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Intracortical inhibition assessed with paired-pulse transcranial magnetic stimulation is modulated during shortening and lengthening contractions in young and old adults

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Running Head: Age- and movement related changes in intracortical inhibition

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Abstract

Background: The modulation of intracortical inhibition is thought to be impaired in older adults, which may contribute to their reduced fine motor control, particularly during lengthening muscle contractions.

Objective: To quantify the magnitude of intracortical inhibition and movement performance during postural, shortening and lengthening contractions of a hand muscle in young and old adults.

Methods: In 18 young (23.2 ± 4.2) and 16 old (70.6 ± 6.5) subjects, paired-pulse transcranial magnetic stimulation (TMS) was used to assess short- (SICI) and long-interval intracortical inhibition (LICI) during a movement task involving the first dorsal interosseous muscle. The task required a constant load (50 g) to be slowly lifted and lowered using the index finger while single- or paired-pulse TMS was delivered during the shortening or lengthening contraction.

Results: Relative to postural contractions, SICI during shortening contractions was reduced by 29% in young subjects ($P < 0.0001$) and 43% in old subjects ($P < 0.0001$), whereas SICI during lengthening contractions was reduced by 11% in young subjects ($P = 0.0004$) and 33% in old subjects ($P < 0.0001$). Furthermore, SICI was significantly less in older adults during lengthening contractions (P-values < 0.01). For LICI, inhibition was not influenced by contraction type in old subjects, but was increased by 11% during shortening contractions ($P < 0.0001$) and 9% during lengthening contractions in young subjects ($P = 0.0008$). In addition, old subjects showed significantly less LICI than young subjects in each movement phase (both P-values < 0.05).

Conclusions: Shortening and lengthening contractions with a constant load are associated with a modulation of GABAergic inhibition that is altered by healthy ageing.

Keywords: Transcranial magnetic stimulation, gamma aminobutyric acid, ageing, anisometric contractions

Abbreviations: AMT, active motor threshold; SP, silent period; FDI, first dorsal interosseous muscle; fMRI, functional magnetic resonance imaging; GABA, gamma aminobutyric acid; LICI, long-interval intracortical inhibition; M1, primary motor cortex; MCP, metacarpophalangeal joint; MEP, motor evoked potential; MSO, maximum stimulator output; MVC, maximum voluntary contraction; RMT, resting motor threshold; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

Introduction

A growing body of evidence suggests that the neural control of lengthening contractions represents a unique component of movement control. This includes observations that voluntary activation, electromyography (EMG), force generation and spinal motoneuron excitability are all different during lengthening contractions [1, 2]. Furthermore, recent evidence from studies using a range of neurophysiological and neuroimaging techniques have provided compelling support for distinct patterns of cortical activity during lengthening contractions [3-11]. In addition, lengthening contractions are also associated with reduced motor performance [12-14]. Interestingly, the magnitude of this deficit is thought to be increased by advancing age, with greater impairments in performance observed in old adults during lengthening movements [13, 15-18], which may contribute to the increased incidence of falls in the elderly [19].

Although age-related differences in neuromuscular function are well established [20] our understanding of the CNS mechanisms contributing to this movement deficit in old adults is limited. One factor that may contribute to this impaired motor performance is changes in inhibitory neurotransmission within primary motor cortex (M1) mediated by the neurotransmitter gamma amino-butyric acid (GABA). In young subjects, transcranial magnetic stimulation (TMS) has been used to show that the modulation of local GABAergic inhibition is important for motor performance during isometric contractions [21-24]. Furthermore, variations in GABAergic inhibition during shortening and lengthening muscle contractions have also been proposed in young subjects [7, 8, 25], suggesting that these circuits may contribute to the accurate performance of slow movements. However, these previous studies have relied on the assessment of GABAergic inhibition from measures of the EMG silent period (SP) duration following TMS during shortening and lengthening

contractions [7, 8, 25], which is difficult to interpret and highly sensitive to changes in spinal excitability (for review, see; [26]). As previous studies with paired-pulse TMS have shown that a reduced ability to modulate GABAergic inhibition prior to contraction is associated with impaired motor performance in older adults [27], it is possible that age-related changes in the modulation of M1 GABAergic inhibition during movements (particularly lengthening contractions) may contribute to the movement performance deficits commonly observed in the elderly.

The main aim of the current study was therefore to investigate variations in GABAergic inhibition within contralateral M1 of young and old subjects during functional movements that involve shortening and lengthening contractions. We used paired-pulse TMS to assess $GABA_A$-mediated short-interval intracortical inhibition (SICI) and $GABA_B$-mediated long-interval intracortical inhibition (LICI), which provides a more robust assessment of M1 GABAergic inhibition compared with previous studies involving the SP [28]. As previous findings suggest that lengthening contractions are associated with disinhibition of contralateral M1 [7, 8, 25], we expected that lengthening movements would also be associated with a reduction in SICI and LICI. In addition, as the activity-dependent modulation of inhibitory tone is thought to be reduced in old adults [27, 29, 30], and this has been related to impaired motor performance in the elderly [27], we expected that old individuals would demonstrate less modulation of cortical inhibition during movement, and that this would be associated with greater motor deficits in older adults.

Methods

Eighteen young (mean ± SD: 23.3 ± 4.2 years; 9 females) and 16 old (70.6 ± 6.5 years, 9 females) healthy subjects were recruited from the university and wider community to participate in the current study. Exclusion criteria included a history of neurological or

psychiatric disease, or current use of psychoactive medication (sedatives, antipsychotics, antidepressants etc.). Hand preference and laterality was assessed using the Edinburgh Handedness Inventory [31]. All experimentation was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the declaration of Helsinki. Each subject provided written, informed consent prior to participation.

Experimental arrangement

Subjects were seated in a chair with their right arm abducted approximately 45° at the shoulder. The right hand and forearm was pronated on a purpose built manipulandum, similar to that described previously [32], which was located on a table in front of the subject. The index finger was extended over a cavity within the manipulandum, while the third, fourth and fifth fingers were flexed around the edge of the cavity at the level of the metacarpophalangeal (MCP) joint. The thumb was extended against a padded support on the manipulandum and the forearm was strapped to an adjustable rest. A strap was also placed across the hand to minimise movement. This position allowed abduction-adduction of the index finger that was isolated to activation of the first dorsal interosseous (FDI) muscle. A circular plastic cast placed around the distal end of the index finger was attached to a 50 g load via a length of low compliance line. The line ran over a pulley attached to the edge of the manipulandum, suspending the load in mid-air. Within this setup, abduction movements corresponded to raising the load (shortening contraction), while adduction movements corresponded to lowering the load (lengthening contractions), with the combined movements against the load defined hereafter as an anisometric contraction.

Surface EMG was used to record responses from the FDI muscle of the right hand. Two Ag-AgCl electrodes (1.5 cm diameter) were attached to the skin over the muscle in a belly-tendon montage, with a strap around the wrist grounding the electrodes. Acceleration of the

index finger in the abduction-adduction plane was measured using a uniaxial accelerometer (V94-41, Coulbourn Instruments, Whitehall, PA) that was placed on the medial surface of the plastic cast attached to the index finger. Position of the index finger was assessed via a potentiometer where the rotational axis was aligned with the MCP joint and securely attached along the length of the index finger. EMG was amplified (300 X) and band-pass filtered (20 Hz high pass, 1 kHz low pass) using a CED1902 (Cambridge Electronic Design, Cambridge, UK). EMG, position and acceleration signals were digitized at 2 kHz using a CED1401 interface (Cambridge Electronic Design), before being recorded and stored offline for analysis. To facilitate muscle relaxation when required, real-time EMG signals were displayed under high gain (50 μV/ division) on an oscilloscope placed in front of the subject.

Experimental Procedures

Maximal Voluntary Contraction. Index finger abduction force during maximum voluntary contraction (MVC) was assessed for each subject. MVCs were conducted with the hand positioned on the manipulandum as described above and with 0° of index finger abduction. When instructed, subjects abducted the lateral surface of the index finger against a force transducer (LC1205-K020; A&D Mercury Pty Ltd, Australia) placed in-line with the distal phalanx. Subjects were required to produce maximum force for 3 s in several repetitions, separated by 30 s rest, until the maximal force of three trials were within a 10% margin. The largest force recorded during these trials was chosen as the subject's MVC. To optimise force production, feedback was displayed on a computer monitor placed at eye level in front of the subject, and verbal encouragement was provided by the experimenter.

Postural, shortening and lengthening contractions. Subjects performed two types of low-intensity contractions against a 50 g inertial load: 1) postural contractions, during which the index finger was held abducted at a constant position of 10° from the index fingers neutral

position; and 2) anisometric contractions, during which the subject performed abduction-adduction movements of the index finger over a 20° range of motion. For both contraction types, a display screen showing two cursors was placed at eye level in front of the subject. One cursor represented the position of the index finger, while the second represented a target position. Subjects performed the required movement by matching the position cursor to the target cursor. During postural contractions, the target cursor was static, representing the required abduction angle, whereas during anisometric contractions, the target cursor formed a triangular template representing a constant velocity contraction of 4 degs/s. The assessment of intracortical inhibition during postural contractions required subjects to maintain index finger abduction for approximately 4 minutes, while the assessment of intracortical inhibition during movement required the completion of 72 shortening and 72 lengthening contractions (see below). At the beginning of both postural and anisometric contractions, subjects were instructed to match the position of the target cursor as accurately as possible at all times. During the contractions, encouragement to perform the task accurately was also provided by the experimenter.

Transcranial magnetic stimulation. TMS was applied to the left primary motor cortex using a figure-of-eight coil (external wing diameter 9 cms) with two Magstim 200^2 magnetic stimulators connected via a Bistim unit (Magstim, Dyfed, UK). The coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, with the handle pointed backwards and laterally, producing an anteriorly directed current flow in the brain. The coil was positioned on the scalp over the location producing an optimum response in the relaxed FDI muscle. This location was marked on the scalp for reference and continually checked throughout the experiment. During resting and postural measurements, TMS was delivered at 0.2 Hz. However, during anisometric measurements, the rate of TMS delivery depended on which contraction phase the previous stimulus had been applied, with a frequency of 0.14 Hz

occurring when a stimulus on the lengthening phase followed a stimulus on the shortening phase, and a frequency of 0.08 Hz occurring when a stimulus on the shortening phase followed a stimulus on the lengthening phase.

Resting and Active motor thresholds (RMT and AMT, respectively) were obtained in FDI while the TMS coil was placed at the optimal location over primary motor cortex. RMT was defined as the minimum TMS intensity producing a response amplitude ≥ 50 μV in three out of five trials in resting FDI muscle, and expressed relative to the maximum stimulator output (MSO). Active motor threshold (AMT) was defined as the minimum TMS intensity producing a response amplitude ≥ 200 μV in three out of five trials while subjects performed the postural contraction at 10° of index finger abduction. In addition, AMT was also assessed separately for shortening and lengthening contractions. Due to time constraints, this assessment utilised a modified version of the anisometric contraction described above; subjects abducted and adducted the index finger over a 10° range of motion, from 5° to 15° of index finger abduction, with stimuli applied at 10°. This ensured that stimuli were applied at a comparable muscle length to that used during all other assessments.

Intracortical inhibition. Contraction phase-dependent changes in intracortical inhibition were assessed by examining measurements of SICI and LICI recorded during postural, shortening and lengthening contractions of FDI. To ensure that each subject exhibited a moderate level of inhibition during the postural contraction (baseline) that could be modulated (increased or decreased) during movement, the intensity of the conditioning stimulus for SICI and LICI was adjusted during the postural contraction to produce an ~50% reduction (range 25 to 75% reduction) in the amplitude of a 2 mV test MEP (when assessed in isolation). A test MEP amplitude of 2 mV was used as this produced a consistent and clearly discernable MEP relative to background EMG during each contraction phase, and matched that used during

active contractions in a previous study of intracortical inhibition in older adults [33]. The 2 mV intensity was determined separately for postural, shortening and lengthening contractions. This was performed because preliminary experiments at a constant test TMS intensity produced large variations (range from 1 mV in the postural task to 8 mV during shortening) in test MEP amplitude during the different contraction phases, and these large differences in MEP amplitude would confound the comparison of SICI and LICI between tasks [34, 35]. Measurements of SICI used a 2 ms interstimulus interval (ISI), whereas measurements of LICI used a 150 ms ISI.

For the assessment of baseline inhibition during a postural contraction, both paradigms were applied in the same block, allowing normalisation to a common test alone MEP. As 24 conditioned trials (12 SICI, 12 LICI) and 12 unconditioned trials were included in a block, 36 trials were applied to assess baseline inhibition. For the assessment of contraction type-dependent changes in inhibition, TMS was applied at the midpoint of each contraction phase (i.e., 10° of abduction) to match the joint angle used during postural contractions. Furthermore, while a single movement trial consisted of both shortening and lengthening movements, TMS was only applied on one contraction phase (shortening or lengthening) for each trial. As 24 conditioned (12 SICI, 12 LICI) and 12 unconditioned trials were applied in each phase, a total of 72 trials were used to assess contraction type-dependent changes in intracortical inhibition. However, as a single trial lasted 12 s, the experimental block was broken into 6 blocks of 12 trials, with a 30 s break between blocks, to avoid fatigue and loss of attention.

To enable comparisons with previous studies, SP duration was also assessed from a subset of subjects that demonstrated a reliable SP. These measurements were assessed in each contraction type during application of the test alone MEP. EMG was first rectified then SP

duration was assessed from the time of TMS to the point at which EMG crossed the pre-stimulus mean (using a 200 ms pre-stimulus period). This was calculated using a modified cumulative sum (CUSUM) method [36].

Data Analysis

Data analysis was completed manually by visual inspection of offline EMG. MEP amplitudes from each trial were measured peak-to-peak and expressed in mV. Paired-pulse measurements of intracortical inhibition were quantified by expressing the amplitude of individual conditioned MEPs as a percentage of the average unconditioned MEP amplitude. For all contraction types and in both subject groups, the level of muscle activity in each condition was assessed by quantifying the mean rectified EMG amplitude in the 100 ms prior to the conditioning stimulus for SICI and LICI trials, or the test stimulus for test alone MEP trials. These values were normalised to the mean rectified EMG amplitude recorded during MVC. Motor output during different contraction types was assessed using acceleration SD and the absolute error between position and target cursors. During postural contractions, acceleration SD and absolute error were averaged over the 800 ms prior to application of TMS, whereas during anisometric contractions, acceleration SD and absolute error were averaged over the middle 3 s of each contraction phase. As the muscle twitch associated with TMS would confound the assessment of performance, only phases in which TMS was not applied were used for analysis of movement performance.

Statistical analysis

Normality of distribution was assessed using Kolmogorov-Smirnov tests, while homogeneity of variance was assessed using Levene's test. Measurements that failed to meet these assumptions were analysed using either non-parametric tests (when available) or parametric tests on Log transformed data. Mann-Whitney *U* tests were used to compare age, handedness

and RMT between young and old groups. The effects of contraction type (postural hold, shortening, lengthening) and age (young, old) on AMT and test TMS intensity were investigated using individual 2-way repeated measures analysis of variance ($ANOVA_{RM}$). A 2-way $ANOVA_{RM}$ was also used to investigate the effects of contraction type and age on Log transformed prestimulus EMG data. All main effects and interactions were further investigated using Bonferroni post hoc tests. Individual linear mixed models with repeated measures were used to compare the fixed effects of contraction type and age on indices of performance (acceleration SD, absolute position error), SICI, LICI, SP duration and the amplitude of the test alone MEP within SICI and LICI blocks. For all models, analysis was carried out on Log transformed data, subject was included as a random effect and all significant main effects and interactions were further investigated using Bonferroni post hoc tests. Linear regression of individual subject data was used to investigate associations between measurements of inhibition and indices of motor performance derived from postural and anisometric contractions. Unless otherwise stated, significance was set at $P < 0.05$ for all comparisons. Data not Log transformed prior to analysis are presented as mean ± 95% confidence interval (CI) [lower limit, upper limit], whereas Log transformed data have been back-calculated and are presented as the geometric mean ± 95% CI [lower limit, upper limit].

Results

All subjects completed the experiment in full and without adverse reaction. However, it was not possible to produce the required level of baseline SICI or LICI during postural contractions (i.e., ~ 50% inhibition of test MEP amplitude) in some subjects. Subsequently, not all subjects contribute data to the analysis of both measurements. Fourteen subjects from each age group are included in the analysis of SICI, whereas 15 subjects from each group are

included in the analysis of LICI. A total of 11 young and 13 old subjects contributed data to both measurements.

Baseline characteristics for all subjects are shown in Table 1. The results of the Edinburgh Handedness Inventory showed that the study cohort was, on average, right hand dominant, and that this was not effected by age ($P = 0.4$). Furthermore, no differences were found between groups for RMT ($P = 0.8$), or MVC force ($P = 0.3$), whereas MVC EMG was significantly reduced in older subjects ($P = 0.01$). AMT differed between contraction types ($F_{2,32} = 24.84$, $P < 0.001$), with post hoc analysis showing that AMT during postural contractions was increased relative to both shortening and lengthening contractions ($P < 0.0001$), but not different between shortening and lengthening contractions ($P = 0.03$). Furthermore, there was no difference between age groups ($F_{1,32} = 0.08$, $P = 0.8$) and no interaction between factors ($F_{2,64} = 1.98$, $P = 0.1$). Pre-stimulus EMG differed between age groups ($F_{1,32} = 10.42$, $P = 0.003$), with post hoc testing showing increased activity in old subjects ($P = 0.003$), but there was no difference between contraction types ($F_{2,32} = 1.75$, $P = 0.2$) and no interaction between factors ($F_{2,64} = 0.63$, $P = 0.5$).

Intracortical inhibition

Representative SICI and LICI data from a single old subject (75 years) during each contraction type is shown in Figure 1A and 1B. For this subject, AMT was 33% MSO, 31% MSO and 32% MSO during postural, shortening and lengthening contractions, respectively, while test TMS intensity was 40% MSO, 37% MSO and 36% MSO during postural, shortening and lengthening contractions, respectively. This subject showed SICI of 66% during postural contractions, which was reduced to 85% during shortening contractions and 68% during lengthening contractions (Figure 1A). For LICI, inhibition of 52% was obtained

during postural contractions, and this was reduced to 63% and 87% during shortening and lengthening contractions, respectively (Figure 1B).

Short interval intracortical inhibition. For all subjects that demonstrated a moderate level of baseline SICI, the amplitude of the test alone MEP used to assess SICI during each contraction type is shown for both young (n = 14) and old (n = 14) subjects in figure 2A. The test alone MEP varied between contraction types ($F_{2,553}$ = 2.97, P = 0.05), but post hoc testing failed to show any significant differences between specific contraction types (all P-value > 0.08) Furthermore, test MEP amplitude was comparable between age groups ($F_{1,25}$ = 0.005, P = 0.9) and there was no interaction between factors ($F_{2,553}$ = 2.12, P = 0.1). The TMS intensity used to produce the test alone MEP differed between contraction types ($F_{2,26}$ = 52.83, P < 0.001), with post hoc analysis showing that the intensity required during postural contractions (young, 48.7 [45.1, 52.3] MSO; old, 47.6 [42.7, 52.4]% MSO) was greater than during either lengthening (young, 45.0 [41.9, 48.1] MSO; old, 44.3 [39.6, 49.0]% MSO) contractions (P-values < 0.001) or shortening (young, 43.1 [39.8, 46.3]% MSO; old, 42.6 [38.3, 46.8]% MSO), and that the TMS intensity during lengthening contractions was greater than during shortening contractions (P = 0.001). However, no effect of age ($F_{1,26}$ = 0.08, P = 0.8) or interaction between factors ($F_{2,52}$ = 0.19, P = 0.8) was found.

Variations in SICI during each contraction type are compared between young and old subjects in figure 2B. The magnitude of SICI differed between contraction types ($F_{2,553}$ = 88.03, P < 0.001) and age groups ($F_{1,25}$ = 5.35, P = 0.03), and there was an interaction between factors ($F_{2,553}$ = 5.35, P = 0.005). In young subjects, post hoc analysis showed that SICI during shortening contractions was reduced relative to both postural and lengthening contractions, whereas SICI during lengthening contractions was reduced relative to postural contractions (all P-values < 0.001). In old subjects, SICI during both shortening and

lengthening contractions was reduced relative to postural contractions ($P < 0.001$). Age-related comparisons within each contraction type showed that SICI was not different between age groups during postural ($P = 0.3$) or shortening contractions ($P = 0.06$), but was reduced in old subjects during lengthening contractions ($P = 0.002$).

Long interval intracortical inhibition. For all subjects that demonstrated the target level of baseline LICI (15 young, 15 old), the amplitude of the test alone MEP used to assess LICI in each contraction type is shown in Figure 3A. The test MEP varied between contraction types ($F_{2,521} = 6.18$, $P = 0.002$), with post hoc testing showing that test MEP amplitude was reduced during lengthening contractions relative to both postural ($P = 0.01$) and shortening contractions ($P = 0.002$). Despite this, there was no difference between age groups ($F_{1,28} = 0.83$, $P = 0.4$) and no interaction between factors ($F_{2,521} = 1.22$, $P = 0.3$). The TMS intensity used to generate the test alone MEP varied between contraction types ($F_{2,28} = 36.08$, $P < 0.001$), with post hoc testing showing that the intensity of the test stimulus during the postural contraction (young, 47.4 ± 2.0% MSO; old, 46.8 ± 2.2% MSO) was greater than during either shortening (young, 41.9 ± 1.8% MSO; old, 42.7 ± 2.0% MSO) or lengthening (young, 44.1 ± 1.7% MSO; old, 44.3 ± 2.2% MSO) contractions (P-values < 0.001), and greater during the lengthening than shortening contractions ($P = 0.002$). However, stimulus intensities were not different between age groups ($F_{1,28} = 0.002$, $P = 0.9$) and there was no interaction between factors ($F_{2,56} = 0.69$, $P = 0.5$).

The magnitude of LICI in each contraction phase is compared between groups in figure 3B. LICI differed between contraction types ($F_{2,670} = 5.04$, $P = 0.007$) and age groups ($F_{1,27} = 6.73$, $P = 0.02$), and there was an interaction between factors ($F_{2,670} = 9.26$, $P < 0.001$). For young subjects, post hoc analysis showed that the magnitude of LICI was increased during both shortening and lengthening contractions when compared to postural contractions (both

P-values < 0.001), but was not different between shortening and lengthening contractions (*P* = 0.5). For old subjects, the magnitude of LICI was not different between contraction types (all *P*-values > 0.1). Age-related comparisons within each contraction type showed that LICI was not different between groups during postural contractions (*P* = 0.3), but significantly reduced in old subjects during both shortening (*P* = 0.003) and lengthening (*P* = 0.003) contractions.

EMG Silent Period The duration of the SP in each contraction type is compared between a subset of young and old subjects that demonstrated a reliable SP (13 young and 14 old) in Figure 4. Subject data was considered reliable if CUSUM analysis provided an accurate estimate of SP duration (assessed via visual comparison with raw data) for at least 6 out of 12 trials in all contraction types. Furthermore, the amplitude of the test MEP, which is known to effect SP duration [37], was not different between age groups or contraction types (see above). For all subjects, SP duration was not different between age groups ($F_{1,25}$ = 0.64, *P* = 0.4), but differed between contraction types ($F_{2,401}$ = 67.39, *P* < 0.001) and there was an interaction between factors ($F_{2,401}$ = 11.69, *P* < 0.001). In young subjects, post hoc analysis showed that SP duration during lengthening contractions was reduced relative to postural contractions (*P* < 0.001), whereas SP duration during shortening contractions was reduced relative to both postural (*P* < 0.001) and lengthening contractions (*P* < 0.001). In old subjects, the SP during shortening contractions was reduced relative to both postural (*P* < 0.001) and lengthening (*P* = 0.001) contractions. Age-related comparisons within each contraction type showed that the SP duration was reduced in young subjects during shortening contractions (*P* = 0.01).

Motor output during anisometric movements

Absolute movement error differed between contraction types ($F_{2,1554}$ = 1559.14, P < 0.001) and age groups ($F_{1,34}$ = 7.03, P = 0.01), and there was an interaction between factors ($F_{2,1554}$ = 5.74, P = 0.003; Figure 5A). For both age groups, post hoc testing showed that movement error during shortening contractions was greater than during postural contractions, and greater during lengthening than either shortening or postural contractions (P < 0.001 for all comparisons). Age-related comparisons within each contraction type showed that movement error was significantly increased in older adults during shortening (P < 0.001) and lengthening (P = 0.005) contractions, but unaffected by age during postural contractions (P = 0.3).

The SD of Acceleration during movement also differed between contraction types ($F_{2,1353}$ = 2176.68, P < 0.001) and age groups ($F_{1,32}$ = 4.79, P = 0.04), and there was an interaction between factors ($F_{2,1353}$ = 9.74, P < 0.001; Figure 5B). Post hoc testing showed that, in both groups, the SD of acceleration during shortening contractions was greater than postural contractions, and greater during lengthening contractions than during either shortening or postural contractions (P < 0.001 for all comparisons). Age-related comparisons within each contraction type showed that acceleration SD was significantly increased in old adults during both postural (P = 0.03) and shortening contractions (P = 0.02).

Linear regression

Linear regression of individual subject data was used to investigate associations between measures of intracortical inhibition and movement performance, as well as between paired- and single-pulse TMS measure of intracortical inhibition, during each contraction type in young and old subjects. No significant correlations were found between motor performance (acceleration SD or movement tracking error) and either the magnitude or modulation of (i.e.,

difference between measurements during postural and anisometric contractions) intracortical inhibition (Table 2). However, a significant association between the magnitude of SICI and the SP was found in young but not old subjects during shortening contractions (young, r^2 = 0.47, P = 0.01; old, r^2 = 0.10, P = 0.3), with a tendency towards a similar association during lengthening contractions (young, r^2 = 0.28, P = 0.08; old, r^2 = 0.06, P = 0.4). No significant relationship was found between LICI and the SP in either contraction type or group. Within each age group, linear regression analysis was also used to investigate whether pre-stimulus EMG predicted the change in inhibition observed during each movement phase. Results of these analyses showed no significant relationship between pre-stimulus EMG and the magnitude of SICI or LICI during either shortening or lengthening contractions in either group.

Discussion

The current study investigated age-related changes in intracortical inhibition with paired-pulse TMS during constant-load shortening and lengthening contractions involving the index finger. At least 4 new findings related to the cortical control of movement were obtained from this experimental approach. First, performance of constant-load shortening and lengthening contractions is accompanied by a reduction of SICI in both young and old adults. Second, performance of shortening and lengthening contractions is accompanied by increased LICI in young but not old subjects. Third, there was less GABAergic inhibition during movements in older adults. Fourth, these changes in inhibition appear to be unrelated to age-related differences in motor performance during movement.

SICI is reduced during movement in young and old adults

Reductions in the magnitude of SICI during isometric muscle activation have been well documented [21-24, 38], and suggested to reflect modulation of $GABA_A$ inhibition that is likely to be cortical in origin [39, 40]. However, the current study is the first to investigate if SICI within contralateral M1 is also modulated during movement when lifting and lowering a constant load. In young subjects, we found reductions in SICI during movement that differed between contraction types, with greater disinhibition observed during shortening contractions. These observations suggest that although both shortening and lengthening contractions are associated with a reduction of $GABA_A$-mediated inhibitory tone within M1, a greater disinhibition of this circuit is apparent during slow shortening contractions to lift loads.

Previous studies using electroencephalography (EEG) in young subjects have reported that movement related cortical potentials are greater during lengthening than shortening contractions [10, 11], suggesting that reductions in inhibitory tone should be greatest during muscle lengthening. However, a more recent study using functional magnetic resonance imaging (fMRI) has localised this increased cortical activity during lengthening contractions to higher order motor areas, such as the pre-supplementary motor area and anterior cingulate cortex [9]. The same study reported that activity within M1 (the area of focus in the current study) was actually increased during *shortening* contractions [9]. It therefore seems likely that the greater disinhibition of SICI we observed during shortening contractions is a reflection of this enhanced motor cortical activity during muscle shortening.

In old subjects, a reduction in SICI was also observed during movement. However, in contrast to the young group, the magnitude of this modulation was not different between shortening and lengthening contractions. This lack of phase-specificity could suggest that old

adults demonstrate a reduced ability (or need) to differentially modulate $GABA_A$-mediated inhibition during slow shortening and lengthening contractions with a light (50 g) load. We have previously observed age-related reductions in the ability to modulate $GABA_A$-mediated inhibition during different isometric motor tasks [30], and there is reduced modulation of SICI during movement preparation in old adults [27]. Taken together, these findings may reflect a loss of task-specificity in the modulation of inhibitory neurotransmission in older adults.

Changes in LICI and the SP during anisometric contractions

Although this is the first study to investigate movement-related changes in the magnitude of LICI, several previous studies have assessed changes in the duration of the SP, an alternative assessment of $GABA_B$-mediated inhibition [41], during anisometric contractions in young subjects [7, 8, 25]. While two of these reported reduced SP duration during lengthening contractions [7, 8], the third reported reduced SP duration during shortening contractions [25]. In support of Sekiguchi *et al.*, [25], the greatest reduction in SP duration within the current study was seen during shortening contractions, although this effect was reduced in old adults. As Duclay and colleagues targeted muscles of the lower leg, whereas Sekiguchi and colleagues and the current study targeted an intrinsic hand muscle, it seems possible that physiological differences in the target muscle contributed to these inconsistencies [42]. Furthermore, both Sekiguchi *et al.*, [25] and Duclay *et al.*, [7] used a constant intensity test stimulus to compare silent period durations between shortening and lengthening contractions, which likely result in variations in the test MEP amplitude during each contraction, confounding measurements of silent period duration [37].

Both LICI and the SP are thought to have contributions from $GABA_B$ mediated inhibitory neurotransmission. However, this has been more clearly defined for LICI [43-45], with some

evidence suggesting that the SP may reflect composite activity of both $GABA_A$ and $GABA_B$ receptors [46], as well as have contributions from brain areas 'upstream' from M1 [47]. Our assessment of LICI therefore provides a more precise measure of changes in $GABA_B$ mediated inhibition within M1 during shortening and lengthening contractions. In contrast to SP duration, our findings demonstrate that LICI in young subjects was greater during both shortening and lengthening contractions, suggesting increased $GABA_B$ mediated inhibition within M1 during movement in healthy young subjects. This increase in LICI is consistent with a previous report that the EEG derived N100 response is greater during movement preparation in young subjects [48]. Despite this, LICI in old subjects was unaffected by contraction type, suggesting that the ageing process results in reduced modulation of intracortical $GABA_B$-mediated circuitry during movement. These changes in LICI were unrelated to the changes in SP during movements in young and old subjects, which may indicate an altered contribution of $GABA_B$ inhibition to SP duration during movements. In contrast, there was a significant association between SICI and SP in young subjects, suggesting that there may be a greater contribution of $GABA_A$ to the CSP duration during slow movements.

Age-related differences in GABAergic inhibition during movements

Previous literature suggests contradictory effects of age on SICI and LICI during both relaxation [27, 29, 49-62] and isometric muscle activation [30, 33, 63], with variations in methodology and subject characteristics likely contributing to this heterogeneity. Despite this, as the conditioning stimulus intensity was adjusted to produce 50% inhibition of the test MEP during postural contractions, our findings could not have been confounded by any age-related differences in inhibition at baseline. Within the current study, we found that inhibition during movement was consistently reduced in old adults irrespective of measurement or contraction

type. Interestingly though, this occurred through an increased movement-related modulation of SICI, but decreased movement-related modulation of LICI. As reductions in inhibitory tone are thought to facilitate the activation of cortical areas required for the generation of movement [21], this non-specific cortical disinhibition could allow the generation of stronger descending commands for movement in an attempt to maintain motor output in spite of age-related neuromuscular insufficiencies. However, while disinhibition is required for the generation of motor commands, accurate performance during movement also relies on an adequate balance between excitation and inhibition in M1, resulting in the finely tuned motor commands necessary for precise movements. An alternative interpretation of our data could therefore be that the generalised cortical disinhibition observed in old adults may not provide the optimal balance to maximise performance during movement, resulting in impaired motor function. This possibility remains to be explored.

Movement-related changes in inhibition and motor performance

Within the current study, absolute tracking error and acceleration SD of the index finger were both increased in old adults, suggesting that old subjects performed these tasks with reduced accuracy and steadiness. However, linear regression analysis of individual subject data failed to demonstrate any significant associations between the indices of performance used in the present study (movement accuracy and steadiness) and measures of SICI, LICI and the SP. These findings suggest that age-related changes in inhibitory modulation during slow movements are unlikely to account for age-related deficits in these measures of motor performance. However, several limitations may have contributed to the lack of interaction between measures of inhibition and movement performance. First, the measures of inhibition and motor performance were obtained in separate movement trials, as the muscle twitch following the TMS pulse influenced movement accuracy. Second, changes in task

performance (i.e., motor learning) over the 72 trials included in the anisometric task may have obscured interactions between inhibition and performance. Finally, in order to assess the effect of the modulation of intracortical inhibition on movement-related motor performance, it was essential to test subjects that displayed a moderate level of inhibition during the postural task (baseline). The possibility exists that this may have biased our findings, as it has previously been shown that abnormal facilitation (rather than inhibition) in resting muscle may be associated with impaired manual dexterity [59]. However, motor performance during shortening and lengthening contractions was similar in the excluded subjects that did not have moderate baseline inhibition during the postural task (4 SICI, 3 LICI) compared with the included sample population, so it is unlikely that this influenced our motor performance data.

Methodological considerations

A pivotal aspect of the current study was to match the amplitude of the test MEP between young and old adults in each contraction type. This was necessary because the magnitude of inhibition recorded during paired-pulse TMS paradigms varies depending on the amplitude of the test MEP [34]. While the amplitude of the test MEP was matched between contraction types for SICI, the test MEP for LICI was slightly reduced during lengthening contractions. As the magnitude of LICI was not different between shortening and lengthening contractions, it seems unlikely that variations in the test MEP confounded our findings. In addition, pre-stimulus EMG was increased in old adults, which may confound our measures of inhibition. However, this was not different between contraction phases, and linear regression analysis failed to show any significant interaction between EMG activity and measures of inhibition. We therefore feel that this factor had limited influence on our findings. Finally, as we did not

assess peripheral excitability, we cannot exclude the possibility that changes at the spinal level may have contributed to our results.

In conclusion, we used paired-pulse TMS to assess age-related differences in intracortical inhibition during slow shortening and lengthening contractions when lifting and lowering a constant load with the index finger. We found that $GABA_A$-mediated SICI was reduced during shortening and lengthening contractions in both young and old subjects, whereas $GABA_B$-mediated LICI was increased during both shortening and lengthening contractions in young adults only. These task-related changes resulted in reduced GABAergic inhibition during movements in old compared with young subjects. These differences were accompanied by reduced task accuracy and steadiness during shortening and lengthening contractions in older adults, but there was no association between measures of intracortical inhibition and task performance in individual subjects. These findings suggest that shortening and lengthening muscle contractions are associated with the modulation of GABAergic inhibition, and that this modulation is altered in older adults. However, the functional implications of these differences in intracortical inhibition during movements in older adults require further investigation.

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Disclosures

The authors declare no conflict of interest

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Figure 1. Representative data showing variations in SICI (A) and LICI (B) during postural, shortening and lengthening contractions. An example of a single trial for the postural and anisometric tasks, demonstrating the target position, position of the index finger (C) and the associated index finger acceleration (D), are also shown.

Figure 2. Effects of contraction type on SICI compared between young and old adults. The amplitude of the test alone MEP used to assess SICI *(A)* and the magnitude of SICI *(B)* are compared between young *(black bars)* and old *(white bars)* subjects during postural *(left columns)*, shortening *(middle columns)* and lengthening *(right columns)* contractions. The dotted horizontal line represents no inhibition, with values below 100% showing inhibition of the test MEP. Data are presented as the geometric mean and 95% confidence interval. $^{\#}P < 0.05$ when compared to postural; $^{\dagger}P < 0.05$ when compared to postural and shortening contractions; $^{*}P < 0.05$ between age groups.

Figure 3. Effects of contraction type on LICI compared between young and old adults. The amplitude of the test alone MEP used to assess LICI *(A)* and the magnitude of LICI *(B)* are compared between young *(black bars)* and old *(white bars)* subjects during postural *(left columns)*, shortening *(middle columns)* and lengthening *(right columns)* contractions. The dotted horizontal line represents no inhibition, with values below 100% showing inhibition of the test MEP. Data are presented as the geometric mean and 95% confidence interval. $^{\#}P < 0.05$ when compared to postural contractions; $^{\ddagger}P < 0.05$ when compared to postural and shortening contractions.

Figure 4. Effects of age and contraction type on the duration of the EMG SP. Data show the geometric mean SP duration (and 95% confidence interval) for a subset of 13 young *(black bars)* and 14 old adults *(white bars)* during postural *(left columns)*, shortening *(middle columns)* and lengthening *(right columns)* contractions. $^{\#}P < 0.05$ when compared to postural

contractions; $^{\dagger}P < 0.05$ when compared to postural and shortening contractions; $^{\ddagger}P < 0.05$ when compared to postural and lengthening contractions; $^{*}P < 0.05$ between age groups.

Figure 5. Motor performance during different contraction types in young and old adults. Performance during postural, shortening and lengthening contractions was investigated by comparing the absolute error between finger and target positions *(A)* and the SD of acceleration during movement *(B)* between young *(black bars)* and old *(white bars)* subjects. Data are presented as the geometric mean and 95% confidence interval. $^{\#}P < 0.05$ when compared to shortening contractions; $^{\dagger}P < 0.05$ when compared to postural and shortening contractions; $^{*}P < 0.05$ between age groups.

Table 1. Subject Characteristics

	Young	Old
Age (years)	23.3 [21.3, 25.2]	70.6 [67.4, 73.8][a]
Handedness (L.Q)	0.93 [0.89, 0.98]	0.84 [0.72, 0.96]
MVC force (N)	31.7 [26.5, 36.9]	28.2 [23.4, 32.9]
RMT (%MSO)	43.5 [40.6, 46.4]	44.8 [40.6,49.0]
MVC EMG (mV)	0.38 [0.32, 0.43]	0.28 [0.23, 0.32][a]
AMT (%MSO)		
-Postural	37.7 [35.2, 40.1]	37.8 [33.8, 41.9]
-Shortening	35.8 [33.5, 38.2][b]	34.5 [31.1, 37.9][b]
-Lengthening	36.3 [34.2,38.5][b]	35.7 [32.0, 39.3][b]
Pre-stimulus EMG (% MVC EMG)		
-Postural	*5.9 [5.2, 6.6]	*10.6 [9.2, 12.2]
-Shortening	*5.7 [5.1, 6.5]	*10.2 [8.9, 11.7]
-Lengthening	*5.9 [5.2, 6.6]	*10.2 [9.0, 11.6]

[a]$P < 0.05$ compared to young; [b]$P < 0.05$ compared to postural; *values show the geometric mean generated by back-calculation of log transformed data

Table 2. Relationship between ICI and performance measures

	Log(Acceleration SD)		Log(Movement Error)	
	r^2	*P* - value	r^2	*P* - value
Shortening				
Log(SICI)				
Young	0.06	0.4	0.003	0.9
Old	0.01	0.7	0.02	0.7
Log(LICI)				
Young	0.2	0.1	0.006	0.8
Old	0.0005	0.9	0.007	0.8
Lengthening				
Log(SICI)				
Young	0.02	0.6	0.009	0.7
Old	0.1	0.2	0.004	0.8
Log(LICI)				
Young	0.03	0.6	0.1	0.2
Old	0.01	0.7	0.03	0.5