Investigating Age-Related Changes in Motor Cortex Excitability Underlying Fine Motor Control

Brittany Rurak

Murdoch University

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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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Brittany Kelsey-Rey Rurak

24/10/16
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Abstract
There is an age-related decline in fine motor control. Functional changes in the primary motor cortex may help explain the age-related decline in fine motor control. Both facilitatory and inhibitory processes in the motor cortex are important for the execution of movement. The aims of the current study were to systematically and comprehensively investigate age-related changes in motor cortical facilitation and inhibition and to investigate the role of these processes in fine motor control. In healthy younger ($n = 26$) and older adults ($n = 21$), fine motor control was measured using the Purdue pegboard and a unimanual circle task. Paired-pulse transcranial magnetic stimulation (TMS) was used to measure short-interval intracortical facilitation (SICF) and short-interval intracortical inhibition (SICI) acting on an intrinsic hand muscle (important for fine motor control). Results show no difference in SICF between younger and older adults. When SICI was measured using TMS parameters corresponding to high levels of SICF, older adults showed less SICI than younger adults. When SICI was measured using TMS parameters corresponding to low levels of SICF, there was no difference in SICI between younger and older adults. Older adults showed a relationship between SICI and fine motor control, suggesting greater SICI results in better performance on fine motor control tests. Together findings suggest a complex interaction between the balance of facilitation and inhibition, and that this is affected by age and influences fine motor control.

Keywords: aging, fine motor control, primary motor cortex, transcranial magnetic stimulation, short-interval intracortical facilitation, short-interval intracortical inhibition
Investigating Age-Related Changes in Motor Cortex Excitability Underlying Fine Motor Control

Older adults are gradually becoming a larger cohort of the general population and will represent ~16% of the world’s population by 2050 (Baudisch, 2015; Christensen, Doblhammer, Rau, & Vaupel, 2009). Aging is accompanied by a decrease in motor control, which include coordination difficulties, slowing of movement, and difficulty with balance, when compared to younger adults (Burke & Barnes, 2006; Ranganathan, Siemionow, Sahgal, & Yue, 2001; Sale & Semmler, 2005; Sterr & Dean, 2008). Age-related decline in motor control is particularly pronounced in hand performance (Dolcos, Rice, & Cabeza, 2002; Francis & Spirduso, 2000). The human hand’s intrinsic ability to finely manipulate objects with speed and accuracy is instrumental in achieving daily life tasks, such as using cutlery, buttoning shirts, and tying shoes (Causby, Reed, McDonnell, & Hillier, 2014; Lee & Tsang, 2001). The ability to finely manipulate objects is defined as fine motor control and involves the coordination of hand muscles to produce precise movements, such as grasping, manipulating objects between the thumb and finger, lifting, and producing force (Vieluf, 2012; Wang, Bohannon, Kapellusch, Garg, & Gershon, 2015). Older adults consistently show a decline in fine motor control, supported by slower performance and accuracy than younger adults on performance measures such as finger tapping (Mattay et al., 2002), card reaching (Doyen & Carlier, 2002), and the Purdue pegboard (Clark, Loftus, & Hammond, 2011; Marneweck, Loftus, & Hammond, 2011). Subsequently, age-related loss of manual dexterity has important ramifications for older adult’s quality of life and for their independence to complete daily living tasks. Additionally, given that older adults are living longer, this means they may also need to stay in the workforce longer,
which often requires fine motor control (e.g., receptionist, surgeons, machine works). Therefore, it is important to investigate the causes of the age-related decline in fine motor control.

Growing evidences shows that there are structural and functional changes in the healthy aging brain, such as a decrease in grey matter (Cabeza, 2002) and white matter (Salat et al., 2005), which may have a role in the decline of fine motor control (Krampe, 2002; Mattay et al., 2002; Ward & Frackowiak, 2003). The primary motor cortex (M1) in particular undergoes changes with advancing age, which may also underlie the age-related decline in fine motor control (Badawy, Loetscher, Macdonell, & Brodtmann, 2012). The M1 provides an orderly representation of the body mapped on its surface and controls all muscles of the body (Raz & Rodrigue, 2006). Additionally, the M1 contains the majority of corticospinal outputs to muscles. The corticospinal tract is one of the largest descending tracts which is a pathway from the M1, down to the spinal cord, to the muscle. Therefore, the M1 is responsible and important for the execution of movement, including fine motor control (Muellbacher et al., 2002; Reis et al., 2008).

Advances in functional neuroimaging techniques have greatly contributed to understanding age-related changes in the M1 and the role of these changes in fine motor control (Seidler et al., 2010; Spreng, Wojtowicz, & Grady, 2010). Functional imagining shows conflicting findings when investigating the relationship between the M1 and motor performance in older compared to younger adults, which show: older adults have greater activation in the M1 than younger adults (Calautti, Serrati, & Baron, 2001; Eyler, Sherzai, Kaup, & Jeste, 2011), older adults have less activation in the M1 than younger adults (Hutchinson et al., 2002), and there are no differences between older and younger adults in the M1 (Daselaar, 2003). These
findings suggest that healthy aging may have different cortical changes impacting fine motor control. Nevertheless, the discrepancy in findings may be attributed to age-related changes in inhibitory and facilitatory processes in the M1, which imagining studies are unable to measure. Hence, while imaging studies are important to showing altered functional activity during movements in older adults, the nature of this activation (inhibitory and facilitatory processes) cannot be determined from imagining. Investigating inhibitory and facilitatory processes (i.e., excitability of M1), may underlie the age-related decline in fine motor control.

Inhibitory and facilitatory processes are largely influenced by the major neurotransmitters gamma-aminobutyric acid (GABA) and glutamate (Chen, 2004; Stagg, 2014). Several lines of evidence suggest both inhibition and facilitation in the M1 are contributing factors to the progressive decline of fine motor control relative to normal aging (Kaiser, Schuff, Cashdollar, & Weiner, 2005; Seidler et al., 2010). Facilitation and inhibition are thought to shape motor output by exciting relevant excitatory output cells and blocking irrelevant excitatory output cells (Zoghi, Pearce, & Nordstrom, 2003). Hence, the excitability of M1 requires a complex balance between facilitation and inhibition to initiate effective neuronal processing and cortical motor output (Calautti et al., 2001; Chen, 2004). Abnormal levels of facilitation and/or inhibition is demonstrated in various neurological impairments ascribing movement dysfunctions, such as Parkinson’s disease and focal hand dystonia (Lefaucheur, 2005; Zeuner, 2005). Therefore, it is important to investigate the balance of facilitation and inhibition in healthy older adults. A neurophysiological procedure called transcranial magnetic stimulation, can be used to measure the excitability of M1, as it preferentially measures inhibitory and facilitatory processes by employing different stimulation parameters.
**Transcranial Magnetic Stimulation**

Transcranial magnetic stimulation (TMS) can be used to measure the excitability of facilitatory and inhibitory processes in M1 (Chen, 2004). TMS is a non-invasive, non-painful technique used to stimulate the human cortex (Rossini, Rossini, & Ferreri, 2010). A high voltage current is discharged through an insulated wound coil, which induces a rapidly changing magnetic field perpendicular to the plane of the coil (Hallett, 2007). This magnetic field passes through the scalp and the skull with little attenuation and induces a flow of electrical current in the underlying tissue (Rossini et al., 2010). If a single TMS pulse is delivered to the hand area of the M1, this results in excitation of intracortical interneurons (Roth, Amir, Levkovitz, & Zangen, 2007). This activation of intracortical interneurons elicits action potentials along the corticospinal tract, resulting in activation in the contralateral hand muscle. The activation in the hand muscle results in a muscle twitch, known as a motor evoked potential (MEP; Di Lazzaro et al., 2004). MEP elicited by single-pulse TMS (a pulse sufficient in intensity to elicit a MEP) provides a measure of corticospinal excitability, that is, a measure of excitability of the pathway from M1 (i.e., point of stimulation) to the muscle from which the MEP was recorded (Pell, Roth, & Zangen, 2011). TMS can also be used to measure the excitability of specific inhibitory and facilitatory circuitries acting within the M1, that is to say, intracortical inhibition and intracortical facilitation, respectively. Paired-pulse TMS releases two distinct stimuli with varying short inter-stimulus interval between (ISI; i.e., time interval), which measures intracortical circuitries mediating motor output, including fine motor control.

**Short-interval Intracortical Facilitation**

To measure intracortical facilitation using paired-pulse TMS, a first TMS pulse (stimulus 1; S1) precedes a second TMS pulse (stimulus 2; S2) by 1.3-4.5 ms
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(Figure 1). S1 is delivered at a suprathreshold intensity, which is an intensity sufficient to elicit an MEP when delivered alone. S2 is delivered at a subthreshold intensity, which is not sufficient in eliciting a MEP when delivered alone. The MEP elicited by this paired-pulse protocol is greater than the MEP elicited by S1-alone (i.e., by a single suprathreshold TMS pulse). The greater MEP elicited by paired-than single-pulse TMS is due to the preferential activation of intracortical facilitatory circuits by the paired stimuli (Kujirai et al., 1993). This activation is known as short-interval intracortical facilitation (SICF). When a range of different ISIs are applied (i.e., the interval between S1 and S2), a SICF recruitment profile can be made, which shows three prominent peaks for facilitation (Figure 2); the first peak (Peak 1) and strongest occurring at ISI of 1.1-1.7ms, the second at peak two (Peak 2) 2.3-2.9ms, and the third at peak three (Peak 3) 4.1-4.5ms (Ziemann, Rothwell, & Ridding, 1996). SICF is thought to be mediated by glutamate, however, pharmacological research shows GABA also plays a role in mediating SICF (Paulus et al., 2008; Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998). Intracortical facilitation modulates M1 output during the preparation of a manual grasp and is particularly important for movements requiring fine motor control (Cattaneo et al., 2005).
Figure 1. Stimulus one (S1) represents a single-pulse trial which shows the motor evoked potential (MEP; peak-to-peak amplitude) following the pulse (top panel). S1 paired with stimulus two (S2) represents a paired-pulse trial, which shows the short-interval intracortical facilitation MEP (peak-to-peak amplitude; bottom panel). In between S1 and S2 is the inter-stimulus interval.
Figure 2. Short-interval intracortical facilitation (SICF) profile showing three prominent peaks of facilitation and two troughs where minimal facilitation occurs at marked inter-stimulus intervals (ms). The strongest facilitation occurs at Peak 1, followed by Peak 2, then Peak 3. SICF ratio is quantified as the ratio of the mean paired-pulse MEP amplitude to the mean single-pulse MEP amplitude. Ratios greater than 1.0 indicate the presence of facilitation.

Intracortical Inhibition

To measure intracortical inhibition using paired-pulse TMS, the first TMS pulse is a subthreshold conditioning stimulus (CS), which precedes a suprathreshold test stimulus (TS) by 2-3 ms (Figure 3; Kujirai et al., 1993). The MEP elicited by this paired-pulse protocol is smaller than the MEP elicited by the TS-alone (i.e., by a single suprathreshold TMS pulse). The smaller MEP elicited by paired- than single-pulse TMS is due to the preferential activation of intracortical inhibitory circuits. This activation is known as short-interval intracortical inhibition (SICI). Pharmacological studies provide strong evidence that SICI is mediated by GABAergic inhibition, which is the major inhibitory neurotransmitter in the human M1 (Ilic et al., 2002; Kujirai et al., 1993; Ziemann, Lonnecker, Steinhoff, & Paulus, 1996). Intracortical inhibition modulates M1 output during execution of movement
and is particularly important for movements requiring fine motor control (Seidler et al., 2010).

**Figure 3.** Test stimulus (TS) represents a single-pulse trial which shows the motor evoked potential (MEP; peak-to-peak amplitude) following the pulse (top panel). Conditioning stimulus (CS) represents a paired-pulse trial, which shows the short-interval intracortical inhibition MEP (peak-to-peak amplitude; bottom panel). In between CS and TS is the inter-stimulus interval.

**Age-related Changes in Facilitation and Inhibition**

There is a large body of literature investigating age-related changes in intracortical inhibition; only more recent investigations have investigated age-related changes in intracortical facilitation. Many studies have used paired-pulse TMS to measure SICI in younger and older adults. A recent meta-analysis investigating age-related changes in SICI showed findings are inconsistent: some show SICI is reduced in older adults compared to younger adults (Marneweck et al., 2011; Peinemann, Lehner, Conrad, & Siebner, 2001), some show SICI is increased in older adults compared to younger adults (McGinley, Hoffman, Russ, Thomas, & Clark,
2010; Smith, Sale, Higgins, Wittert, & Pitcher, 2011), and some show no significant
difference in SICI between older and younger adults (Oliviero et al., 2006; Rogasch,
Daskalakis, & Fitzgerald, 2015). Inconsistent SICI findings may be due to
methodological differences, such as small sample sizes and underrepresentation of
older adults, or, age-related changes in intracortical facilitation could affect measures
of SICI and explain the discrepancy in findings.

Two recent studies have highlighted age-related changes in intracortical
facilitation. First, Clark et al. (2011) investigated intracortical facilitation in the first
dorsal interosseous muscle (FDI; hand muscle important for fine motor control)
using a SICF evoking TMS protocol with three different ISIs (1.5, 2.5, and 4.5ms) in
younger and older adults. SICF at these ISIs were then correlated with fine motor
control in younger and older adults, using a Purdue pegboard test, which requires
participants to pick up small pegs and place them in holes as fast as they can. Clark
et al. (2011) demonstrated that older adults show increased SICF when compared to
younger adults at ISI of 1.5ms, which corresponds to Peak 1. This suggests the
excitability of intracortical facilitatory circuits in older adults is more excitable than
younger adults at Peak 1. There was a negative correlation between SICF at Peak 1
and performance on the Purdue pegboard test in younger and older adults, suggesting
reduced intracortical facilitation results in more pegs inserted. In contrast, younger
adults showed increased SICF compared to older adults when using ISI of 2.5ms,
which corresponds to Peak 2. This suggests the excitability of intracortical
facilitatory circuits in younger adults is more excitable than older adults at Peak 2.
There was a positive correlation between SICF at Peak 2 and performance on the
Purdue pegboard test in younger and older adults, suggesting greater intracortical
facilitation results in more pegs inserted. Younger and older adults showed no
difference in SICF when measured at ISI of 4.5ms, which corresponds to Peak 3. This suggests that the excitability of intracortical facilitatory circuits is similar in younger and older adults at this ISI. Collectively, Clark et al. (2011) demonstrate there are age-related changes in SICF that contribute to fine motor control. More specifically, Clark et al. (2011) demonstrate the importance of Peak 1 (older adults have greater SICF resulting in fewer pegs inserted) and Peak 2 (older adults have less SICF resulting in fewer pegs inserted) in fine motor control of older adults.

Second, Marneweck et al. (2011) investigated intracortical inhibition in the FDI using a SICI evoked TMS protocol in younger and older adults. SICI was then correlated with fine motor control in younger and older adults, using a Purdue pegboard test, which requires participants to pick up small pegs and place them in holes as fast as they can. Marneweck et al. (2011) demonstrated that older adults show reduced SICI when compared to younger adults. This suggests the excitability of intracortical inhibitory circuits in older adults is less excited than younger adults. There was a negative correlation between SICI and performance on the Purdue pegboard test in younger and older adults, suggesting greater intracortical inhibition results in more pegs inserted. Interestingly, this study found that some older adults show atypical facilitation, rather than inhibition, meaning older adults inhibitory processes were shifting to facilitatory processes. This atypical facilitation showed a negative relationship with performance on the Purdue pegboard test, suggesting increased atypical facilitation results in fewer pegs inserted. Collectively, this shows that older adults have a shift in the balance of intracortical inhibition and intracortical facilitation, in favor of facilitation, and this age-related change contributes to fine motor control in older adults.
In summary, there are marked age-related changes in intracortical properties which impact fine motor control. First, Clark et al. (2011) shows older adults have reduced SICF at Peak 2, resulting in poorer performance in fine motor control. This is an important finding, as other research suggests SICF2.5 shows the importance for the preparation of a manual grasp and is sensitive while preparing a grasp for smaller objects (e.g., a bar; Cattaneo et al., 2005; Parikh, Davare, McGurrin, & Santello, 2014). Second, Clark et al. (2011) and Marneweck et al. (2011) both show age-related changes in intracortical properties, in favor of facilitation, both resulting in poorer fine motor control in older adults. Clark et al (2011) showed older adults had greater facilitation in SICF at Peak 1, while Marneweck et al. (2011) showed older adults had reduced SICI and atypical facilitation. As previously mentioned, pharmacological studies suggest a relationship between SICF and GABA (i.e., inhibition; Paulus et al., 2008). Hence, greater facilitation in SICF may be contributing to the reduced SICI and atypical facilitation found in older adults; which may help explain the decline in fine motor control. In summary, it seems feasible to systematically examine SICF, SICI, and the influences of SICF on SICI, and the role of these intracortical properties in fine motor control of younger and older adults.

SICF and SICI are both short-acting intracortical processes that interact and both influence MEP amplitudes. Research suggests the excitability of SICF circuits contributes to measures of SICI (Ziemann, Rothwell, et al., 1996), and the balance between SICF and SICI can be examined by individualizing the ISI at which the paired-pulses are delivered (Peurala, Müller-Dahlhaus, Arai, & Ziemann, 2008). When a range of ISIs are applied, SICF shows a Peak 1, Trough 1, and Peak 2 (Figure 2). If SICI is measured using an ISI at which a SICF peak occurs, the contribution of SICF to the measure of SICI will be greater than if SICF is measured
at an ISI at which a SICF trough occurs. The later providing a more pure measure of SICI.

Given the importance of inhibition in the execution of fine motor control (Seidler et al., 2010), it is also important to comprehensively measure SICI. The majority of previous research used only a single CS intensity when measuring SICI in OA. SICI is affected by CS intensity and produces a u-shape curve when lower to increasingly higher intensities are applied. SICI increases with increasing CS intensities, reaching maximum SICI at moderate CS intensities, and then SICI decreases with further increases in CS intensity (Figure 4). This provides a measure of the sensitivity of SICI circuits, as the descending limb reflects the progressive recruitment of the inhibitory circuits that mediate SICI, while the ascending limb is thought to reflect SICF, as net inhibition shifts to facilitation.

Figure 4. Recruitment u-shape curve shows short-interval intracortical inhibition (SICI) at a range of condition stimuli (CS). U-shape demonstrates SICI increases with increasing CS, reaching max SICI at moderate CS intensities, and then SICI decreases with further increases in CS intensity. SICI ratio is quantified as the ratio of the mean paired-pulse MEP amplitude to the mean single-pulse MEP amplitude. Ratios less than 1.0 indicate the presence of inhibition.
Taken together, the aim of the current study was to systematically and comprehensively investigate age-related changes in SICF and SICI, and investigate the role of age-related changes in these processes with fine motor control. To address these aims, paired-pulse TMS was used to measure SICF at a range of ISIs to partially characterize the SICF function (i.e., Peak 1, trough, Peak 2) for all individuals. Paired-pulse TMS was then used to measure SICI using parameters that target Peak 1 and the Trough of each individual's SICF function. Furthermore, a range of CS intensities was used to obtain a comprehensive measure of SICI. The Purdue pegboard and a unimanual circle task were used to measure fine motor control. Five hypotheses resulted from these aims, which included:

1. Older adults will show greater SICF at Peak 1 than younger adults.
2. Older adults will show reduced SICF at Peak 2 than younger adults.
3. At moderate CS, older adults will show less SICI at the Peak than younger adults.
4. At moderate CS, there will be no differences in SICI at the Trough in younger and older groups.
5. Older adults SICF (Peak 1 and Peak 2) and SICI processes (Peak and Trough) will be associated with a decline in fine motor control.

**Methods**

**Participants**

Forty-seven right-handed participants, 26 younger adults ($M_{age} = 24.08$ years, $SD = 4.87$ years, age range: 18-35, 13 females) and 21 older adults ($M_{age} = 72.01$ years, $SD = 7.52$ years, age range: 61-86, 16 females) participated. Right-handed
individuals recruited to minimize heterogeneity; evidence suggests left-handed individuals tend to present atypical lateralization of brain functions (Buckingham & Carey, 2015; Cirillo, Rogasch, & Semmler, 2010).

**Sampling procedures.** Younger participants were undergraduate psychology students \( n = 14 \) recruited from Murdoch University, and people from the local community \( n = 12 \). Undergraduates received course credit for participation and others received a coffee and parking voucher for participation. Research predominately uses university samples, which regulates convenience sampling bias (Clark et al., 2011; Marneweck et al., 2011). Therefore, it was important to recruit from the local community so the sample could be more representative of the general population. Older adults were recruited from flyers posted in the local community (Appendix A) and from brief presentations illustrating the experiment; presentations conducted 2-3 times a week (for 2 months) at exercise classes. This may have created bias as all older adults that were recruited live an active lifestyle (see discussion). Older adults received a coffee and parking voucher for participation. The procedure for this study was approved by Murdoch University’s Human Research Ethics Committee (Appendix B), a project summary was made accessible to the public as per Ethics requirements (Appendix C), and informed written consent was obtained from all participants (Appendix D) after they acknowledged their understanding of the research (Appendix E).

**Sample size.** Small sample sizes have previously been used to investigate age-related changes in M1 and fine motor control (less than 27 participants), therefore, the intended sample size was 30 young and 30 older adults to increase generalizability (Bhandari et al., 2016). Seventy-three participants began the experiment but some were excluded (6 younger; 14 older) due to having a high
threshold (high thresholds may cause the participant discomfort; breaching an ethical principle of ‘do no harm’; American Psychological, 2002) or were unable to sustain total relaxation of the hand (voluntary movement interferes with MEP amplitudes).

A brief safety screening questionnaire was administered to exclude individuals who had any health conditions, such as existing neurological conditions or were taking drugs affecting the central nervous system (see Appendix F), as per the international guidelines for the safe use of TMS (Rossini et al., 2015). Participants who responded in the affirmative on any of these items were excluded from the study for safety purposes (2 younger; 4 older).

**Materials and Measures**

The 10-item Edinburgh Handedness Inventory (Appendix G; Oldfield, 1971), was used to measured handedness, measured as laterality quotient with scores ranging from -100 (extreme left-handedness) to +100 (extreme right-handedness). Participants with a laterality quotient below 70 were excluded (younger: $M = 90, SD = 15.29$; older: $M = 95, SD = 8.66$). Cognitive impairment was controlled for as it has been found to affect fine motor control (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2006); only older adults scoring within the normal range ($\geq 26$) on the Montreal Cognitive Assessment scale (Appendix H) were tested ($M = 28, SD = 1.58$; Nasreddine et al., 2005). Both the inventory and cognitive assessment provide good reliability and validity (Freitas, Prieto, Simoes, & Santana, 2014; Veale, 2014).

**Fine motor control measures.** Fine motor control was measured using two subtests of the Purdue pegboard (Lafayette Instrument Model 32020). First, participants were required to use their right hand to individually pick up pegs from a well and insert them in a vertical line of small holes within 30 seconds. The total number of pegs placed in the holes was scored. Second, participants were required
to use both hands to place and assemble 4-item objects within 60 seconds. A completed assembly comprises a pin, washer, collar, and a second washer, which expresses a point each. The total number of assemblies achieved within 60 seconds was scored. Using both hands activates both hemispheres in the brain (Mattay et al., 2002), which introduces a limitation to the current study as only the left hemisphere was measured. Nevertheless, the Purdue pegboard shows excellent reliability for participants aged over 60 years (Desrosiers, Hebert, Bravo, & Dutil, 1995).

Fine motor control was also measured using a unimanual circle tracing task on a digitizing tablet (WACOM Intuos 2 Graphic Tablet, Model No. XD-1212-U). Participants traced the outline of a circle (70-mm diameter) continuously for 10 seconds, completing this task four times. Participants were told to trace the outline as quickly and accurately as possible (Figure 5). Participants traced the circle in the counter-clockwise direction with the right hand (Carson, Thomas, Summers, Walters, & Semjen, 1997).
Figure 5. Data from two representative younger participants (top panels) and two representative older participants (bottom panels), showing their right-handed tracing of the circle (70-mm). Mean circularity (Circ), mean period (Per; s), X-diameter (X; mm), Y-diameter (Y; mm) and number of cycles of acceleration/deceleration (Ac/Dec) are shown for each trial.

Electromyographic recordings. Participants were seated comfortably in a height-adjustable chair with both their forearms rested on a cushion. Participants were advised to remain relaxed, silent, and awake during the procedure (corticospinal activity is increased during movement and talking, and decreased during sleep; Hallett, 2007). The FDI is a hand muscle important for object manipulation, precision grasping, and assists with the abduction of the index finger (Gilles & Wing, 2003). Electromyographic (EMG) activity was recorded from the FDI using Ag-AgCl surface electrodes taped over the belly and tendon of the FDI, with ground electrodes at the wrist and elbow. The EMG signal was amplified.
(1000x; CED 1902 amplifier), band pass filtered (10-1000Hz) and digitized at a sampling rate of 4kHz (CED 1401 interface).

**Transcranial magnetic stimulation.** Single-pulse and paired-pulse stimuli, produced by a Magstim 200 connected through a BiStim module to a figure-of-eight coil (70-mm diameter). The coil was tangentially placed over the left M1 with the handle positioned backward and rotated away from the midline by ~45°. This coil positioning induces a posterior-anterior current flow in the brain, which preferentially activates inhibitory and facilitatory interneurons (Di Lazzaro et al., 2004). Administering a suprathreshold TMS pulses over the cortical representation of the hand area of the left M1 elicits MEP from the FDI. The hotspot (optimal spot for eliciting MEP for the FDI) is located by conducting systematic movements (i.e., anterior-posterior plane movements, then lateral-medial plane movements). The hotspot is then marked with a washable marker on a custom-made snugly fitting cap to ensure reliable and accurate coil replacement. All TMS pulses were delivered at this hotspot.

**Pulse-characteristics.** Resting motor threshold (RMT) is the minimum stimulus intensity (as a percentage of machine stimulation output; %MSO) required to elicit MEPS of at least 50 uV in amplitude in at least 5 out of 10 consecutive trials. RMT represents corticospinal excitability and is determined by increasing and decreasing the intensity by 1% of machine output (Rossini et al., 2015). RMT is calculated as a percentage for the S2 and CS of the paired-pulse TMS protocols. One millivolt was determined as the stimulus intensity for S1 and TS of the paired-pulse TMS protocols, which evoked an average MEP of 1 mV in amplitude in at least 5 out of 10 consecutive trials in the resting FDI. Accurate determination of 1mV was important because S1-alone and TS-alone produce single-pulse MEPs...
which act as a baseline measure to compare to the mean paired-pulse MEP amplitude.

**Short-interval intracortical facilitation.** Paired-pulse TMS (two pulses) delivered S1 at 1mV preceded S2 at 90% RMT, by one of 10 pseudo-randomized ISI: 1.3, 1.5, 1.7, 1.9, 2.1, 2.3, 2.5, 2.7, 2.9, and 3.1ms. There was a total of 11 conditions: single-pulse TMS (S1-alone) and paired-pulse TMS at each of the 10 ISIs. Single and paired-pulse stimuli were delivered over five blocks. Each block comprised of 42 trials: 12 single-pulse (S1-alone) and three paired-pulse for each ISI. Order of stimulus delivery was pseudo-randomized. Each block took approximately 5 minutes. Total time for five blocks was approximately 25 minutes.

After the fifth SICF block, preliminary data analyses were performed to identify the paired-pulse parameters that elicited: (1) maximum facilitation (i.e., Peak 1), and (2) minimum facilitation (i.e., Trough). Mean MEP was calculated for single-pulses and each of the 10 paired-pulse conditions. Then, mean MEP for each paired-pulse conditions expressed as the ratio of the mean single-pulse MEP was calculated (i.e., SICF ratio). The largest ratio indicated maximum facilitation. The smallest ratio indicated minimum facilitation. The individually optimized ISI, at which the peak and trough occurred, were used for the SICI protocol, which will be defined as SICI_{Peak} and SICI_{Trough}. Time for calculations was approximately 10 minutes.

**Short-interval intracortical inhibition.** Paired-pulse TMS (two pulses) delivered CS at one of seven different stimuli preceded TS at 1 mV. Pseudo-randomized CS comprised: 50%, 60%, 70%, 80%, 90%, 100%, and 110%. The ISI was subjective to each participant’s optimal Peak 1 ISI and Trough ISI, as described
above. There was a total of eight conditions: single-pulse TMS (TS-alone) and paired-pulse TMS at each of the seven CS. Single and paired-pulse stimuli were delivered over four blocks with the Peak 1 ISI, and four blocks with the Trough ISI (total eight blocks). Each block comprised of 40 trials: 12 single-pulse (TS-alone) and four paired-pulse for each CS. Each block took approximately 4.5 minutes. Total time for eight blocks was approximately 35 minutes.

**Experimental Procedure**

Testing was conducted on the Murdoch University campus in a quiet room. Single sessions: 2 hours for younger adults and 2.5 hours for older adults. Older adult’s sessions were longer due to having an additional task (i.e., MoCA) and greater voluntary movement during TMS than younger adults. Greater voluntary movement during TMS required the application of additional trials to compensate for trials contaminated with voluntary movement. Order of administration: (1) Purdue pegboard, (2) unimanual circle task, (3) SICF, (4) SICI. This may have caused an order effect, because the behavioural tasks may have been demanding for some participants, resulting in fatigue during TMS protocol (fatigue reduces corticospinal activity; Hallett, 2007).

**Data Analysis**

EMG output was monitored throughout the experimental session for voluntary muscle activity. Each individual trial of EMG activity was visually inspected offline. Trials displaying EMG activity exceeding .50 mV within 100ms of the first pulse released in a paired-pulse TMS protocol were discarded as it indicates voluntary movement. Peak-to-peak amplitude was obtained from the 40 ms of EMG activity beginning 10 ms after the pulse was delivered. Means for single- and paired-pulses were calculated. Each participant’s mean paired-pulse
MEP amplitude was expressed as a ratio of their mean single-pulse MEP amplitude (i.e., SICF ratio and SICI ratio). The unimanual circularity task provided time and pen pressure on a digitizing tablet sampled at 100 Hz with a computer software. Accuracy, speed, and smoothness were calculated offline, using a custom-made analysis script (outlined in Faulkner, 2009). Prism Graphpad (version 7) was used to create graphs.

**Statistical analyses.** Statistical analyses were performed using IBM SPSS Statistics 21. Assumptions were tested. Shapiro-Wilk statistics showed a number of measures were moderately violated, but t-test and ANOVAs are robust against moderate violations of normality and therefore allow for the interpretation of these parametric statistics (Nimon, 2012). Equal variance not assumed was applied when homogeneity of variance was violated. Greenhouse-Geisse was applied when Mauchly’s Test of Sphericity was violated. The performance of both behavioural tasks: (1) Purdue pegboard: right hand and assembly, and (2) unimanual circle task: mean circularity (accuracy), mean period (speed; s), and mean cycles of acceleration-deceleration (smoothness of movement), were analyzed using independent t-tests with age group (younger, older) as the between-subjects factor. Single-pulse characteristics (RMT, S1 and TS, and single-pulse MEP) were analyzed using independent t-tests with age group (younger, older) as the between-subjects factor. A mixed repeated measure analysis of variance (ANOVA) was used for analysis of SICF with the between-subject factor of age (younger, older) and a within-subject factor of ISI (1.3, 1.5, 1.7, 1.9, 2.1, 2.3, 2.5, 2.7, 2.9, 3.1 ms). A mixed repeated measure ANOVA was used for analysis of SICI\textsubscript{Peak} and SICI\textsubscript{Trough} with the between-subject factors of age (younger, older) and within-subject factors of CS (50%, 60%, 70%, 80%, 90%, 100%, 110%). Pearson’s bi-variate correlations
were used for analysis of the relationship between the behavioural tasks (Purdue pegboard subtests and unimanual circle task) and SICF at ISI 1.3ms (SICF_{1.3}), SICF at ISI 2.5ms (SICF_{2.5}) SICI_{Peak}, and SICI_{Trough}. Separate Pearson’s bi-variate correlation analyses were used for younger and older adults. Independent t-tests were used when there was a significant main effect or interaction. All tests were two-tailed and statistical significance was accepted at an alpha level of $p < .05$ (as analyses are exploratory). All values (MEP amplitude, behavioural task scores) are expressed as mean ± standard error of the mean (SEM). Ratios greater than 1.0 indicates the presence of facilitation and ratios less than 1.0 indicate the presence of inhibition.

**Results**

**Functional Results**

**Purdue pegboard.** Table 1 shows mean (SEM) number of pegs inserted in the holes with the right hand and mean (SEM) number of objects assembled during the assembly subtest. Independent sample $t$-tests used to compare Purdue pegboard performance scores between young and older adults, showed younger adults placed significantly more pegs with the right hand ($t(45) = 5.04, p < .001$, two-tailed, $d = 1.48$), and assembled more objects ($t(45) = 6.02, p < .001$, two-tailed, $d = 1.77$) than older adults.
Table 1

The Mean (SEM) Number of Pegs Inserted and Objects Assembled in the Subtests of the Purdue Pegboard Test by Younger and Older adults

<table>
<thead>
<tr>
<th>Peg-inserting subtests</th>
<th>Right Hand</th>
<th>Assembly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>16 (1.86)</td>
<td>36 (5.48)</td>
</tr>
<tr>
<td>Older</td>
<td>12 (2.54)</td>
<td>26 (6.59)</td>
</tr>
</tbody>
</table>

Unimanual circle task.

Mean circularity. Figure 6 shows mean (+SEM) circularity for younger and older adults from the circle tracing task with the right hand. An independent t-test used to compare the circularity performance (i.e., mean circularity, mean period, and acceleration-deceleration) tracing a circle showed no statistically significant differences between younger and older adults ($t(45) = -.92, p = .362$, two-tailed, $d = -.28$).

Figure 6. shows mean (+SEM) circularity for younger ($n = 26$) and older adults ($n = 21$) from the circle tracing task with the right hand.
**Mean period (s).** Figure 7 shows mean (+SEM) speed (i.e., mean period) for younger and older adults from the circle tracing task with the right hand. An independent t-test used to compare the speed performance tracing a circle, showed statistical significance between younger and older adults \((t(45) = 2.08, p = .043, \text{two-tailed}, d = .59)\). This shows younger adults take longer to trace the circle than older adults.

![Figure 7. Mean (+SEM) speed (i.e., mean period) for younger (n = 26) and older adults (n = 21) from the circle tracing task with the right hand. *p < .05.](image)

**Mean cycles acceleration-deceleration.** Figure 8 shows mean (+SEM) number of smoothness of movements (acceleration-deceleration) for younger and older adults from the circle tracing task with the right hand. An independent t-test used to compare the smoothness of movement (acceleration-deceleration per cycle) when tracing a circle, showed statistical significance between younger and older adults \((t(42.83) = 2.64, p = .011, \text{two-tailed}, d = .74)\). This shows older adults have smoother movements when tracing the circle than younger adults.
Figure 8. Mean (+SEM) number of acceleration-deceleration per cycle for younger ($n = 26$) and older adults ($n = 21$) from the circle tracing task with the right hand. *$p < .05$.

Neurophysiological Results

Pulse characteristics. Table 2 shows mean (±SEM) of RMT, S1 and TS stimulus intensity (both reported as %MSO) and single-pulse MEP (i.e., S1-alone and TS-alone) for younger and older adults. Independent t-test used to compare pulse characteristics, showed older adults had significantly higher RMT and S1/TS stimulus intensity than younger adults (RMT: $t(45) = -2.17, p = .035$, two-tailed, $d = -.64$; S1 and TS: $t(45) = -3.02, p = .004$, two-tailed, $d = -.89$). There was no statistically significant difference between single-pulse MEPs in younger and older adults ($t(45) = .89, p = .378$, two-tailed, $d = .26$).
Mean (±SEM) of RMT, test stimulus intensity (both reported as %MSO) and single-pulse MEP for younger and older adults

<table>
<thead>
<tr>
<th></th>
<th>RMT (%MSO)</th>
<th>S1 and TS (%MSO)</th>
<th>Single-pulse MEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>53.54 ± 8.43</td>
<td>61.88 ± 10.21</td>
<td>1.02 ± 0.51</td>
</tr>
<tr>
<td>Older</td>
<td>59.14 ± 9.79</td>
<td>70.76 ± 10.46</td>
<td>0.92 ± 0.33</td>
</tr>
</tbody>
</table>

Note. RMT = Resting motor threshold; MSO = Motor stimuli output; MEP = Motor evoked potential; S1 = stimulus one; TS = test stimulus.

Short-Interval Intracortical Facilitation

Figure 9 shows SICF ratios for each of the 10 ISIs (1.3-3.1ms with .20ms intervals) in younger and older adults (ratio greater than 1.0 reflects facilitation; larger ratios reflect greater facilitation). A mixed repeated measure ANOVA performed to test for difference in SICF across the 10 ISIs between younger and older adults. The ANOVA showed a significant main effect of ISI ($F(2.81, 126.54) = 19.28, p < .001, \eta_p^2 = .30$) but no main effect of age ($F(1, 45) = .10, p = .752, \eta_p^2 = .00$) and no age and ISI interaction ($F(2.81, 126.54) = .57, p = .622, \eta_p^2 = .013$).
Figure 9. SICF ratios (mean paired-pulse MEP amplitude expressed as a ratio of mean single-pulse MEP amplitude) for each of the 10 ISIs (1.3-3.1ms with .20ms intervals) in younger (n = 26) and older adults (n = 21). Ratio greater than 1.0 reflects facilitation; larger ratios reflect greater facilitation). Error bars show standard error of the mean (±).

Short-Interval Intracortical Inhibition at the Peak

Figure 10 shows SIC_I\text{peak} ratios for each of the seven CS (50-110% with 10% increments) in younger and older adults (ratios less than 1.0 reflects inhibition; smaller ratios reflect greater inhibition). Measuring a range of CS intensities as a function of SICI provides a quadratic shape, and therefore, quadratic contrasts were used to comply with the shape. A mixed repeated measure ANOVA performed to test for difference in SIC_I\text{peak} across the seven CSs between younger and older adults. The ANOVA showed a significant main effect of CS (F(1, 45) = 97.73, p < .001, \( \eta^2_p = .69 \)) and of age and CS interaction (F(1, 45) = 4.98, p = .031, \( \eta^2_p = .10 \)), but no main effect of age (F(1, 45) = .01, p = .935, \( \eta^2_p = .00 \)). The main effect of CS was expected as ratios less than 1.0 at 60-80% reflecting inhibition, ratios greater than 1.0 at 90-110% reflecting a shift from inhibition to facilitation. The interaction between CS and age was further investigated using independent t-tests to examine the
difference in SICIPeak between young and older adults at each of the seven CS. At CS of 80%, younger adults show significantly greater SICIPeak than older adults ($t(45) = -2.267, p = .028$, two-tailed, $d = -.67$). No significant difference in SICIPeak between younger and older adults at any of the other CS intensities were found (all $t_{45} < -1.75$, all $p > .09$).

Figure 10. SICIPeak ratios (mean paired-pulse MEP amplitude expressed as a ratio of mean single-pulse MEP amplitude) for each of the seven CS (50-110% with 10% increments) in younger ($n = 26$) and older adults ($n = 21$). A ratio less than 1.0 reflects inhibition; smaller ratios reflect greater inhibition. Error bars show standard error of the mean ($\pm$). *$p < .05$.

Short-Interval Intracortical Inhibition at the Trough

Figure 11 shows SICITrough ratios for each of the seven CS (50-110% with 10% increments) in younger and older adults (ratios less than 1.0 reflects inhibition; smaller ratios reflect greater inhibition). Measuring a range of CS intensities as a function of SICI provides a quadratic shape, and therefore, quadratic contrasts were used to comply with the shape. A mixed repeated measure ANOVA performed to test difference in SICITrough across seven CSs between younger and older adults. The ANOVA showed a significant main effect of CS ($F(1, 45) = 45.38, p = .001, \eta_p^2 =$...
.50) and of age and CS interaction ($F(1, 45) = 10.91, p = .002, \eta^2 = .20$), but no main effect of age ($F(1, 45) = 2.49, p = .122, \eta^2 = .05$). The interaction between CS and age was further investigated using independent t-tests to examine difference in SICITrough between young and older adults at each of the seven CS. At CS of 50% (CS50) and CS 110% (CS110), young adults show significantly greater facilitation than older adults (CS50: $t(45) = 2.74, p = .009$, two-tailed, $d = .80$; CS110: $t(45) = 2.70, p = .011$, two-tailed, $d = .72$). No significant difference in SICITrough between younger and older adults at any of the other CS intensities were found (all $t_{45} < 2.00$, all $p > .051$).

Figure 11. SICITrough ratios (mean paired-pulse MEP amplitude expressed as a ratio of mean single-pulse MEP amplitude) for each of the seven CSs (50-110% with 10% increments) in younger ($n = 26$) and older adults ($n = 21$). Ratio less than 1.0 reflects inhibition; smaller ratios reflect greater inhibition. Error bars show standard error of the mean (±). *$p < .05$.

Relationships between Fine Motor Control and SICF and SICI

Purdue pegboard test and SICF1.3. Figure 12 shows scatterplots of the relationship between the performance of the Purdue pegboard subtests and SICF1.3
for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between performance in the two Purdue pegboard subtests and SICF\textsubscript{1.3} in younger and older adults. In younger adults, significant negative correlations were found between SICF\textsubscript{1.3} and right hand performance ($r(26) = -.44, p = .024, 95\% \text{ CI} [-.71, -.06]$) and objects assembled ($r(26) = -.41, p = .036, 95\% \text{ CI} [-.69, -.03]$). In older adults, there were no significant correlations between SICF\textsubscript{1.3} and Purdue pegboard subtests (both $r_{21} < -.27$, both $p > .24$).

*Figure 12.* Scatterplots show the relationship between performance on the Purdue pegboard subtests (number of inserted pegs with the right hand and objects assembled) and SICF\textsubscript{1.3} for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels). *$p < .05$. 

Unimanual circle task and SICF1.3. Figure 13 shows scatterplots of the relationship between the performance of the unimanual circle task and SICF1.3 for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between the performance of the unimanual circle task and SICF1.3 in younger and older adults. There were no significant correlations between performance of the unimanual circle task and SICF1.3 in younger (all $r_{26} < .31$, all $p > .12$) or older adults (all $r_{21} < .19$, all $p > .41$).

Figure 13. Scatterplots of the relationship between performance of circle tracing with the right hand on the unimanual circle task: (a) mean circularity, (b) mean period, and (c) acceleration-deceleration, and SICF1.3 for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels).

Purdue pegboard subtests and SICF2.5. Figure 14 shows scatterplots of the relationship between the performance of the Purdue pegboard subtests and SICF2.5 for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between performance in the two Purdue pegboard subtests and SICF2.5 in younger and older adults. There were no significant
correlations between performance of the right hand subtest and assembly subtest in younger (both $r_{26} < -.37$, both $p > .06$) or older adults (both $r_{21} < -.23$, both $p > .33$).

Figure 14. Scatterplots showing the relationship between performance on the Purdue pegboard subtests (number of inserted pegs with the right hand and objects assembled) and SICF$_{2.5}$ for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels).

**Unimanual circle task and SICF$_{2.5}$.** Figure 15 shows scatterplots of the relationship between the performance of the unimanual circle task and SICF$_{2.5}$ for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between the performance of the unimanual circle task and SICF$_{2.5}$ in younger and older adults. There were no significant correlations between performance of the unimanual circle task and SICF$_{2.5}$ in younger (all $r_{26} < -.12$, all $p > .57$) or older adults (all $r_{21} < .37$, all $p > .10$).
Figure 15. Scatterplots of the relationship between performance of circle tracing with the right hand on the unimanual circle task: (a) mean circularity, (b) mean period, and (c) acceleration-deceleration, and SICF2.5 for younger \((n = 26; \text{top panels})\) and older adults \((n = 21; \text{bottom panels})\).

**Purdue pegboard subtests and SICIpeak.** Figure 16 shows scatterplots of the relationship between the performance of the Purdue pegboard subtests and SICIpeak (at the CS 80%) for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between performance in the two Purdue pegboard subtests and SICIpeak in younger and older adults. There were no significant correlations between performance of the right hand subtest and assembly subtest in younger (both \(r_{26} < .22, \text{both } p > .28\)) or older adults (both \(r_{21} < -.14, \text{both } p > .53\)).
Figure 16. Scatterplots of the relationship between the performance of the Purdue pegboard subtests (number of inserted pegs with the right hand and objects assembled) and SICI\textsubscript{Peak} (at the CS 80%) for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels). Ratios below 1.0 indicate inhibition.

**Unimanual circle task and SICI\textsubscript{Peak}**. Figure 17 show scatterplots of the relationship between the performance of the unimanual circle task and SICI\textsubscript{Peak} (at the CS 80%) for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between performance in the unimanual circle task and SICI\textsubscript{Peak} in younger and older adults. In young adults, a significant positive correlation was found between SICI\textsubscript{Peak} and cycles of acceleration-deceleration ($r(26) = .402$, $p = .042$, CI [.02, .68]), but no significant correlations between SICI\textsubscript{Peak} and mean period or mean circularity (both $r_{26} < -.30$, both $p > .13$). In older adults, there
were no significant correlations between SICI_{Peak} and the circle tasks (all $r_{21} < .32$, all $p > .16$).

![Figure 17](image)

*Figure 17.* Scatterplots of the relationship between performance of circle tracing with the right hand on the unimanual circle task: (a) mean circularity, (b) mean period, (c) acceleration-deceleration, and SICI_{Peak} (at the CS 80%) for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels). Ratios below 1.0 indicate inhibition. *$p < .05$.

**Purdue pegboard test and SICI_{Trough}**. Figure 18 shows scatterplots of the relationship between performance of the Purdue pegboard subtests and SICI_{Trough} (at the CS 80%) for younger and older adults. Pearson’s bi-variate correlations were performed to test for relationship between performance in the two Purdue pegboard subtests and SICI_{Trough} in younger and older adults. In younger adults, a significant negative correlation was found between SICI_{Trough} and right hand performance ($r(26) = -.41, p = .040, 95\% \text{ CI } [-.69, -.02]$), but not for assembly ($r(26) = -.08, p = .682, 95\% \text{ CI } [-.46, .31]$). In older adults, a significant negative correlation was found
between $SICI_{Trough}$ and right hand performance ($r(21) = -.48, p = .029, 95\% \text{ CI} [-.75, -.06]$), but not for assembly ($r(21) = -.30, p = .187, 95\% \text{ CI} [-.65, .15]$).

**Figure 18.** Scatterplots of the relationship between performance of the Purdue pegboard subtests (number of inserted pegs with the right hand and objects assembled) and $SICI_{Trough}$ (at the CS 80%) for younger ($n = 26$; top panels) and older adults ($n = 21$; bottom panels). Ratios below 1.0 indicate inhibition. *$p < .05$.

**Unimanual circle task and SICI_{Trough}**. Figure 19 shows scatterplots of the relationship between the performance of the unimanual circle task and $SICI_{Trough}$ (at the CS 80%) for younger and older adults. Pearson’s bi-variate correlations were performed to test for a relationship between performance in the unimanual circle task and $SICI_{Trough}$ in younger and older adults. In younger adults, there were no significant correlations between $SICI_{Trough}$ and the circle tasks (all $r_{26} < .15$, all $p >$
In older adults, there were no significant correlations between SICI_{Trough} and the circle tasks (all $r_{21} < .19$, all $p > .41$).

Discussion
This study further defined age-related changes in intracortical inhibition and intracortical facilitation, and the role of these processes in fine motor control. There were five findings. First, there was no significant difference in SICF between younger and older adults at Peak 1 (ISI 1.1-1.7ms), in contrast to the first hypothesis. Second, there was no significant difference in SICF between younger and older adults at Peak 2 (ISI 2.3-2.9ms), in contrast to the second hypothesis. Third, older adults showed significantly reduced SICI_{Peak} than younger adults, consistent with the third hypothesis. Fourth, there was no significant difference in SICI_{Trough} in younger...
and older adults, which is consistent with the fourth hypothesis. Fifth, older adults had a significant relationship between $SIC_{r\text{ough}}$ and the right-hand subtest of Purdue pegboard test, consistent, in part with the fifth hypothesis.

**Older Adults have Poorer Fine Motor Control than Younger Adults**

The Purdue pegboard test is a commonly used measure of speed and precision of finger dexterity and was used here to investigate changes in fine motor control with age. Results showed older adults inserted and assembled significantly fewer pegs and objects than younger adults. This suggests an age-related decline in fine motor control, which is consistent with a large body of literature (Clark et al., 2011; Francis & Spirduso, 2000; Marneweck et al., 2011).

In the current study, a unimanual circle task was also used to measure fine motor control. The circle task required participants to engage in fine motor control by tracing the outline of a circle (70-mm diameter) with their right hand; mean circularity (accuracy), mean period (speed), and mean cycles acceleration-deceleration (smoothness of movement) were measured. There were no age-related differences in mean circularity between younger and older adults, but younger adults showed slower performance with more mean periods of acceleration-deceleration than older adults. This suggests movements of younger adults are slower and less smooth than older adults, which is in contrast to findings using other measures of fine motor control (Carson et al., 1997). An explanation for these current results is not clear. It is possible that despite younger and older adults receiving exactly the same instructions, younger adults who were participating for course credit could have been less attentive and used less effort than older adults. However, it is not possible to determine this from the current study.
No Age-Related Difference in SICF

Paired-pulse TMS was used to measure SICF in younger and older adults. SICF was measured at a range of ISIs, to obtain a function comprising: Peak 1, Trough 1, and Peak 2. The results showed no differences in SICF between younger and older adults at Peak 1 (ISI 1.1-1.7ms). This suggests that the excitability of intracortical facilitatory circuits are similar in younger and older adults, which is inconsistent with a previous study, in which older adults showed greater facilitation than younger adults at ISI 1.5ms, which corresponds to Peak 1 (Clark et al., 2011). The current study characterised SICF function, rather than testing at a single ISI, which showed that younger and older adults SICF Peak 1 (maximum facilitation) occurred at 1.3ms, not at 1.5ms as measured by Clark et al. (2011). In the current study, while there was no significant difference in SICF between younger and older adults, SICF at 1.3ms was numerically greater in younger than older adults. This suggests that younger adults show greater facilitation when compared to older adults, in contrast to Clark et al. (2011) findings. Nevertheless, this is speculative, due to no statistical significance. It is not clear why current findings contrast these of Clark et al. (2011).

It has been argued that SICF2.5 offers a sensitive measure of the facilitation of excitatory processes which precede and produce fine motor control (Cattaneo et al., 2005; Clark et al., 2011; Parikh et al., 2014). The current study showed no age-related difference in SICF between younger and older adults at Peak 2 (ISI 2.3-2.9ms). This suggests the excitability of intracortical facilitatory circuits are similar in younger and older adults. This is inconsistent with a previous study, in which younger adults showed greater facilitation than older adults at ISI of 2.5ms, which corresponds with Peak 2 (Clark et al., 2011). The current study characterised SICF function, rather than testing at a single ISI, which showed both younger and older
adults Peak 2 occurred at 2.9ms, not at 2.5ms as measured by Clark et al. (2011). In the current study, while there was no significant difference in SICF between younger and older adults, SICF\textsubscript{2.5} was numerically greater in younger than older adults, which resembles the findings from Clark et al. (2011). This may suggest that SICF at Peak 2 is important for the decline in fine motor control in older adults, however, this is speculative, due to no statistical significance.

Taken together, current results do not support increased excitability of intracortical facilitatory circuits at Peak 1 or Peak 2 in older compared to younger adults. Interestingly, both younger and older adults showed a shift in SICF, that is, both younger and older adults showed higher levels of intracortical facilitation at different intervals than that measured by Clark et al. (2011). This shows the sensitivity of SICF at different intervals and prompts future research to use more intervals to evaluate SICF in older and younger adults.

**SICI as a Function of CS Intensity is Affected by Age**

Paired-pulse TMS was used to measure SICI in younger and older adults. SICI measured at a range of CSs, to obtain a recruitment curve to measure the sensitivity of SICI circuits. In addition, ISI of paired-pulse trials was individualised to obtain a measure of SICI at Peak 1 and at the Trough. The former reflects the net effect of the activation of SICF and SICI circuits, and the latter preferential activates SICI circuits, resulting in a ‘purer’ measure of inhibition as there is a minimal contribution from SICF.

**Older adults have reduced SICI\textsubscript{Peak} at moderate CS.** SICI measured at Peak 1, the ISI at which SICF was greatest in each individual, showed a significant interaction between age and CS. Additionally, there was significantly reduce SICI\textsubscript{Peak} at CS 80\% in older than younger adults, but no difference in SICI\textsubscript{Peak} at the
other CS between younger and older adults. This suggests the excitability of intracortical inhibitory circuits is less excited in older than younger adults. This is consistent with previous research showing greater $\text{SICI}_\text{Peak}$ in younger than older adults (Marneweck et al., 2011; Peinemann et al., 2001). It is important to note that ISI was individualised to the Peak 1, and therefore the measure of $\text{SICI}_\text{Peak}$ at this ISI is likely a net effect of SICF and SICI influences.

Marneweck et al. (2011) showed age-related changes in SICI when using paired-pulse TMS. More specifically, their findings showed some older adults have atypical facilitation, that is, SICI ratios greater than 1.0 in response to paired-pulse TMS. Similarly, Clark et al. (2011) showed age-related changes in SICF when using paired-pulse TMS. More specifically, their findings showed older adults have greater facilitation compared to younger adults at Peak 1. Research suggests the excitability of SICF circuits contributes to measures of SICI (Ziemann, Rothwell, et al., 1996), and therefore, it was thought that greater facilitation in older adults SICF may contribute to the atypical facilitation found when preferentially measuring SICI in older adults. Although the current study showed no significant differences in SICF at Peak 1, the findings of reduced SICI when measured at an ISI corresponding to the Peak 1, suggests that the balance between facilitation and inhibition is shifted more towards facilitation than inhibition in older than younger adults. That is, SICF is contributing to SICI. It is important to note that this is speculative due to no significance.

**No age-related difference in SICI$_\text{Trough}$ at moderated CS.** SICI measured at the trough, the ISI at which SICF was the least active in each individual, preferentially activates SICI circuits. This acts as a purer measure of SICI because there is less of an influence from SICF on SICI. The results showed a significant age
and CS interaction, and older adults had significantly greater SICI_{\text{trough}} at CS 50% and 110% compared to younger adults. This is the first study to obtain SICI measures from the complete SICI CS intensity function in older adults. Figure 11 shows a U-shaped curve in SICI with increasing CS intensity in younger but not older adults. This suggests that SICI circuits in younger adults are more sensitive to changing CS intensity than older adults. That is, with a small change in input (i.e., CS intensity) SICI circuits are influenced to a great extent in younger than older adults.

While the age-related difference in SICI_{\text{trough}} was observed at the lowest and highest CS intensities tested here, there was no difference in SICI measure at moderate CS intensities between younger and older adults. This suggests no age-related difference in the excitability of intracortical inhibitory circuits (i.e., GABA) at moderate CS intensities. This is in contrast to the current results measuring SICI at Peak 1, where younger adults showed more SICI than older adults. As previously mentioned, SICI measured at the Peak 1 ISI is likely influenced more by the activation of SICF circuits than SICI measured at trough ISI. Previous SICI findings are inconsistent with some research showing SICI is greater in older than younger adults (McGinley et al., 2010; Smith et al., 2011), SICI is greater in younger than older adults (Marneweck et al., 2011; Peinemann et al., 2001), and no difference in SICI between young and older adults (Oliviero et al., 2006; Rogasch et al., 2015). Inconsistency in the literature could reflect the balance between SICF and SICI, and changes in this balance with age. This may prompt future research to implement SICI_{\text{trough}} for a purer measure of intracortical inhibition, without the influence of SICF.
In summary, there was no difference in SICF at Peak 1 and Peak 2 in younger and older adults. There was reduced SICI at Peak 1 in older compared to younger adults at CS 80%. There was no difference in SICI at the Trough in older and younger adults at moderate CS intensities. Taken together, the SICF (Peak 1 and Peak 2), SICI\textsubscript{Peak}, and SICI\textsubscript{Trough} results suggest complex interactions between the intracortical facilitatory process and intracortical inhibitory process, and that the inhibitory and facilitatory balance might be affected by age.

**Relationship between SICF\textsubscript{1.3} and Fine Motor Control**

To investigate the functional role of SICF\textsubscript{1.3} in fine motor control, relationships between SICF\textsubscript{1.3} and Purdue pegboard performance were examined in younger and older adults. In younger adults, Purdue performance subtests were moderately negatively associated with SICF\textsubscript{1.3}. This suggests, greater SICF results in fewer pegs inserted and objects assembled. Thus, this may suggest a role of SICF in fine motor control, and that large facilitation is detrimental to fine motor control in younger adults. This is consistent with Clark et al. (2011) who showed greater SICF at ISI 1.5ms was significantly associated with Purdue pegboard performance. In older adults, there was no relationship between SICF\textsubscript{1.3} and Purdue pegboard performance. It is worth noting that a greater number of younger than older adults showed very large SICF ratios. This is important because individuals who show very large SICF ratios are potentially driving the negative relationships between SICF\textsubscript{1.3} and Purdue pegboard performance in younger adults. This is similar to the findings of Clark et al. (2011), in which atypical facilitation in older adults played an important role in the relationship between SICF and Purdue pegboard performance. In the current study, only one older adult showed atypical facilitation, and it is unclear why older adults did not show atypical facilitation. A possible explanation
could be sampling bias, as our older adults were all recruited from a ‘healthy’ population.

To further investigate the functional role of SICF_{1.3} in fine motor control, relationships between SICF_{1.3} and unimanual circle task were examined in younger and older adults. There were no associations between SICF_{1.3} and measures of circle performance in younger or older adults. This suggests no functional role of SICF measured at the Peak 1 in fine motor control. While the circle drawing task was included as a potentially more sensitive measure to age-related decline in fine motor control compared to the Purdue pegboard, age comparisons of performance showed younger adults had slower and less smooth performance than older adults, suggesting this might not be the case. The absence of any relationships between SICF_{1.3} and performance on the circle task suggests that SICF might not play a role in the continuous, smooth control required for the circle task.

**Relationship between SICF_{2.5} and Fine Motor Control**

To investigate the functional role of SICF_{2.5} in fine motor control, relationships between SICF_{2.5} and Purdue pegboard performance were examined in younger and older adults. In younger and older adults, there were no associations between SICF_{2.5} and performance on both Purdue pegboard subtests. This suggests there is no functional role of SICF_{2.5} in fine motor control. This is inconsistent with previous research suggesting the importance of SICF_{2.5} in fine motor control (Calautti et al., 2001; Clark et al., 2011).

To further investigate the functional role of SICF_{2.5} in fine motor control, relationships between SICF_{2.5} and unimanual circle task were examined. In younger and older adults, there were no associations between SICF_{2.5} and performance on the unimanual circle measures. This is inconsistent with previous research suggesting
the importance of $SICF_{2.5}$ in fine motor control (Cattaneo et al., 2005; Clark et al., 2011).

**Relationship between $SICI_{\text{Peak}}$ and Fine Motor Control**

To investigate the functional role of $SICI_{\text{Peak}}$ in fine motor control, relationships between and Purdue pegboard performance were examined in younger and older adults. In younger and older adults, there was no association between $SICI_{\text{Peak}}$ and Purdue pegboard subtests. This suggests there is no functional role of SICI measured at the Peak in fine motor control.

To investigate the functional role of $SICI_{\text{Peak}}$ in fine motor control, relationships between fine motor control and $SICI_{\text{Peak}}$ with circle performance was examined in younger and older adults. In younger adults, there were no relationships between $SICI_{\text{Peak}}$ and mean circularity or mean period, but there was a positive association between cycles of acceleration-deceleration and $SICI_{\text{Peak}}$. This suggests greater SICI results in more smooth movements. In older adults, there were no relationships between $SICI_{\text{Peak}}$ and circle performance. Given the lack of age-effects in circle performance described above, this finding of SICI and acceleration-deceleration in younger adults should be interpreted with caution.

**Relationship between $SICI_{\text{Trough}}$ and Fine Motor Control**

To investigate the functional role of $SICI_{\text{Trough}}$ in fine motor control, relationships between $SICI_{\text{Trough}}$ and Purdue pegboard performance were examined in younger and older adults. SICI measured at the trough is a purer measure of SICI than SICI at the peak (i.e., a better measure of GABA). In younger and older adults, there were moderate negative correlations between $SICI_{\text{Trough}}$ and the right hand Purdue pegboard performance. This suggests greater $SICI_{\text{Trough}}$ results in more pegs inserted with the right hand, which is consistent with previous findings (Marneweck
et al., 2011). The current findings add to existing literature suggesting the role of SICI in manual dexterity. There were no relationships between SICI\textsubscript{Trough} and assembly in both younger and older adults, which is inconsistent with Marneweck et al. (2011). This may be partially explained by the current study having fewer atypical facilitators than the sample presented in Marneweck et al. (2011) findings.

To investigate the functional role of SICI\textsubscript{Trough} in fine motor control, relationships between fine motor control and SICI\textsubscript{Trough} with circle performance was examined in younger and older adults. There were no associations between SICI\textsubscript{Trough} and measures of circle performance in younger or older adults. This suggests no functional role of SICI\textsubscript{Trough} in fine motor control.

**Single-pulse Characteristics**

First, older adults showed significantly higher RMT values compared to younger adults. Second, the stimulus intensity required to elicit an average MEP of 1mV (for S1 and TS) was significantly higher in older than younger adults. Collectively, these findings suggest a decrease in corticospinal excitability with age, which corresponds with a current meta-analysis (Bhandari et al., 2016). There was no age-related difference in the single-pulse TMS (~1mV), which was important because single-pulse MEP acted as the baseline across participants.

**Limitations**

The current study had several limitations. First, the samples used may not have been representative of the general population. Older adults presented in this study were physically active; as they were recruited from senior exercise classes. Previous research has shown physical activity can help maintain functionality both within hand performance and brain functions (Kornatz, Christou, & Enoka, 2005). This suggests older adults may have had better Purdue pegboard performance than
what would be demonstrated in a broader population-based sample. Second, both age groups were predominately females. Several studies suggest the menstrual cycle and menopause can influence cortical excitability (C. Freitas, Farzan, & Pascual-Leone, 2013; Tecchio et al., 2008). Third, it is important to note that while the focus of the current study was to identify the role of cortical changes in age-related motor decline, aging is also accompanied by changes in subcortical and peripheral structures and functions, which may also contribute to age-related motor decline (Scherder, Dekker, & Eggermont, 2008). This suggests other subcortical and peripheral structures and functions may have acted as a confound, which decreases the internal validity.

**Future research**

The current study had several future research suggestions. First, it would be interesting to examine the SICF profile (i.e., using ISIs similar to the current study) in both hemispheres to see whether greater facilitation would be present. This would allow research to also investigate bimanual movement, rather than unimanual movement. The underlying mechanisms of greater facilitation may be driven by bilateral brain functions. Second, the balance between SICF and SICI (i.e., $SICI_{peak}$ and $SICI_{Trough}$) should be investigated within both hemispheres, as age-related changes in M1 functions are not restricted to the dominant M1 (Hammond, 2002). Neuroimaging shows more bilateral activation in M1 in older compared to younger adults during movement (Mattay et al., 2002). Hence, investigating hemisphere asymmetry in SICF and SICI with age, and the relationship with bimanual control may provide greater ecological validity in the wider context.
**Conclusion**

This study further defined age-related intracortical facilitatory and intracortical inhibitory changes and its relationship with fine motor control. First, there was no age-related difference in SICF at Peak 1. Second, there were no age-related differences in SICF at Peak 2. Third, at moderate CS intensities, older adults showed reduced SICI at Peak 1 compared to younger adults. Fourth, at moderate CS intensities, there were no age-related differences in SICI at the trough in older and younger adults. Fifth, there was a relationship between SICI at the Trough and fine motor control in older adults, suggesting greater SICI results in greater pegs inserted. The current study makes a valuable contribution to the literature examining age-related changes in intracortical facilitation and inhibition. Together findings suggest a complex interaction between the balance of inhibition and facilitation, and that this is affected by age and influences fine motor control. Understanding cortical changes underlying the decline of fine motor control in older adults may generate better treatment, resulting in a more comfortable transition into senescence, and a reduction in the burden on medical and welfare infrastructure. Future research should look at hemisphere asymmetry changes in this facilitatory and inhibitory balance with age, and the role in fine motor control.
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Appendix A

Recruitment Flyer for Older Adults

RESEARCH PARTICIPANTS WANTED

Examining relationships between brain function and movement in older adults.

We are looking for healthy volunteers aged 60 – 85 years to participate in studies investigating how ageing affects brain function associated with movement.

The studies will involve an assessment of the pathway from the brain to the hand muscles by giving a series of brief (painless) magnetic pulses that make the hand twitch briefly. The electrical activity in these muscles will be measured with electrodes taped to the skin.

To volunteer participants must be aged between 60-85 years. Participants should NOT have:
• Neurological impairment or epilepsy
• A cardiac pacemaker
• Metal implants in the brain or skull

This study will be conducted at the psychophysiology laboratory at Murdoch University. The study will take approximately 2 hours and parking can be arranged.

If you are interested and would like more information, please contact:

Brittany Rurak (Student of Bachelor of Psychology: Honours)
School of Psychology and Exercise Science, Murdoch University
B_rurak@hotmail.com 0415 423 493

Dr Ann-Marie Vallence (PhD)
School of Psychology and Exercise Science, Murdoch University
a.vallence@murdoch.edu.au 9360 7464

THIS STUDY HAS BEEN APPROVED BY MURDOCH UNIVERSITY RESEARCH ETHICS (2014/247)
Appendix B
Ethics Approval

Thursday, 29 January 2015

Dr Ann-Marie Vallence
School of Psychology and Exercise Science
Murdoch University

Dear Ann-Marie,

Project No. 2014/247
Project Title Examining connectivity between motor areas of the ageing brain and motor function

Thank you for addressing the conditions placed on the above application to the Murdoch University Human Research Ethics Committee. On behalf of the Committee, I am pleased to advise the application now has:

OUTRIGHT APPROVAL

Approval is granted on the understanding that research will be conducted according to the standards of the National Statement on Ethical Conduct in Human Research (2007), the Australian Code for the Responsible Conduct of Research (2007) and Murdoch University policies at all times. You must also abide by the Human Research Ethics Committee’s standard conditions of approval (see attached). All reporting forms are available on the Research Ethics and Integrity web-site.

I wish you every success for your research.

Please quote your ethics project number in all correspondence.

Kind Regards,

[Signature]

Dr. Erich von Dietze
Manager
Research Ethics and Integrity

cc: Prof Peter Drummond
Appendix C

Summary of Project

Ethics Project Number: 2014/247
Researcher: Brittany Kelsey-Rey Rurak
Supervisor: Dr. Ann-Maree Vallence
Co-supervisors: Dr. Geoff Hammond and Dr. Hakuei Fujiyama
Research Completed: October 2016

Context and Research Aims:

Age-related decline in fine motor control has been well documented. Fine motor control is important for carrying out everyday tasks, such as tying shoelaces or buttoning a shirt. As we age, the area of the brain that controls fine motor control (i.e., motor cortex) undergoes changes. Changes in the motor cortex might help explain the decline in fine motor control in older adults. The motor cortex has excitatory output cells which communicate information from the motor cortex to the muscle(s), resulting in fast and efficient movements. Excitatory output cells are controlled by facilitatory and inhibitory circuits, which help shape motor output by facilitating relevant output cells and inhibiting irrelevant output cells. One can think of this as turning ‘on’ relevant output cells and turning ‘off’ irrelevant output cells depending on the desired signal to the muscle(s). Research has shown the motor cortex requires a complex balance between these facilitatory and inhibitory neurons.

The balance between facilitation and inhibition plays a particularly important role in the execution of fine motor control. Recent research has shown older adults show greater facilitation than inhibition in the motor cortex. Greater facilitation in the motor cortex is defined as atypical facilitation. Older adults with atypical facilitation tend to show a greater decline in fine motor control.

Age-related changes in facilitation and inhibition circuits can be measured using a non-invasive brain stimulation technique called, transcranial magnetic stimulation (TMS), applied over the brain’s motor cortex controlling the hand muscles that are important for fine motor control. The aim of the current study was to investigate whether inhibition or atypical facilitation or both are impacting the loss fine motor control in older adults.

Methodology:

Fine motor control was measured using the Purdue pegboard test (inserting pegs into holes on a board) and unimanual circle drawing (tracing the outline of a circle on a tablet). Inhibition and facilitation processes were measured using TMS applied over the area of the motor cortex responsible for the hand muscles used for fine motor control in younger \( n = 26 \) and older adults \( n = 21 \). TMS delivers two (painless and safe) pulses of different intensities separated by a short time interval.

When measuring facilitation with TMS procedures, it is important to use different time intervals between the two-pulses, because it shows when facilitation is most active, and when facilitation is least active. When measuring inhibition with TMS procedures, it is important to use different pulse intensities, because it shows when inhibition is most active, and when inhibition is least active. To summarize, the time intervals and the strength of the pulse used, are important measurements.
Changes in facilitation and inhibition were compared to the performance on the fine motor control tests (i.e., Purdue pegboard and circle drawing).

**Results:**
There were no differences between facilitatory processes in the motor cortex of younger and older adults. When inhibition was measured during periods corresponding to high levels of facilitation, older adults showed less inhibition than younger adults. When inhibition was measured during periods corresponding to low levels of facilitation, there was no difference in inhibition between younger and older adults. There was a relationship between inhibition and fine motor control in older adults. This relationship between inhibition and fine motor control indicates that greater inhibition was associated with better fine motor control.

**Discussion:**
This study further defined age-related changes in facilitation and inhibition in the motor cortex and the role of these processes in fine motor control. There were four findings. First, facilitatory processes are similar in younger and older adults. Second, facilitation processes may have a greater influence on inhibitory processes in older than younger adults. Third, inhibitory processes are similar in younger and older adults when facilitation is minimal. Four, inhibition has a relationship with fine motor control in older adults. Taken together, these findings suggest there is a complex interaction occurring between facilitatory and inhibitory processes, and that this interaction is affected by age and influences fine motor control. Without the use of fine motor control, daily life tasks may be challenging. It is important to continue investigating age-related changes in fine motor control, as the decline in motor skills may impact older adults quality of life, independence, and their performance in a workplace.
Appendix D

Murdoch University Consent Form

Examine relationships between brain function and movement in older adults.

THIS STUDY HAS BEEN APPROVED BY MURDOCH UNIVERSITY RESEARCH ETHICS (2014/247)

1. I agree voluntarily to take part in this study.

2. I have read the Information Sheet provided and been given a full explanation of the purpose of this study, the procedures involved and of what is expected of me.

3. The researcher has answered all my questions and has explained possible problems that may arise as a result of my participation in this study.

4. I understand I am free to withdraw from the study at any time without needing to give any reason.

5. I understand I will not be identified in any publication arising out of this study.

6. I understand that my name and identity will be stored separately from the data, and these are accessible only to the investigators. All data provided by me will be analysed anonymously using code numbers.

7. I understand that all information provided by me is treated as confidential and will not be released by the researcher to a third party unless required to do so by law.

Name of participant: ________________________________

Signature of Participant: __________________________ Date: ……/ ……/ ……

__________________________

I confirm that I have provided the Information Letter concerning this study to the above participant; I have explained the study and have answered all questions asked of me.

Name of researcher: ________________________________

Signature of researcher: __________________________ Date: ……/ ……/ ……
Appendix E

Information Letter

Examiner relationships between brain function and movement in older adults.

This study has been approved by Murdoch University Research Ethics (2014/247)

This information sheet is intended to provide you with sufficient information to make an informed decision about participating in this study. If there is any aspect that is not clear to you, please discuss this with one of the investigators.

Nature and purpose of the study

The human brain is capable of undergoing reorganisations throughout life. These reorganisations are the basis for modifications in behaviour. For example, when you learn a new movement (known as a motor skill), such as playing the piano, the areas of the brain that control movement (motor areas) are reorganised. These modifications allow you to improve your performance. With advancing age, changes in motor areas of the brain occur. In these experiments, we will use non-invasive transcranial magnetic stimulation to assess age-related changes in motor areas of the brain and examine relationships between these changes and deficits in the performance of motor skills in healthy younger and older adults.

What will the study involve?

The experiments will be conducted in a psychophysiology laboratory at Murdoch University. During each session, you will be seated in a comfortable arm chair. The experimental process will take approximately 2 hours, and you may be asked to attend several sessions.

Questionnaires

You will be asked to complete a series of questionnaires. These questionnaires will provide us with information on your general health and well-being, physical activity levels, and hand preference during normal daily activities.

Recording from forearm muscles

During the study muscle activity will be recorded from a small hand muscle. The muscle activity will be measured by taping small recording electrodes on top of each hand.

Transcranial Magnetic Brain Stimulation

Transcranial magnetic stimulation, or TMS, is a technique that employs a magnetic field to painlessly activate the brain. A coil is held over the scalp by the experimenter and a brief current pulse flows through the coil. This in turn generates a magnetic field that activates the brain beneath the coil. If the coil is held over the motor cortex, we can see the effects of stimulation by recording responses produced in muscles of the hand and forearm. These responses are recorded with the electrodes taped to the skin overlaying the muscles. The stimuli can be felt as brief mechanical ‘taps’ on your scalp. You will also hear a click when the pulse is discharged through the coil. Small muscle movements evoked by the TMS may also be felt in the hand. The technique of TMS is painless and non-invasive. It has been in use for more than 15 years and is used routinely to investigate activity of the motor system. Three different TMS protocols will be used in this study, each described in detail below. During an experimental session, you will undergo one or more of these TMS protocols.
Paired-pulse transcranial magnetic stimulation

Paired-pulse TMS will be used to measure the activity of pathways in the primary motor cortex; the part of the brain involved in execution of voluntary movement. Paired-pulse TMS consists of two pulses separated by short time intervals (1-3 ms). The stimuli can be felt as brief mechanical ‘taps’ on your scalp and you will also hear a click when the pulse is discharged through the coil. Small muscle movements evoked by the TMS may be felt.

As a matter of policy we exclude any persons for our study who have a history of epilepsy or stroke, or who have metal implants in the skull, or cardiac pacemakers. If you have any of these, please inform the investigators prior to commencing the study. If you have any doubts about whether you should participate, please discuss them with one of the investigators. Additionally, you will be required to complete a safety questionnaire that will identify any possible contraindications for the use of TMS.

Motor Tasks

Tasks are designed to measure fine motor control. The first task involves picking up small objects and placing them in particular locations, in particular orders. The second task requires you to trace a small circle and a large circle. The tasks will be performed in 1 minute blocks at the start of the experimental session.

What are the risks?

We wish to make it clear that although these techniques are used both diagnostically and in research laboratories around the world, all experiments involve a small but finite risk. Very occasionally it has been reported by other groups that subjects may experience a mild and temporary headache after TMS. In our experience this is very rare. It is our policy to exclude any subjects with cardiac pacemakers, metal implants in the skull or a history of stroke or epilepsy.

All participants’ details will remain confidential except as required by law. Although we plan to publish the results of this study, participants will only be identified by a participant number.

You are free to withdraw from this study at any time without having to explain your reasons for doing so.

If you have concerns either before or following the experiment, please contact:

Brittany Rurak
Bachelor of Psychology (Honours)
School of Psychology and Exercise Science
Murdoch University
Tel: 0415 423 493
Email: b_rurak@hotmail.com

Dr Ann Marie Vallance
NUMRC Peter Doherty Fellow
School of Psychology and Exercise Science
Murdoch University
Tel: 9360 7464
Email: a.vallance@murdoch.edu.au

This study has been approved by the Murdoch University Human Research Ethics Committee (Approval 2014/29). If you have any questions or concerns about the ethical conduct of this research, and wish to talk with an independent person, you may contact Murdoch University’s Research Ethics Office (Tel: 08 9360 6677 or email ethics@murdoch.edu.au). Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.
Appendix F

Transcranial Magnetic Stimulation Safety Screen

<table>
<thead>
<tr>
<th>Transcranial Magnetic Stimulation (TMS) Safety Screen</th>
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<tbody>
<tr>
<td><strong>Name:</strong></td>
</tr>
<tr>
<td><strong>Date:</strong></td>
</tr>
<tr>
<td><strong>Age:</strong></td>
</tr>
</tbody>
</table>

Please answer the following:

1. Do you have epilepsy or have you ever had a convulsion or a seizure? [ ] Yes [ ] No
2. Have you ever had a fainting spell or syncope? If yes, please describe in which occasions in the space provided below. [ ] Yes [ ] No
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness? [ ] Yes [ ] No
4. Have you ever undergone brain surgery? [ ] Yes [ ] No
5. Do you experience migraines/cluster headaches? [ ] Yes [ ] No
6. Do you have any hearing problems or ringing in your ears? [ ] Yes [ ] No
7. Do you have cochlear implants? [ ] Yes [ ] No
8. Are you pregnant or is there any chance that you might be? [ ] Yes [ ] No
9. Do you have metal in the brain, skull, or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, please specify type of metal. [ ] Yes [ ] No
10. Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)? [ ] Yes [ ] No
11. Do you have a cardiac pacemaker or intra-cardiac lines? [ ] Yes [ ] No
12. Do you have a medication infusion device? [ ] Yes [ ] No
13. Are you taking any medications? (Please list) [ ] Yes [ ] No
14. Have you ever had a stroke? [ ] Yes [ ] No
15. Did you ever undergo TMS in the past? [ ] Yes [ ] No
   If so, were there any problems? [ ] Yes [ ] No
16. Did you ever undergo MRI in the past? [ ] Yes [ ] No
   If so, were there any problems? [ ] Yes [ ] No

Subject signature: __________________________________________
Experimenter name: ___________________________ Signature: ___________________________

If you answered yes to any of the above, please provide details (use reverse if necessary):

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

Page 1 of 1

CRICOS Provider Code: 00115J
ABN 61 515 365 313
Appendix G

Edinburgh Handedness Inventory

Edinburgh Handedness Inventory

Name: ____________________________________________

Please indicate with a one (1) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put a two (2).

If you are indifferent, put a one in each column (1 | 1).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

<table>
<thead>
<tr>
<th>Task / Object</th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Drawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Throwing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Scissors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Toothbrush</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Knife (without fork)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Spoon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Broom (upper hand)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Striking a Match (match)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Opening a Box (lid)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total checks: LH = \_ \_ \_ RH = \_ \_ \_

Cumulative Total CT = LH + RH = \_ \_ \_

Difference D = RH - LH = \_ \_ \_

Result R = (D / CT) × 100 = \_ \_ \_

Interpretation:
(Left Handed: R < -40)
(Ambidextrous: -40 ≤ R ≤ +40)
(Right Handed: R > +40)

---

Appendix H

Montreal Cognitive Assessment

### Montreal Cognitive Assessment (MOCA)

**Version 7.1 Original Version**

<table>
<thead>
<tr>
<th><strong>VISUOSPATIAL / EXECUTIVE</strong></th>
<th><strong>NAME:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End</strong></td>
<td>Education:</td>
</tr>
<tr>
<td><strong>Copy cube</strong></td>
<td>Sex:</td>
</tr>
<tr>
<td><strong>Draw CIRCLE (Ten past eleven)</strong></td>
<td>Date of birth:</td>
</tr>
<tr>
<td>1st trial</td>
<td><strong>DATE:</strong></td>
</tr>
<tr>
<td>2nd trial</td>
<td></td>
</tr>
<tr>
<td>Contour</td>
<td></td>
</tr>
<tr>
<td>Numbers</td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td></td>
</tr>
</tbody>
</table>

**MEMORY**: Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th><strong>FACE</strong></th>
<th><strong>VELVET</strong></th>
<th><strong>CHURCH</strong></th>
<th><strong>DAISY</strong></th>
<th><strong>RED</strong></th>
<th><strong>POINTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/5</td>
</tr>
<tr>
<td>1st trial</td>
<td>21 8 5 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd trial</td>
<td>7 4 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ATTENTION**: Read list of digits (1 digit/sec). Subject has to repeat them in the forward order.

<table>
<thead>
<tr>
<th><strong>Serial 7 subtraction starting at 100</strong></th>
<th><strong>No points</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>2</td>
</tr>
<tr>
<td>88</td>
<td>3</td>
</tr>
<tr>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td>72</td>
<td>5</td>
</tr>
<tr>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>3 pts, 2 correct</td>
<td></td>
</tr>
<tr>
<td>2 pts, 1 correct</td>
<td></td>
</tr>
<tr>
<td>1 pt, 0 correct</td>
<td></td>
</tr>
<tr>
<td>0 pts</td>
<td></td>
</tr>
</tbody>
</table>

**LANGUAGE**: Repeat: I only know that John is the one to help today.

<table>
<thead>
<tr>
<th><strong>Fluency / Name maximum number of words in one minute that begin with the letter T</strong></th>
<th><strong>No points</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

**ABSTRACTION**: Similarity between e.g., banana - orange = fruit

<table>
<thead>
<tr>
<th><strong>DELAYED RECALL</strong></th>
<th><strong>Optional</strong></th>
<th><strong>ORIENTATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Date</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

Administered by: ____________________________

Add 1 point if ≥ 12 yr edu

(Translated from French by Montréal Cognitive Assessment, 2005)