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# Increased intracortical inhibition in elderly adults with anterior-posterior current flow: a TMS study.

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**Running Head:** intracortical inhibition in the elderly

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## HIGHLIGHTS

- We show no age-related difference in intracortical inhibition using a conventional (posterior-anterior) transcranial magnetic stimulation (TMS) coil orientation.
- Using the more sensitive (anterior-posterior) TMS coil orientation, we show increased intracortical inhibition in older adults.
- Reversing TMS current direction could be helpful to assess subtle differences in intracortical inhibition in clinical populations.


## ABSTRACT

*Objective:* All previous studies using TMS to assess short-interval intracortical inhibition (SICI) in older adults have used a conventional coil orientation, which produces posterior-to-anterior (PA) current flow in the motor cortex. However, no studies have examined SICI in older adults by reversing the coil to induce anterior-to-posterior (AP) current flow, which is considered more sensitive at detecting SICI. Therefore, we investigated age-related changes in SICI using both PA and AP TMS across different conditioning stimulus intensities and muscle activation states.

*Methods:* In 22 young and 20 older adults, SICI was assessed using PA and AP coil orientations, across a range of conditioning stimulus intensities (70-90% active motor threshold), and whilst participants kept their first dorsal interosseous (FDI) muscle either relaxed or active (2 N force).

*Results:* There were no age-related differences in SICI using conventional PA TMS in resting or active FDI muscle. However, SICI was increased in elderly participants when assessed with reverse coil AP TMS in resting FDI.

*Conclusions:* Coil orientation is a key factor to consider when assessing age-related differences in SICI.

*Significance:* Reverse coil AP TMS can reveal age-related changes in SICI, which were previously not evident with conventional PA TMS. This may have implications for the assessment of SICI in some clinical populations that may show subtle differences in SICI circuitry.

## 1. Introduction

One of the inevitable consequences of human ageing is a reduction in performance of many cognitive and motor tasks. In the motor domain, elderly adults are much slower at performing various fine motor tasks (Sale et al., 2005), make more errors in motor tasks requiring accuracy (Christou et al., 2011), and are more likely to fall (Fasano et al., 2012). Despite these pronounced functional deficits, the neural correlates which contribute to age-related decline in function are less understood. It is well established that normal ageing is accompanied by large-scale changes in brain structure. Older adults have reduced grey (Courchesne et al., 2000) and white matter (O'Sullivan et al., 2001) volume. Further, older adults tend to recruit larger areas of the brain to perform cognitive (Logan et al., 2002) or motor tasks (Ward et al., 2003). Although the aforementioned large-scale changes in brain structure and function are well accepted, there is less agreement on how the ageing process influences local neuronal function. A logical target to investigate age-related changes in local neuronal function is the motor cortical inhibitory network, as this network is critical in the fine control of hand muscles (Zoghi et al., 2003). Therefore, the overarching aim of the present project was to assess whether motor cortical intracortical inhibition is altered in the elderly human brain.

The function of motor cortical inhibitory networks can be assessed non-invasively in humans using transcranial magnetic stimulation (TMS). If the intensity of a single pulse of TMS is strong enough, it can depolarise the underlying cortical neurons which ultimately leads to an evoked motor response in the periphery. This motor response, known as a motor evoked potential (MEP), is recorded from the surface electromyogram (EMG) (Hallett, 2000). Importantly, if this suprathreshold stimulus is preceded 1-5 ms earlier by a subthreshold conditioning TMS pulse, intracortical inhibitory neurons activated by the conditioning pulse reduce the size of the suprathreshold stimulus, and is referred to as short-interval intracortical inhibition (SICI)(Kujirai et al., 1993). The SICI networks activated by paired-pulse TMS are believed to be GABAergic and are dysfunctional in a number of movement disorders such as Parkinson's disease (Ridding et al., 1995) and focal hand dystonia (Beck et al., 2008). Further, SICI has been shown to be important in the fractionated and selective activation of hand muscles (Zoghi et al., 2003). In this context, a reduction in SICI is involved in selecting the appropriate muscle(s) to perform a movement.

Several studies have probed the function of these SICI circuits in the elderly with paired-pulse TMS using a conventional coil orientation that produces posterior-to-anterior (PA) current flow in the brain (Peinemann et al., 2001; Kossev et al., 2002; Rogasch et al., 2009; Cirillo et al., 2010; McGinley et al., 2010; Opie et al., 2014). By reversing the coil to induce anterior-to-posterior (AP) current flow in the brain, corticospinal neurons are preferentially excited by neural elements that are susceptible to SICI (Di Lazzaro et al., 2012), which is not the case with a conventional (PA TMS) coil orientation. Thus, an AP coil orientation provides a more sensitive indirect assessment of SICI effects on the MEP (Zoghi et al., 2003). Such a coil orientation has not been used to investigate SICI in elderly humans. Therefore, the present study sought to examine SICI in resting and active muscle using the more sensitive reverse coil (AP) TMS approach, and comparing it with conventional PA TMS in young and older adults. Given that alterations in SICI may contribute to reduced motor performance in older adults, and that AP TMS is more selective for SICI circuitry, it was hypothesized that age-related differences in SICI would be influenced by the TMS coil orientation.

## 2. Methods

Data from forty-two participants were used in the analysis. This included 22 young (8 males; 24 ± 3 years) and 20 elderly (11 males; 70 ± 7 years) participants. All were right-handed, determined using the Edinburgh Handedness Inventory (Oldfield, 1971), with Laterality Quotient (LQ) values > 0.82. Each participant completed an Adult Safety Screening Questionnaire (Keel et al., 2001) and signed informed written consent documents prior to participating in the study. Participants with any history of heart attack or stroke, brain injury or surgery, diabetes, or current use of any medications known to alter cortical excitability (e.g., anti-depressant medication) were excluded from the study. Experiments were conducted with the approval of the University of Adelaide Human Research Ethics Committee, and were in accordance with the requirements of the Declaration of Helsinki.

During the experiment participants were seated in a comfortable dental chair with cushions supporting the head and neck. The left arm was abducted slightly at the shoulder to allow the participants to rest the forearm on a table beside the chair. The hand was maintained in a prone position so that the index finger could press against a load cell when the participant attempted to abduct the digit at the metacarpophalangeal articulation. The thumb was kept in

a relaxed and comfortable, abducted position by a wooden block so that it was away from the index finger and the remaining fingers were held away from the index finger with a velcro strap.

## 2.1 Apparatus and recording

The surface electromyogram (EMG) was recorded from the first dorsal interosseous (FDI) and the abductor digiti minimi (ADM) muscles of the left hand using adhesive bipolar silver/silver chloride electrodes (3M Red Dot, Ontario Canada). A lip-clip electrode was used to ground participants (Turker et al. , 1988). EMG signals were amplified (1000x), filtered (bandwidth 5-500 Hz) and digitized (2 kHz) using a CED Power 1401 interface (CED Ltd, Cambridge UK) and stored for offline analysis. A load cell was used to quantify isometric abduction force of the left index finger during the activation trials. During these trials, participants were instructed to abduct their index finger against the load cell to maintain a force output of 2 N. A digital oscilloscope placed in front of the participant was used to help the participant maintain the target force level.

All participants performed a series of manual performance tests prior to the TMS experiment using the left hand only. These included a Purdue pegboard test in which subjects were required to take pegs from a shallow well and place as many as they can into small holes in 30 seconds. This was repeated three times and the average score was then used for further analysis. Subjects subsequently performed two finger-tapping tests. In the first, the left index finger was used to tap a computer key as many times as possible in 15 seconds (Table 1). In the second task, the index finger and fifth digit were alternately activated to tap two different computer keys (Table 1). Participants also performed a maximal voluntary isometric contraction (MVC) of FDI which was measured using the same load cell used for the isometric activation trials. The ADM MVC was quantified from the maximum EMG obtained during maximal isometric abduction of the fifth (little) finger.

## 2.2 Transcranial Magnetic Stimulation (TMS)

TMS was applied to the right motor cortex using a figure-of-eight stimulating coil (90 mm in diameter), connected to two monophasic Magstim 200 magnetic stimulators (Magstim Company Limited, UK) *via* a Bistim module (Magstim Company Limited, UK) so that both

stimulators discharged through the same coil. For TMS trials inducing current flow in a posterior-to-anterior (PA) direction in the underlying motor cortex, the coil was positioned over the optimal site for a MEP in the contralateral FDI muscle, and oriented with the handle pointing backwards at 45º from the inter-hemispheric line towards the side of the hemisphere being stimulated. This coil orientation preferentially activates $I_1$-waves in corticospinal neurons at low TMS intensities (Sakai et al., 1997). For TMS trials inducing anterior-to-posterior (AP) current in motor cortex, the coil was rotated 180º to that which was used for PA trials, so that the handle pointed forward and 45º from the inter-hemispheric line towards the side of the non-stimulated hemisphere. This coil orientation preferentially activates late $I_3$-waves in corticospinal neurons at low TMS intensities (Sakai et al., 1997). Reference points were marked on the scalp to guide coil placement for each orientation.

Threshold TMS intensity was determined for PA and AP coil orientations at rest and with FDI active for each individual. Resting motor threshold (RMT) for FDI was assessed while the muscle was completely relaxed. There were two criteria used to establish RMT. First, RMT was taken as the lowest TMS intensity producing an average MEP with peak-to-peak amplitude >50 μV (mean of 5 successive TMS pulses). This measure of RMT was established by online averaging of the MEPs. The second criterion used to establish RMT was that the peak-to-peak amplitude of MEPs in single trials was required to exceed 50 μV in 3 of 5 successive trials. Thus, RMT was established only when both criteria were fulfilled for each participant. Active motor threshold (AMT) was assessed while subjects activated FDI during an isometric index finger abduction of 2 N. AMT was defined as the lowest TMS intensity producing an average MEP (n = 10) with peak-to-peak amplitude >100 μV, with at least 5 of 10 MEPs in the sequence having amplitude >100 μV. TMS intensity was adjusted in increments and decrements of 1% maximum stimulator output (MSO) during the determination of RMT and AMT.

To assess SICI in FDI, a paired-pulse TMS paradigm was used. This consisted of a subthreshold conditioning TMS pulse (expressed as a percentage of AMT) followed 3 ms later by a suprathreshold, test TMS pulse (Kujirai et al., 1993). Three conditioning stimulus intensities were used (70% AMT, 80% AMT, 90% AMT). The test stimulus intensity with PA or AP stimulation was adjusted to produce an MEP in FDI of ~1 mV at rest with each coil orientation. This TMS intensity was used for both rest and FDI active trials. For each conditioning intensity, 10 paired-pulse trials and 10 test alone trials were obtained, and the

order of these trials was randomised. SICI was quantified by expressing average conditioned MEPs as a percentage of average test alone MEPs. Onset latencies of the FDI test alone MEPs produced with both coil orientations were examined for evidence of I-wave activation (Hanajima et al., 1998; Zoghi et al., 2003). The latency of the test MEP was determined as the time from the onset of the TMS-evoked artefact until the first detectable deviation from baseline of the EMG associated with the MEP. Previous research has shown that when muscle activity, coil orientation and stimulus intensity are systematically manipulated, the latency of the MEP changes in ~1.5 ms increments (Hanajima et al., 1998; Zoghi et al., 2003). This is consistent with the firing rate of I-waves of ~600 Hz (Ziemann et al., 2000). A longer latency would be consistent with motoneurons being brought to threshold by the TMS by a later I-wave volley. The order of the conditioning intensities and coil orientations used was randomised. During SICI trials, participants viewed an oscilloscope display of FDI and ADM EMG at high gain and also index finger abduction force. For rest trials, participants were instructed to keep the entire hand and arm as relaxed as possible. Trials were excluded where voluntary EMG activity was detected in either FDI or ADM. In the FDI active state, participants performed an isometric abduction of 2 N with the index finger while attempting to keep ADM completely relaxed. This was done with the assistance of the visual feedback from the oscilloscope. Participants practised the task for several minutes prior to the TMS experiment to optimise their performance. Pre-stimulus EMG was assessed for FDI and ADM from a 47 ms epoch (50 – 3 ms preceding each single and paired-pulse TMS trial) (Zoghi et al., 2003) in both the rest and active conditions. This was to ensure that all subjects were performing the task correctly.

### 2.3 Statistical analysis

Age and manual performance tests were compared between groups by unpaired student's t-tests. Handedness scores (LQ values) were not normally distributed and were therefore compared between groups using the Mann-Whitney U-test. Mean pre-stimulus EMG was quantified off-line and analysed using a three-way repeated measures analysis of variance (ANOVA) with between-subject factor Age (young, old), and within-subject factors Muscle State (rest, active) and Coil Orientation (AP, PA). Separate three-way repeated measures ANOVAs were also conducted to investigate the effect of Age, Muscle State and Coil Orientation on threshold TMS intensity, test MEP latency, TMS intensity, and test MEP

amplitude. Individual mixed-model analyses were used on the data for FDI to examine the fixed effects of Age, Muscle State, Coil Orientation and Conditioning Intensity (70%, 80% and 90% AMT) on SICI. Subject was included as a random effect, and data were fitted with an autoregressive covariance structure (PASW software, version 18.0; SPSS, Chicago, IL, USA). Significant interactions were further investigated using Bonferroni corrected custom contrasts. Linear regression of individual subject data was used to examine correlations between SICI (PA and AP TMS at each conditioning intensity and muscle state) and measures of motor performance (pegboard score, single and double tap) in each age group. A significance level of $P < 0.05$ was used for all comparisons. Data are expressed as mean ± SEM.

## 3. Results

As expected, there were significant differences between groups in age and manual performance. Mean age of the young participants was 24 ± 1 years (n = 22) and 69 ± 2 years (n = 20) for the elderly (t-test, $P < 0.001$). Young participants performed better than the elderly for all three tests of manual performance, with a 33% difference on the pegboard scores, 21% difference on single tap, and 55% difference on alternate tap (Table 1). Handedness was not different between age groups. Mean LQ (range) was 0.97 (0.82 - 1.00) in the young and 0.96 (0.82 - 1.00) in the elderly (U test, $P > 0.05$). These data are shown in Table 1.

Insert Table 1 near here

There was no significant difference in prestimulus EMG between the young and elderly participants (Age, $F_{1,80} = 0.23$ , $P = 0.63$). The ability to keep ADM relaxed while selectively activating FDI did not differ for young and elderly participants (Age x Activation State x Muscle: $F_{1,80} = 0.51$, $P = 0.48$). ANOVA revealed a significant effect of activation state ($F_{1,80} = 60.92$, $P < 0.0001$) and significant interaction between Activation State and Muscle ($F_{1,80} = 59.28$; $P < 0.0001$). *Posthoc* analysis revealed a significant increase in FDI EMG ($P < 0.0001$), but not ADM EMG, during the FDI Active state compared to rest. This indicates a selective activation of FDI for this task, which was similar for both young and elderly participants.

### 3.1 Baseline cortical excitability

The threshold TMS intensity for evoking an MEP in FDI was higher in elderly *vs.* young participants for both PA and AP TMS, and rest and FDI active trials (Table 2). Three-way ANOVA revealed a significant effect of Age ($F_{1,40} = 4.47$, $P < 0.05$), Muscle State ($F_{1,40} = 305.4$, $P < 0.0001$), and Coil Orientation ($F_{1,40} = 165.3$, $P < 0.0001$). None of the interactions involving Age in the ANOVA were significant, indicating that the reduction in TMS threshold with FDI activation (*vs.* rest) and PA TMS (*vs.* AP TMS) were similar for young and elderly participants.

FDI threshold MEP latency was longer in the elderly by ~ 2 ms (Table 2; $F_{1,40} = 21.15$, $P < 0.0001$). Threshold MEP latency was also longer at rest ($F_{1,40} = 51.8$, $P < 0.0001$) and with AP TMS ($F_{1,40} = 202.3$, $P < 0.0001$). The interaction between Muscle State and Coil Orientation was significant ($F_{1,40} = 8.04$, $P < 0.01$), with a larger difference in threshold MEP latency between AP and PA TMS with FDI active compared to rest (2.4 ms *vs.* 1.7 ms). Importantly, none of the interaction terms involving Age were significant in the ANOVA, indicating that the effects of muscle activation and coil orientation on MEP threshold latency were similar in young and elderly participants.

Insert Table 2 near here

3.2 Short-interval intracortical inhibition

The TMS intensity used to evoke a test MEP in the assessment of SICI was similar between age groups ($F_{1,40} = 0.83$, $P = 0.37$). In the young group the mean TMS intensity was 68 ± 2% MSO with PA TMS, and 88 ± 3% MSO with AP TMS. Corresponding values in the elderly were 74 ± 3% and 90 ± 3%, respectively. The test TMS intensity was higher with AP TMS than PA TMS ($F_{1,40} = 126.98$, $P < 0.0001$). Test MEP amplitude in the SICI trials did not differ significantly between young and elderly participants ($F_{1,80} = 0.90$, $P = 0.35$), but were higher with a PA coil orientation ($F_{1,80} = 5.55$, $P = 0.02$).

Insert Figure 1 near here

The assessment of FDI SICI in young and elderly participants during rest and FDI activation revealed that SICI was influenced by conditioning intensity, activation state, coil orientation and age (all P values < 0.001). Importantly, however, there was also a coil orientation and conditioning intensity interaction ($P = 0.01$), and a coil orientation, activation state and conditioning intensity interaction ($P < 0.001$). *Posthoc* pair-wise comparisons revealed that

SICI was increased in older adults during rest with an AP coil orientation, but this was restricted to the 90% RMT conditioning stimulus intensity (Fig 1B). None of the other coil orientation x conditioning stimulus intensity comparisons differed between young and old participants. However, there existed strong trends towards main effects of age for the PA coil orientation in active muscle (Fig 1C; P = 0.06) and AP coil orientation in active muscle (Fig 1D; P = 0.05). When SICI between young and elderly participants was compared using the "conventional" approach (i.e., PA coil orientation during rest; Fig 1A), there were no significant differences between groups at any of the conditioning intensities.

Linear regression analysis showed no significant correlations between SICI (coil orientation, conditioning intensity or muscle state) and Purdue pegboard performance or single finger tap in young or old adults. However, there were weak correlations between SICI and alternate finger tap with AP TMS at 80% and 90% AMT for young (80% AMT, $r^2 = 0.27$, P =0.01; 90% AMT, $r^2 = 0.25$, P =0.02) but not old subjects (80% AMT, $r^2 = 0.07$, P =0.27; 90% AMT, $r^2 = 0.04$, P =0.43) in resting muscle. No other correlations were statistically significant for all other measures of SICI and alternate finger tap.

## 4. Discussion

The ageing process in humans leads to a myriad of functional deficits. Despite this well documented age-related decline in function, the neural substrate responsible for the deterioration in function remains elusive. In the motor domain, the intracortical inhibitory network is involved in the precise control of the fingers (Zoghi et al., 2003). The purpose of this study was to investigate the function of the motor cortical intracortical inhibitory network in a cohort of healthy young and elderly participants, who demonstrated clear age-related differences in performance on a variety of dexterity tasks. Using the most sensitive indirect measures of SICI in humans (an anterior-posterior coil orientation), we show increased levels of intracortical inhibition in a resting muscle of older adults. Further, with the most commonly used approach to probe intracortical inhibition (posterior-anterior coil orientation), we show that these same participants show no age-related changes in SICI.

### 4.1 SICI is increased in elderly participants with AP coil orientation

Several previous studies had examined the function of SICI circuits in elderly human participants, and these have yielded mixed results. Some studies have reported an age-related decline in intracortical inhibition (Peinemann et al., 2001), others reported an increase

(Kossev et al., 2002; McGinley et al., 2010), whilst others reported no change (Oliviero et al., 2006; Rogasch et al., 2009; Cirillo et al., 2010; Opie et al., 2014). There are several methodological differences that could have contributed to this. Nevertheless, one consideration that has not been investigated, but which has a profound influence on SICI in young participants (Sakai et al., 1997; Di Lazzaro et al., 2012), is the orientation of the TMS coil.

When a single TMS pulse is delivered to the motor cortex of humans, it produces descending activity down the corticospinal tract (Day et al., 1989). The earliest of these "waves" of activity is referred to as a direct or D-wave. Subsequent waves are referred to as indirect or I-waves. The relative distribution of D- and I-waves is related to a variety of factors, including the intensity of TMS and the direction of the induced current due to the orientation of the coil (Di Lazzaro et al., 2012). When the TMS is oriented in an anterior-posterior direction over motor cortex, later I-waves, termed $I_3$-waves are preferentially activated (Day et al., 1989; Hanajima et al., 1998). These I-waves are more susceptible to SICI (Hanajima et al., 1998; Zoghi et al., 2003) compared to the earlier I-waves that are activated during PA stimulation. Using the more sensitive AP coil orientation we show that SICI is more pronounced in elderly participants compared to young participants. There are a number of possible explanations for this result. First, SICI is influenced by the size of the test stimulus (Opie et al., 2014). However, in our cohort test MEP amplitude was equivalent between young and elderly participants, and thus cannot explain this result. Second, it is possible that there were age-related differences in the recruitment of I-waves with PA and AP stimulation. However, we assessed the latency of the test MEPs with the different coil orientations and activity levels. MEP latency is an indirect, but well-established measure to probe the relative recruitment of D- and I-waves in humans (Nakamura et al., 1997; Zoghi et al., 2003). The mean latency in the AP rest condition, which should preferentially activate $I_3$-waves, was 2-3 ms longer than the condition which preferentially activates $I_1$-waves (PA stimulation during muscle activation). Although elderly participants had longer MEP latencies, importantly, the latency differential was equivalent for both young and elderly participants (see Table 2). Therefore, differential recruitment of I-waves in young and elderly participants is unlikely to explain our result. The most parsimonious explanation, therefore, for our result is that elderly adults exhibit subtle differences in intracortical inhibition and this interacts with the neural elements activated by AP TMS to produce greater SICI. It should be noted, however, that the present study did not use a neuronavigation system to monitor the position of the TMS coil.

Such a system has been shown to reduce the variability of MEPs evoked with TMS (Cincotta et al., 2010), and thus it is possible that a more reliable measure of SICI changes could have been obtained with neuronavigation equipment.

The increase in SICI in the elderly was only evident at high conditioning stimulus intensities (i.e., 90% RMT). This suggests that high stimulus intensities are required to activate the neural elements responsible for SICI modulation. Thus, our findings suggest that the most effective stimulus intensity to probe SICI changes in the elderly is 90% RMT, with an AP coil orientation. It should be pointed out that SICI assessed with high conditioning stimulus intensities and with a 3 ms ISI are known to be confounded by intracortical facilitatory effects when PA TMS is used (Peurala et al., 2008). However, it is now known if this is also the case with AP TMS.

Another interesting finding from the present study was that ageing was associated with an increase in RMT and AMT, which was consistent for both coil orientations. The majority of previous studies which have reported RMT and AMT in young and elderly subjects have shown no age-related change in these measures (Kossev et al., 2002; Wassermann, 2002; Pitcher et al., 2003; Oliviero et al., 2006; Rogasch et al., 2009; Smith et al., 2009; Cirillo et al., 2010; Smith et al., 2011). However, in all cases there is typically a trend towards increased RMT and AMT in elderly participants. This would suggest that there may have been subtle age-related differences in RMT and AMT in these studies, but the effect size was too small. Using a greater sample size than most previous studies, we show that RMT and AMT are increased in older adults with both PA and AP TMS. An increase in RMT and AMT could be explained in several ways. It could reflect a decrease in corticospinal excitability with advancing age. It could also indicate an increase in scalp-to-cortex distance with advancing age (Stokes et al., 2005; Groppa et al., 2012). Thus, a higher stimulus intensity is required to activate the underlying cortical neurons in the elderly. This would be consistent with imaging studies suggesting that the aged brain shows brain-wide atrophy (Fjell et al., 2013). In order to distinguish between these two possibilities, individual structural magnetic resonance imaging scans co-localised to neuronavigated TMS would be required to establish scalp-cortex distance (see Stokes et al., 2007).

### 4.2 No age-related differences in SICI with conventional PA stimulation

When we assessed SICI in young and elderly participants with a "conventional" experimental montage – i.e., PA stimulation during rest, there were no age-related changes in SICI. This is consistent with previous reports of SICI in the elderly (Oliviero et al., 2006; Rogasch et al., 2009; Cirillo et al., 2010; Opie et al., 2014). Importantly, however, when the participants in the present study were also assessed with AP stimulation, a significant age-related change in SICI was evident. This suggests that coil orientation, and specifically using a coil orientation that produces AP current flow in the motor cortex, is critical for probing age-related changes in SICI in humans.

Elderly humans exhibit impaired performance on a variety of dexterity tasks compared to younger participants. The findings of the present study support that observation. Further, the present study found that SICI is increased in the elderly, although this was largely unrelated to the measures of manual performance that we obtained in this study, with no correlations observed between SICI and motor performance in elderly subjects. Therefore, we can only speculate on the potential significance of increased SICI in this population. Intracortical inhibition is thought to exert a tonic suppressive influence on motor output, such that unwanted movements are prevented. In order to produce an isolated, precise finger movement, the relevant neural elements responsible for undertaking a movement are released from inhibition (Zoghi et al., 2003; Stinear et al., 2004). Our findings suggest that the elderly have an increased level of SICI during rest, and that it may be more difficult to suppress this inhibition during a task to perform it correctly. This is supported to some extent by the finding that there was a strong trend to increased SICI during activation of FDI in the elderly (Figure 1D).

In conclusion, we found that SICI in motor cortex was increased in elderly humans at rest, but that this age-related change was only evident when an AP coil orientation was used. We contend that coil orientation is a key factor to consider when assessing age-related differences in SICI with TMS. Further, when the reverse (optimal) coil orientation is used, the neural elements that are susceptible to SICI are activated, and these elements show age-related changes. If earlier I-waves are activated, these elements are more resistant to modulation by SICI, and age-related changes may not be detected. These coil orientation effects may have implications for the assessment of SICI in clinical populations (Berardelli et al., 2008) where

subtle differences in SICI may be revealed with the more selective reverse current (AP) TMS rather than the conventionally used PA TMS.

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**Conflict of Interest**

The authors declare no conflict of interest.

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Figures and legends

Figure 1

Elderly adults have increased SICI, but only with an anterior-posterior coil orientation. Group (mean ± SEM) SICI data from FDI muscle showing effects of posterior-anterior coil orientation (A, C) and anterior-posterior coil orientation (B, D) on SICI in young (black circles) and old (white circles) adults at rest (top panels) and during voluntary activation (bottom panels) of FDI. SICI was assessed with paired-pulse TMS using three different conditioning TMS intensities (70-90% RMT), with an interstimulus interval of 3 ms. SICI was quantified as percentage of MEP amplitude obtained in conditioned trials compared with test-alone trials. * $P < 0.05$.

Tables

**Table 1. Group Characteristics and Manual Performance**

| | Young | Elderly | P Value |
|---|---|---|---|
| n | 22 (8M) | 20 (11M) | — |
| Age (Yrs) | 24 ± 1 | 69 ± 2 | < 0.001 |
| Laterality Quotient | 0.97 [0.82 – 1.0] | 0.96 [0.82 – 1.0] | n.s. |
| Pegboard | 16 ± 1 | 12 ± 1 | < 0.001 |
| Single tap | 272 ± 8 | 224 ± 7 | < 0.001 |
| Double tap | 299 ± 18 | 193 ± 14 | < 0.001 |

Data are shown as mean ± S.E.M, or mean [range]. Significant difference between groups (paired *t* test). n.s., not significant (Mann-Whitney U test).

**Table 2. MEP Latency and TMS intensity at threshold**

| | | Rest | | Active | |
|---|---|---|---|---|---|
| | | Young | Elderly | Young | Elderly |
| Latency (ms) | PA TMS | 24.3 ± 0.4 | 26.6 ± 0.4 | 23.0 ± 0.4 | 25.1 ± 0.4 |
| | AP TMS | 26.0 ± 0.3 | 28.4 ± 0.4 | 25.0 ± 0.4 | 27.9 ± 0.5 |
| Threshold (%MSO) | PA TMS | 56.3 ± 1.4 | 62.6 ± 2.8 | 39.6 ± 1.0 | 47.2 ± 2.4 |
| | AP TMS | 73.2 ± 2.5 | 78.3 ± 3.5 | 56.1 ± 1.8 | 62.3 ± 3.2 |

Data are mean ± S.E.M. FDI threshold MEP latency (ms) and stimulus intensity (% maximum stimulator output; %MSO). Young group, n = 22, Elderly group, n = 20