta, D., Belardinelli, P., Bajo, R., Zipser, C., … & Ziemann, U. (2014). TMS-EEG signatures of GABAergic neurotransmission in the human cortex. *Journal of Neuroscience*, *34*(16), 5603-5612. doi: 10.1523/JNEUROSCI.5089-13.2014

Premoli, I., Király, J., Müller-Dahlhaus, F., Zipser, C. M., Rossini, P., Zrenner, C., … Belardinelli, P. (2018). Short-interval and long-interval intracortical inhibition of TMS-evoked EEG potentials. *Brain Stimulation*. doi: 10.1016/j.brs.2018.03.008

Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., & Müller-Dahlhaus, F. (2014). Characterization of GAGAB-receptor mediated

neurotransmission in the human cortex by paired pulse TMS-EEG. *NeuroImage, 103*, 152-162. doi: 10.1016/j.neuroimage.2014.09.028

Raw, R. K., Kountouriotis, G. K., Mon-Williams, M., & Wilkie, R. M. (2012). Movement control in older adults: does old age mean middle of the road? *Journal of Experimental Psychology Human Perception Performance, 38*, 735-745. doi: 10.1037/a0026568

Ridding, M. C., Taylor, J. L., & Rothwell, J. C. (1995). The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. *Journal of Physiology, 487*(2), 541-548. doi: 10.1113/jphysiol.1995.sp020898

Rogasch, N. C., Daskalakis, Z. J., & Fitzgerald, P. B. (2013). Mechanisms underlying long-interval cortical inhibition in the human motor cortex: a TMS-EEG study. *Journal of Neurophysiology, 109*, 89-98. doi: 10.1152/jn.00762.2012

Rogasch, N. C., Daskalakis, Z.J., & Fitzgerald, P.B. (2015). Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: a TMS-EEG study. *Cortex, 64*, 68-77. doi: 10.1016/j.cortex.2014.10.003

Rogasch, N. C., Sullivan, C., Thomson, R. H., Rose, N. S., Bailey, N. W., Fitzgerald, P. B., . . . Hernandez-Pavon, J. C. (2017). Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. *Neuroimage, 147*, 934-951. doi:10.1016/j.neuroimage.2016.10.031

Rogasch, N. C., Thomson, R. H., Farzan, F., Fitzgibbon, B. M., Bailey, N. W., Hernandez-Pavon, J. C., . . . & Fitzgerald, P. B. (2014). Removing artefacts from TMS-EEG recordings using independent component analysis: Importance

for assessing prefrontal and motor cortex network properties. *Neuroimage, 101*, 425-439. doi:10.1016/j.neuroimage.2014.07.037

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: an update. *Clinical Neurophysiology, 122*, 1686. doi: 10.1016/j.clinph.2010.12.037

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A.; Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120,* 2008-2039. doi: 10.1016/j.clinph.2009.08.016

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . & Ziemann, U. (2015). 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 IFCN Committee. *Clinical Neurophysiology, 126*(6), 1071-1107. doi: 10.1016/j.clinph.2015.02.001

Sainburg, R. L. (2005). Handedness: differential specializations for control of trajectory and position. *Exercise and Sport Sciences Reviews*, *33*(4), 206-213. doi: 10.1097/00003677-200510000-00010

Sanger, T. D., Garg, R. R., & Chen, R. (2001). Interactions between two different inhibitory systems in the human motor cortex. *Journal of Physiology*, *530*(2), 307-317. doi: 10.111/j.1469-7793.2001.0307I.x

Scheiber, M. C. (2001). Constraints on somatotopic organization in the primary motor cortex. *Journal of Neurophysiology*, *86*(5), 2125-2143. doi: 10.1152/jn.2001.86.5.2125

Sinclair, C. & Hammond, G. R. (2007). Reduced intracortical inhibition during the foreperiod of a warned reaction time task. *Experimental Brain Research*, *186*(3), 385-392. doi: 10.1007/s00221-007-1241-4

Smith, M. J., Keel, B. D., Greenberg, L. F., Adams, P. J., Schmidt, D. A., Rubinow, E. M., & Wassermann, E. M. (1999). Menstrual cycle effects on cortical excitability. *Neurology*, *53*(9), 2069-2072. doi: 10.1212/WNL.53.9.2069

Tiffin, J. & Asher, E. (1948). The Purdue Pegboard: norms and studies of reliability and validity. *Journal of Applied Psychology*, *32*(3), 234-247. doi: 10.1037/h0061266

Vallence, A. -M., Schneider, L. A., Pitcher, J. B., & Ridding, M. C. (2014). Long-interval facilitation and inhibition are differentially affected by conditioning stimulus intensity over different time courses. *Neuroscience Letters*, *570*, 114-118. doi: 10.1016/j.neulet.2014.03.060

Vallence, A. -M., Smalley, E., Drummond, P. D., & Hammond, G. R. (2017). Long-interval intracortical inhibition is asymmetric in young but not older adults. *Journal of Neurophysiology*, *118*, 1581-1590. doi: 10.1152/jn.00794.2016

Valls-Solé, J., Pascual-Leone, A., Wassermann, E. M., & Hallett, M. (1992). Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalography and Clinical Neurophysiology*, *85*(6), 355-364. doi: 10.1016/0168-5597(92)90048-G

Wassermann, E. M., Samii, A. Mercuri, B., Ikoma, K., Oddo, D., Grill, S. E., & Hallett, M. (1996). Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. *Experimental Brain Research*, *109*, 158-163. doi: 10.1007/BF00228638

Yamanaka, K., Kadota, H., & Nozaki, D. (2013). Long-latency TMS-evoked potentials during motor execution and inhibition. *Frontiers in Human Neuroscience, 7*, 751. doi: 10.3389/fnhum.2013.00751

Zoghi, M., Pearce, S. L., & Nordstrom, M. A. (2003). Differential modulation of intracortical inhibition in human motor cortex during selective activation of an intrinsic hand muscle. *Journal of Physiology, 550*(3), 933-946. doi: 10.1113/jphysiol.2003.042606