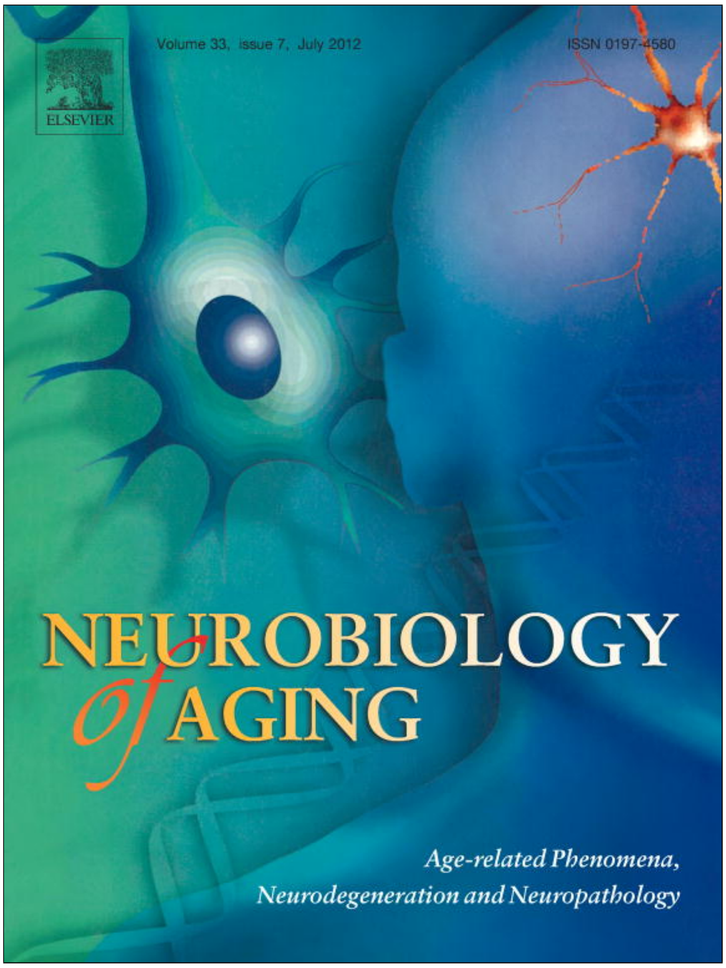
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Age-related differences in corticospinal excitability and inhibition during coordination of upper and lower limbs

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Abstract

The ability to coordinate upper and lower limbs—a prerequisite for many everyday activities—is known to decline with age. Here we report 2 experiments in which transcranial magnetic stimulation (TMS) was used to assess corticospinal excitatory and inhibitory processes in younger and older adults during cyclical hand-foot movements. In experiment 1, motor evoked potentials (MEP) and silent period (SP) durations were measured from the active right extensor carpi radialis (ECR) muscle while it executed rhythmic oscillations in conjunction with the right or left foot. Younger adults exhibited increased SP with ipsilateral limb combinations and decreased SP with contralateral limb combinations, relative to a baseline hand only condition. Strikingly, older adults exhibited a reduced SP when ipsilateral limbs moved in opposite directions. This effect was found to be most pronounced in those older adults who exhibited poor coordination performance, suggesting that the inability to regulate inhibitory processes may underlie age-related degradation of task performance. Experiment 2 examined motor evoked potentials and SP duration in the left extensor carpi radialis which maintained a tonic contraction while the coordination task was undertaken by the right arm and right or left foot. For younger adults, coordination of ipsilateral limbs was accompanied by increased inhibition in the ipsilateral motor cortex than during the coordination of contralateral limbs. No differences in SP between conditions were noted for the older adults. In summary, older adults' reduced ability to coordinate upper and lower limbs may be related to the capacity to regulate inhibitory function in both hemispheres. This study suggests for the first time a direct link between age-related differences in interlimb coordination and the control of corticospinal inhibitory processes.

Keywords: Aging; Motor control; Transcranial magnetic stimulation

1. Introduction

The capacity to produce and learn specific patterns of interlimb coordination is intrinsic to many activities of daily living and recreational activities including walking, manipulating objects, playing musical instruments, and sports. Coordination is a dominant deficit in aging and compromises individual work productivity, mobility, and independence. The loss of the ability to produce smooth coordinated muscle activity results in an increased risk of falls (de Rekeneire et al., 2003) which are the leading cause of injury in elderly adults. Knowledge about the neural basis of age-related coordination deficits in humans, however, is limited.

Previous studies investigating coordination of the upper and lower limbs have shown that certain limb and direction combinations are easier to perform than others. When contralateral limbs are coordinated (e.g., right hand, left foot) comparable accuracy or stability is observed, irrespective of whether the limbs are moved in the same (isodirectional) or opposite (nonisodirectional) directions (Hiraga et al., 2004, 2005; Meesen et al., 2005). In contrast, when movements of an arm and a leg on the same side of the body (ipsilateral) are coordinated, the isodirectional coordination mode is easier (as indicated by higher accuracy and stability) than the nonisodirectional coordination mode (Baldissera et al.,

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1982; Kelso and Jeka, 1992; Serrien and Swinnen, 1997; Swinnen, 2002; Swinnen et al., 1995; Wenderoth et al., 2004). Indeed, it is regularly observed that there is a tendency for transitions to occur from nonisodirectional to isodirectional coordination modes, especially at higher oscillation frequencies, indicating the preferred nature (and increased stability) of the isodirectional mode. Recently, transcranial magnetic stimulation (TMS) has been used to probe the neural correlates associated with the behavioral differences observed in iso- and nonisodirectional coordination of the ipsilateral hand and foot. Byblow and colleagues (Byblow et al., 2007) used a standard paired-pulse TMS paradigm (Kujirai et al., 1993) to study short-interval intracortical inhibition (SICI) in the quiescent forearm extensor (extensor carpi radialis; ECR) during oscillatory dorsiflexion/plantarflexion of the ipsilateral foot. SICI in the ECR was selectively reduced during foot dorsiflexion compared with foot plantarflexion. The authors suggested that lower M1 inhibition during dorsiflexion may facilitate isodirectional movements of the ipsilateral hand and foot, relative to the nonisodirectional mode (Byblow et al., 2007). Reduced cortical inhibition in hand muscles as a result of discrete (Sohn et al., 2005) and phasic (Tazoe et al., 2007) dorsiflexion movements of the ipsilateral foot has also been observed using measurements of silent period (SP) duration. The initial 50–60 ms of the SP is regarded as being due to the refractoriness of the spinal cord (Fuhr et al., 1991), while the latter part ($>$ 100 ms) is likely a result of cortical inhibitory processes (Chen et al., 1999; Fuhr et al., 1991; Terao and Ugawa, 2002).

The disparity between the performance of the isodirectional and nonisodirectional patterns for ipsilateral limbs is particularly prominent for older adults, who exhibit difficulty in suppressing the preferred isodirectional movement pattern (Greene and Williams, 1996; Heuninckx et al., 2004; Serrien et al., 2000). As it seems necessary to inhibit conflicting neural outputs (that tend to promote isodirectional patterns) in order to successfully perform the nonisodirectional pattern (Baldissera and Esposti, 2005; Borroni et al., 2004), an age-related decline of inhibitory control may be responsible for the reduced performance in older adults (Mattay et al., 2002; Spirduso and Choi, 1993). However, this proposition has not been fully examined and, consequently, the relationship between corticospinal inhibition and age-related decline in interlimb coordination performance is not well understood.

There is increasing evidence that, in general, inhibition at both cortical (Oliviero et al., 2006; Peinemann et al., 2001; Sale and Semmler, 2005) and spinal levels (Kido et al., 2004) decreases with advancing age, although there are some studies reporting increased cortical inhibition in older adults (Kossev et al., 2002; McGinley et al., 2010). A question of importance, therefore, is the extent to which the greater difficulty observed in the performance of interlimb movements by older adults, particularly those involving nonisodirectional movements and ipsilateral limbs, is a consequence of reduced inhibitory processes in the aged. In a previous study (Fujiyama et al., 2009) we began to address this issue by investigating the role inhibitory processes have during coordination of the upper and lower limbs. Specifically, we assessed SP duration in the right hand ECR while it made oscillations that were isodirectional or nonisodirectional to concurrent oscillations of the ipsilateral or contralateral foot. Relative to a baseline condition in which SP duration was assessed in the ECR during isolated hand oscillations, SP duration in young adults (age, mean [M] = 21.9 years) was increased (reflecting increased inhibition) during coordination of ipsilateral limbs but was unchanged (relative to baseline) in contralateral coordination modes. In contrast, this task-specific modulation of inhibition was absent for older adults, reflecting a potential deficit in the ability to modulate inhibitory processes with advancing age (Fujiyama et al., 2009). The aim of the present research was to further examine the link between the behavioral differences previously observed between young and older adults in interlimb coordination and inhibitory processes occurring at the level of the motor cortex. Of particular interest in experiment 1 (Exp1), therefore, was a comparison of excitatory and inhibitory processes in high and lower performing older adults. It was hypothesized that lower performing older individuals would exhibit reduced ability to modulate inhibitory processes during performance of the most difficult coordination. In contrast, the higher performing older adults would be hypothesized to exhibit modulation of inhibitory processes akin to the younger adults.

An issue of further interest in Exp1 was whether the age-related differences in the modulation of inhibition processes in the ECR varied as a function of the position of the hand as it moved through the extension phase of the rhythmical flexion and extension movements during interlimb coordination. As spinal excitability in an upper limb is modulated as a function of movement phase during rhythmic arm movement (Zehr et al., 2003), it is possible that modulation of corticospinal inhibition in the ECR may also vary as a function of hand position during the coordination of movements involving an upper and lower limb. It is also well established that activation of the muscles on one side of the body results in increased excitability of the contralateral homologous motor pathway (Carson et al., 2004; Hinder et al., 2010; Hortobágyi et al., 2003; Sohn et al., 2003; van den Berg et al., 2011) and that this crossed-facilitation varies as a function of movement phase during rhythmic oscillations (Carson et al., 2004). This modulation of contralateral circuits also extends to the M1 inhibitory circuitry as has been shown in a recent study investigating whether ballistic force pulses of the right hand modulate inhibitory processes in the ipsilateral motor cortex (Hinder et al., 2010). It was found that SPs measured in the homologous muscle of the left thumb (elicited by TMS applied to the right M1) were decreased during activation of the right thumb. Whether similar changes in SP duration in the motor cortex ipsilateral to the moving hand would also be evident when rhythmic coordination is undertaken and whether the effects differ as a function of age was examined in Experiment 2 (Exp2). Of interest was whether any inhibitory effects on ipsilateral M1 would be modified when the right motor cortex was also involved in the coordination (i.e., when the left foot undertook oscillatory motion), compared with when the coordination pattern was undertaken solely by the left hemisphere (i.e., right hand and foot).

2. Methods

2.1. Participants

Thirty healthy volunteers participated in both Exp1 and Exp2. Fifteen were older adults (9 females, age M = 69.1 years, range 58–84 years) and 15 were younger adults (8 females, age M = 21.1 years, range 18–29 years). All participants completed a brief medical questionnaire to ensure that inclusion criteria for the study were met. The Edinburgh handedness questionnaire (Oldfield, 1971) revealed that all participants were strongly right-handed (> 96.7). Mini Mental State Examination (Dick et al., 1984) was used to screen for cognitive deficits in the older adults. All participants scored within the normal range (score ≥ 26) and were free of any neurological impairment, symptomatic cardiovascular disease, diabetes, or hypertension. Written informed consent was obtained prior to participation in the study. Ethics approval for the study was obtained from the Human Research Ethics Committee (Tas) Network.

2.2. Apparatus

Participants were seated in a custom-made chair consisting of a steel frame with a wooden back support and padded seat (see Fujiyama et al., 2009). The chair had 4 aluminum levers to which the limbs were attached with surgical tape. The hands were attached to the levers with the hands in the fully-prone position such that hand extension resulted in movement in the same direction as foot dorsiflexion. The levers supported the weight of the limbs and enabled extension-flexion and dorsiflexion-plantarflexion movements at the hands and feet, respectively. Limb position data were obtained using high-precision shaft encoders (Penny and Gilles, Christchurch, Dorset, UK, SRH280) coaxial with each lever's axis of rotation. The voltage output from the shaft encoders was sampled at 2000 Hz using a 16-b A/D system (HMS Technologies, Inc, Martinsburg, WV, USA) and was recorded on a computer for off-line analysis. The raw position data were low-pass filtered with a cutoff frequency of 10 Hz using a dual-pass Butterworth filter.

2.3. Movement task

The movement task was similar in both experiments. Each participant performed 3 trials in each of 4 conditions requiring coordination of hand flexion/extension and foot plantarflexion/dorsiflexion: (1) contralateral isodirectional (CNT_ISO) movements required movement of the right hand and left foot in the same direction; (2) contralateral nonisodirectional (CNT_N-ISO) required movements of the right hand and left foot in the opposite direction; (3) ipsilateral isodirectional (IPS_ISO) required movements of the right hand and right foot in the same direction; and (4) ipsilateral nonisodirectional (IPS_N-ISO) movements of the right hand and right foot in opposite directions (Fig. 1A). Each trial lasted 80 seconds and participants were instructed to move in time with an audio metronome (1 Hz) such that 1 movement cycle was completed every second. Furthermore, we provided participants with online visual feedback

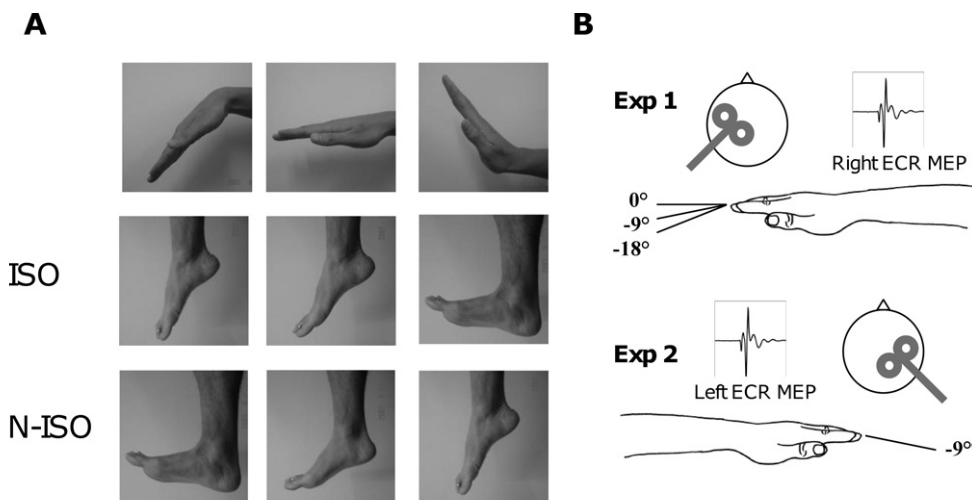

Fig. 1. (A) Cyclical coordination of the hand and foot according to the isodirectional mode (ISO; both limb segments are moved in the same direction) and the nonisodirectional mode (N-ISO; both segments are moved in opposite directions). (B) In experiment 1 (top) transcranial magnetic stimulation (TMS) was delivered at 3 right hand positions (−18°, −9°, 0°, relative to horizontal) eliciting right extensor carpi radialis (ECR) muscle stimulating left M1. In experiment 2 (bottom) TMS was delivered during left hand tonic contraction targeting left ECR stimulating right M1.

of the magnitude of displacements at the hand and foot during trials. The aim was to control amplitude of the movements such that peak flexion and extension displacement at the hand was approximately 72° (peak to peak) from the horizontal (neutral hand position) and peak dorsiflexion/plantarflexion displacement at the foot was approximately 54° (peak to peak). These values were chosen as they represented comparably comfortable amplitudes with respect to the range of motion of each joint. At least 1 familiarization trial was given in each condition prior to recording the 3 experimental trials. The order of conditions was counterbalanced across participants.

2.3.1. Experiment 1

In this experiment there was also a baseline control condition that required phasic oscillations of the right hand only for three 80-second trials. In all conditions (4 coordination modes and the baseline control) participants' left arm remained relaxed in the neutral position. TMS (see 2.4. Transcranial magnetic stimulation) was delivered (to the right ECR hotspot at the predetermined intensity) during execution of the coordination pattern on the basis of the position of the right hand. In each of the movement conditions, a total of 14–16 single pulses of TMS were delivered at each of 3 hand angles: 0° (horizontal), and 9° and 18° below the horizontal line in the extension phase (Fig. 1B). All stimulations were administered during the extension phase, i.e., while ECR was active and the muscle was shortening. The stimuli were applied at random times during a trial, but never in 2 consecutive cycles (i.e., $>$ 2 seconds between consecutive stimulations).

2.3.2. Experiment 2

In this experiment, participants were required to undertake the same 4 coordination patterns as in experiment 1 as well as the right hand only condition. However, in addition to the rhythmic movements involving the right hand and left or right foot, the left hand was isometrically activated, and held at 9° below the horizontal, throughout the 80-second trial. TMS was applied to the motor hotspot for the left ECR (Fig. 1B). Prior to the rhythmic movement conditions (as described above), participants performed a phasic oscillation of the left hand in isolation (1 Hz) with a target movement amplitude of 72° (peak to peak) for a period of 40 seconds. This trial was conducted in order to obtain a target electromyographic (EMG) activity for the left ECR isometric contraction during the subsequent coordination trials. The target EMG level was set at the root mean square (RMS) EMG, averaged across all cycles, evident in time windows of 50 msec, centered at the time at which the hand was at 9° below the horizontal during the extension phase in each cycle. During the coordination trials, participants maintained an isometric extension (of the target magnitude) of the left hand against a plastic strap with the hand 9° below the horizontal line—the tension in the strap was adjusted such that the target EMG level was required to maintain tautness in the strap. On the basis of the results of experiment 1 in which motor evoked potential (MEP) amplitude and SP duration did not differ between hand angles, TMS was delivered (to the left ECR hotspot) during the coordinative movements when the right hand passed through 9° below the horizontal line in the extension phase to the right M1 targeting left ECR. As in experiment 1, 14–16 single pulses of TMS were delivered in each condition. In addition to the oscillatory movement patterns described above, the control condition for this experiment involved a left hand static contraction (80-second duration) of the desired magnitude with the left hand held in a position 9° below the horizontal line. TMS was delivered randomly with at least 5 seconds between pulses.

2.4. Transcranial magnetic stimulation

Single-pulse TMS was applied using a standard figure of 8 coil (7 cm diameter of each wing) connected to a Magstim BiStim Unit (Magstim Company, Dyfed, UK). The coil was held tangentially over the scalp to induce a posterior-anterior current flow and to optimally elicit MEPs in the right (r) ECR (Exp1) or left (l) ECR (Exp2) muscle. EMG signals (2000 Hz sampling rate) from the right ECR (rECR), r flexor carpi radialis (rFCR), left ECR (lECR), and left FCR (lFCR) were collected using Ag/AgCl surface electrodes and were amplified (1000 times) and band-pass filtered (10–500 Hz) prior to sampling using a 16-bit AD system (CED Limited, Cambridge, UK) and recorded on a computer hard drive for analysis off-line. FCR muscle activity was monitored simply for observing excessive EMG activation. The individual resting motor threshold (rMT) was determined as the lowest stimulus intensity that produced MEPs of greater than 50 μV in at least 3 out of 5 consecutive trials (Rossi et al., 2009). rMT was determined for the rECR and lECR prior to beginning experiments 1 and 2. During experimental trials TMS was delivered at the predetermined motor hotspots (rECR hotspot for Exp1, lECR hotspot for Exp2) at a stimulus intensity of 130% rMT.

2.5. Data analysis and measures

2.5.1. Prestimulus EMG

RMS EMG in the 100 ms prior to each TMS pulse was calculated for each trial to allow a comparison of prestimulus EMG across all conditions.

2.5.2. TMS measures

Corticospinal excitability was calculated for each experimental trial as the average peak-to-peak MEP amplitude from all TMS pulses. The average values for each of the 3 trials for each movement condition were then averaged to yield a single value for each condition for each participant. Corticospinal inhibition was determined by the duration of the SP which was defined as the time between TMS delivery and the recurrence of continuous EMG activity. EMG recurrence was determined by calculating the RMS of the prestimulus EMG activity (100 ms preceding TMS delivery) and identifying the point at which poststimulus EMG activity first exceeded 1 SD of the prestimulus level as the end of the SP (Tazoe et al., 2007). In a similar manner to that for MEPs, we then averaged SP durations within each trial, and then over all trials in each condition. For the purposes of statistical analyses, MEP amplitudes and SP durations for each participant were assessed both as raw (nonnormalized) values and as normalized values, i.e., as a percentage of the average value obtained in the corresponding baseline condition.

2.5.3. Relative phase measure

The coordination between limbs was assessed by a measure of relative phase obtained using the following procedure (Garry et al., 2005). Each half-cycle (peak-to-valley, valley-to-peak) was rescaled to the range [1, −1]. This procedure results in a transformed displacement time series approximating a cosine function. Continuous phase-angles (degree) for each limb were obtained by taking the arccosine of each point on the scaled time series; continuous relative phase (RP) was then simply the arithmetic difference of the phase angles of the 2 limbs at each point. Circular statistics (Mardia, 1972) were utilized to calculate mean relative phase and standard deviation of relative phase (SD of RP) which provided a measure of pattern stability.

2.6. Statistical analysis

In presenting results, the data are expressed as mean ± 95% confidence interval. The data were examined using mixed-factor analysis of variance (ANOVA) with Huynh-Feldt epsilon corrections for nonsphericity of variance applied where required. Tukey honestly significant difference (HSD) was used for post hoc analyses as necessary. The level of significance for all tests was set at $p < 0.05$. Cohen's d and partial eta-squared (ηp^2) values were provided as measures of effect size with cutoffs ≥ 0.2 small, ≥ 0.5 medium, and ≥ 0.8 large for Cohen's d and ≥ 0.01 small, ≥ 0.06 medium, and ≥ 0.14 large for ηp^2 (Sink and Stroh, 2006).

SD of RP was examined using ANOVA with repeated-measures factors of limb combination and coordination mode and a between-subject factor of group. Statistical analysis of EMG activity in the left arm muscles (ECR and FCR) and normalized TMS measures consisted of repeated measures ANOVA with the between-factor group and the within-factors limb combination (LC: ipsilateral [IPS], contralateral [CNT]) and coordination mode (CM: isodirectional [ISO], nonisodirectional [N-ISO]). For Exp1, there was an additional within-subject factor of hand ANGLE (−18°, −9°, 0°).

For baseline comparison between groups, nonnormalized MEP amplitudes and SP durations were analyzed using ANOVA with a between-factor group and a within-factor of hand ANGLE (−18°, −9°, 0°) for Exp1 and independent group t tests for Exp2. In order to investigate whether SP durations and MEP amplitudes were modulated in the 4 coordination conditions relative to baseline (right hand only), nonnormalized SP duration and MEP amplitudes in each condition (IPS_ISO, IPS_N-ISO, CNT_ISO, CNT_N-ISO) were averaged across angles and compared with the baseline hand only conditions using pairwise comparisons.

Additionally, we investigated the relationship between intracortical inhibition and interlimb coordination performance in the most difficult (IPS_N-ISO) coordination pattern to assess whether the ability to maintain good performance in this task was associated with a measure of inhibitory function, i.e., SP. We used a median split of the SD of RP data to distinguish between higher performing and lower performing participants in each age group. Planned comparisons were conducted using t tests with Bonferroni corrections to compare SP durations and performance (SD of RP) for the higher and lower performing groups. In this analysis SD of RP and SP duration were averaged across the 3 different hand angles in each condition.

3. Results

As age-related changes in cortical activity during interlimb coordination were of primary interest in the present study, only those main effects and interactions involving GROUP as a factor will be described in detail. Data from 2 older and 2 younger participants were excluded due to unclear SP duration, while in the remaining 13 in each group showed clear demarcation of the onset and offset of the SP. Analyses were therefore conducted with the data from the remaining 26 participants (13 older with 7 females, age M = 67.8 years, range 58–73 years and 13 younger with 7 females, age M = 21.7 years, range 18–29 years). Fig. 2 illustrates typical EMG recordings of the SP following a TMS pulse during ISO and N-ISO coordination modes.

3.1. Experiment 1

3.1.1. Prestimulus EMG for right ECR

RMS EMG recorded during the 50 ms prior to each TMS stimulus was analyzed using a 2 (GROUP) × 2 (LC) × 2 (CM) × 3 (ANGLE) ANOVA. There was a significant main effect of ANGLE, $F(1,24) = 8.95$, $p = 0.001$, $\eta p^2 = 0.27$. Post hoc tests revealed that prestimulus EMG activity at 0° was significantly higher (137.60 ± 16.99 μV) than at 18° below the horizontal line during the hand extension phase (123.05 ± 15.20 μV) ($p < 0.01$). Importantly neither the main effect of GROUP nor interactions including GROUP as a factor were significant (all Fs < 0.69, ps > 0.53), indicating that the level of prestimulus muscle activity was not different for younger and older adults across LC, CM, or hand ANGLE.

3.1.2. Resting motor threshold

rMT for right ECR was 42.6% (± 3.59%) (maximum stimulator output) for the older group, and 41.8% (±

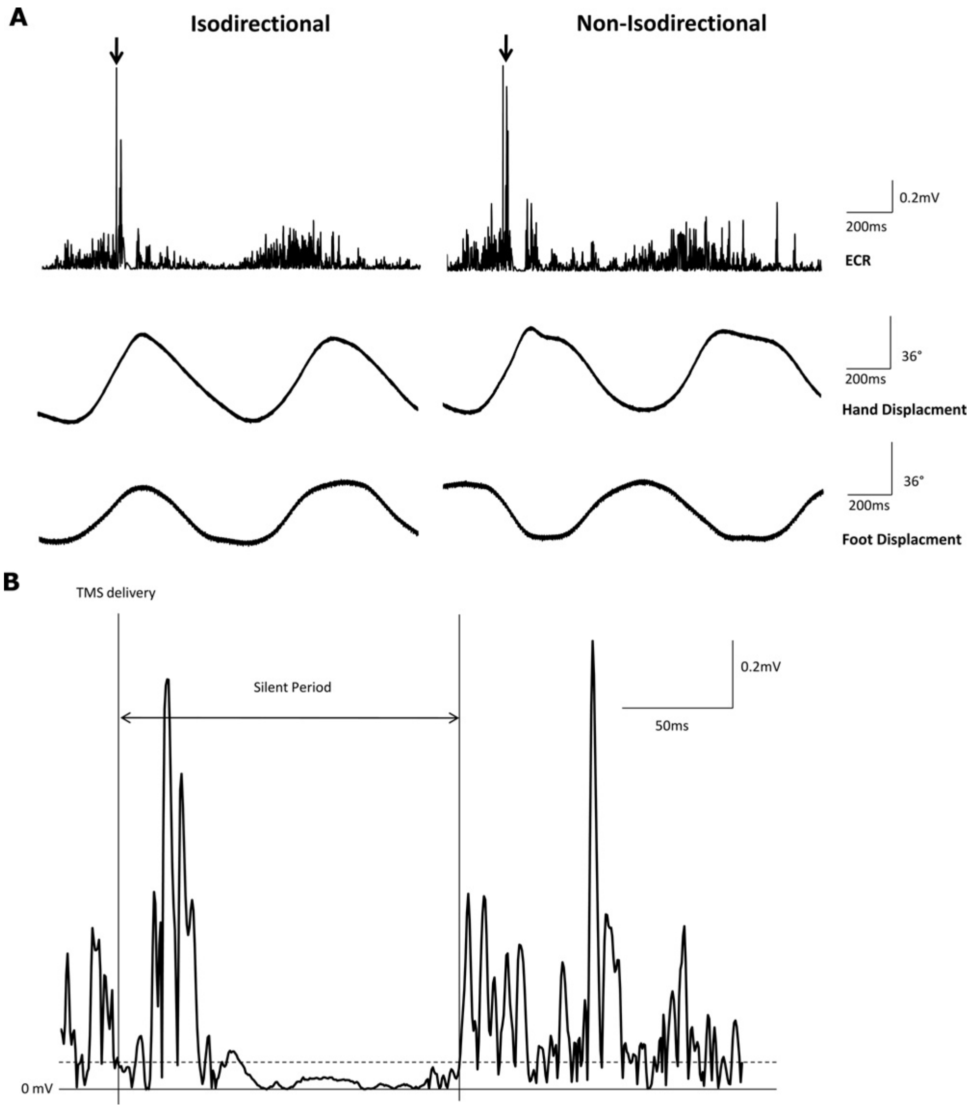

Fig. 2. (A) Electromyographic (EMG) activity in the extensor carpi radialis (ECR) and hand and foot displacements for a single participant during the isodirectional and nonisodirectional coordination modes. The arrows indicate the time of transcranial magnetic stimulation (TMS) delivery in each condition. (B) Silent period (SP) duration was measured from the time of TMS delivery to the recurrence of continuous EMG activity (horizontal dashed line: mean + 1 SD of the root mean square [RMS] of prestimulus EMG activity).

3.20%) for the younger group. The intergroup difference was not statistically significant (independent samples *t* test, $t(24) = 0.34$, $p = 0.73$, $d = 0.14$).

3.1.3. Changes in MEP and SP duration relative to baseline

Table 1 shows nonnormalized MEP amplitude and SP duration in each condition with statistical results of comparisons to the baseline (right hand only).

3.1.3.1. MEP amplitude. For both younger and older adults, marginal significance levels and medium effect sizes in the CNT_ISO condition (Table 1) suggested that MEP amplitude was smaller in young and larger in older group when isodirectional movements were performed with contralateral limbs than the baseline right hand only condition. Younger adults showed higher nonnormalized MEP amplitude in the baseline condition (1.92 ± 0.27 mV) than older adults (1.06 ± 0.20 mV), averaged across all hand angles, $F(1,24) = 10.62$, $p = 0.003$, $\eta p^2 = 0.31$. For normalized MEP amplitude of right ECR, none of the main effects ($ps > 0.20$) or interactions ($ps > 0.13$) were significant. Importantly, the interaction of GROUP × LC × CM was not significant, $F(1,24) = 2.53$, $p = 0.13$, $\eta p^2 = 0.10$, indicating that any observed group effects with respect to SP (see below) are not simply a result of differences in corticospinal excitability.

3.1.3.2. Silent period. Comparison with the baseline right hand only condition revealed that for young adults IPS limb combinations tended to result in longer SP durations (non-

Table 1
Descriptive statistics, probability levels of the pairwise comparisons (vs. baseline), and effect sizes (Cohen's *d*) for right ECR MEP amplitudes, SP durations, and SD of RP in experiment 1

	MEP amplitude				SP				SD of RP	
	M (mV)	95% CI	*p*	*d*	M (ms)	95% CI	*p*	*d*	M (degrees)	95% CI
Younger group										
BL (right hand)	1.92	0.46			140.47	19.05				
IPS_ISO	1.83	0.43	0.181	0.39	147.88	21.32	0.062	0.57	19.29	1.14
IPS_N-ISO	1.84	0.44	0.364	0.26	153.22	24.17	0.114	0.47	24.81	1.79
CNT_ISO	1.80	0.42	0.087	0.52	134.90	20.54	0.275	0.32	20.45	1.50
CNT_N-ISO	1.84	0.40	0.306	0.30	134.33	20.07	0.248	0.34	20.58	1.23
Older group										
BL (right hand)	1.07	0.22			134.16	13.71				
IPS_ISO	1.02	0.26	0.612	0.14	135.47	16.14	0.579	0.16	21.91	2.03
IPS_N-ISO	1.06	0.27	0.917	0.03	117.76	9.79	**0.006**	0.93	33.49	4.05
CNT_ISO	1.19	0.25	0.090	0.50	136.92	15.46	0.208	0.37	21.69	1.49
CNT_N-ISO	1.05	0.25	0.803	0.07	133.29	10.56	0.851	0.05	23.43	1.76

Key: BL, baseline; CI, confidence interval; CNT_ISO, contralateral isodirectional; CNT_N-ISO, contralateral nonisodirectional; ECR, extensor carpi radialis; IPS_ISO, ipsilateral isodirectional; IPS_N-ISO, ipsilateral nonisodirectional; M, mean; MEP, motor evoked potentials; RP, relative phase; SP, silent period. Significant *p* value is shown in bold.

normalized) relative to the right hand only condition; however this effect only approached significance for the IPS_ISO condition (Table 1). For older adults, SP in the IPS_N-ISO condition was significantly shorter than the baseline condition while SP in the other conditions did not differ from baseline. Nonnormalized baseline SP durations of the right ECR (averaged across the 3 angles) did not vary significantly between younger and older adults ($ps > 0.12$). For the normalized right ECR SP, the effect of ANGLE was not significant, $F(1,24) = 0.99$, $p = 0.38$, $\eta p^2 = 0.04$. There was a significant interaction of GROUP × LC × CM, $F(1,24) = 10.48$, $p = 0.004$, $\eta p^2 = 0.30$. As shown in Fig. 3, for the younger group SPs were significantly longer in IPS conditions compared with CNT conditions ($ps < 0.02$). In contrast, SP duration for older adults was significantly shorter during IPS_N-ISO relative to other conditions ($ps < 0.001$).

3.1.4. Behavioral results: SD of RP

There was a significant interaction between GROUP and CM, $F(1,24) = 5.18$, $p = 0.03$, $\eta p^2 = 0.18$. The effect of aging was prominent in N-ISO conditions with older adults (27.59 ± 2.64°) exhibiting larger relative phase SD compared with younger adults (19.99 ± 1.68°) ($p = 0.02$). Furthermore, for older adults the N-ISO modes were less stable than ISO modes (20.72 ± 1.78°) ($p < 0.001$); this was not the case for the younger adults who exhibited a level of stability that was not significantly different in the

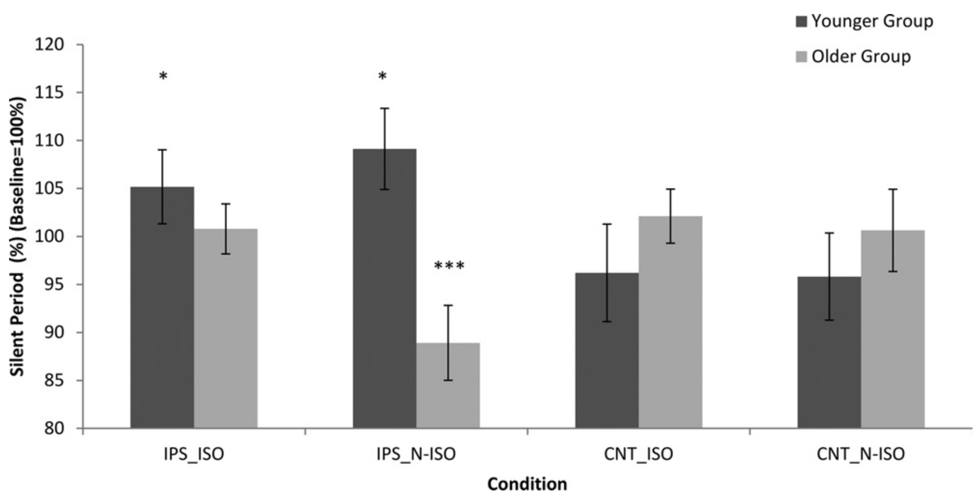

Fig. 3. Mean right extensor carpi radialis (ECR) silent period duration relative to the baseline (hand only) for younger and older groups in experiment 1 (Exp1). Error bars indicate 95% confidence intervals. Asterisks indicate statistically significant differences between conditions in each group (*$p < 0.05$; *** $p < 0.001$). Abbreviations: CNT_ISO, contralateral isodirectional; CNT_N-ISO, contralateral nonisodirectional; IPS_ISO, ipsilateral isodirectional; IPS_N-ISO, ipsilateral nonisodirectional.

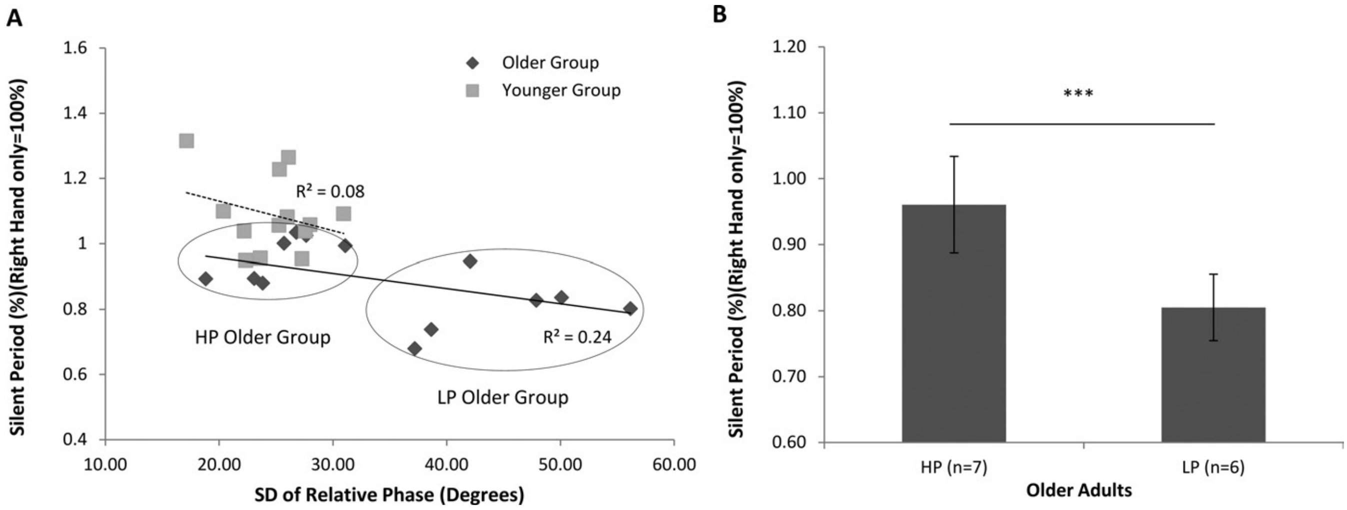

Fig. 4. (A) Mean standard deviation of relative phase (SD of RP) and (B) mean right extensor carpi radialis (ECR) silent period duration relative to the baseline (hand only) for lower (LP) and higher performing (HP) groups in younger and older groups in experiment 1 (Exp1). Error bars indicate 95% confidence intervals. Asterisks indicate statistically significant differences between 2 performance group in older adults (*** $p < 0.001$).

ISO (19.11 ± 1.44°) and N-ISO modes ($p = 0.11$). There was also a significant interaction of GROUP × LC, $F(1,24) = 4.35$, $p = 0.04$, $\eta p^2 = 0.15$. Post hoc analyses revealed that in older adults ipsilateral limb combinations were less stable (27.70 ± 2.60°) than contralateral limb combinations (22.56 ± 1.16°) ($p = 0.002$), while younger adults showed similar performance for ipsilateral (22.05 ± 1.22°) and contralateral limb combinations (20.51 ± 0.97°) ($p = 0.60$) which resulted in a significant age difference for the ipsilateral limb combinations ($p = 0.02$). In summary, older adults demonstrated lower coordination stability than younger adults, particularly when performing the IPS N-ISO mode.

3.1.5. *Relationship between motor performance and inhibitory function in Exp1*

Fig. 4A shows the relationship between motor performance and inhibitory function in the IPS N-ISO coordination mode. Linear regression revealed a nonsignificant relationship between SD of RP (performance) and SP duration (inhibitory function) in younger adults, $r = 0.28$, $p = 0.35$. Although the relationship was also nonsignificant for older adults, the relatively high correlation coefficient ($r = -0.49$) and marginal p-value (0.08) suggest that longer silent periods were associated with improved performance. However, Fig. 4A clearly indicates a bimodal distribution of SD of RP values in the older adults, rendering linear regression somewhat inappropriate. Accordingly, we used a median split (based on performance) to divide the participant groups into high performing and low performing subgroups. For the older group, the high performing ($n = 7$, M = 25.28 ± 2.88°) and low performing ($n = 6$, M = 45.33 ± 5.86°) subgroups exhibited mean performance that was significantly different, $t(11) = 6.32$, $p = 0.001$, $d = 3.42$. Furthermore, the lower performing older subgroup exhibited significantly shorter SP durations than the higher performing older subgroup, $t(11) = 3.51$, $p = 0.004$, $d = 1.93$ (Fig. 4B). Importantly, this effect was not driven by age, as the mean age of the members of each subgroup did not vary significantly (higher performing, M = 69.71, SD = 4.11; lower performing, M = 65.5, SD = 5.13), $t(11) = 1.65$, $p = 0.13$, $d = 0.91$. In contrast to the significant differences in performance and inhibitory function evident in the older subgroups, the 2 performance-based younger subgroups did not exhibit large differences in inhibitory function. Although the 2 subgroups differed in coordination ability (higher performing, $n = 7$; M = 22.31 ± 2.13°; lower performing, $n = 6$, M = 27.64 ± 1.44°), $t(11) = 3.91$, $p = 0.002$, $d = 2.22$; SP duration did not differ significantly between the higher (1.09 ± 0.10) and lower performing young subgroups (1.08 ± 0.08), $t(11) = 0.15$, $p = 0.88$, $d = 0.09$.

3.2. *Experiment 2*

3.2.1. *TMS measures*

3.2.1.1. Prestimulus EMG for left ECR. A 2 (GROUP) × 6 (CONDITION; left hand isometric contraction only, IPS_ISO, IPS_N-ISO, CNT_ISO, CNT_N-ISO, right hand phasic) ANOVA revealed a main effect of GROUP, $F(1,24) = 4.75$, $p = 0.04$, $\eta p^2 = 0.17$, indicating that younger adults had a significantly higher prestimulus EMG activity (82.99 ± 0.86 μV) than older adults (50.30 ± 0.95 μV). The main effect of CONDITION and interaction between GROUP and CONDITION was not significant ($Fs < 1.71$, $ps > 0.14$), indicating that prestimulus EMG activity was comparable across conditions in each group.

3.2.1.2. Resting motor threshold. An independent t test, $t(24) = 0.72$, $p = 0.48$, $d = 0.29$, revealed that rMT did not

Table 2
Descriptive statistics, probability levels of the pairwise comparisons (vs. baseline), and effect sizes (Cohen's *d*) for right ECR MEP amplitudes, SP durations, and SD of RP in experiment 2

	MEP amplitude				SP				SD of RP	
	M (mV)	95% CI	*p*	*d*	M (ms)	95% CI	*p*	*d*	M (degrees)	95% CI
Younger group										
BL (left hand)	1.45	0.31			144.87	17.02				
IPS_ISO	1.58	0.35	0.273	0.32	149.04	14.57	0.303	0.30	18.78	1.80
IPS_N-ISO	1.89	0.57	0.079	0.53	156.76	14.50	**0.016**	0.77	21.73	2.74
CNT_ISO	1.86	0.60	0.069	0.55	145.66	15.15	0.898	0.04	19.29	2.29
CNT_N-ISO	1.85	0.65	0.142	0.44	141.80	16.40	0.585	0.16	18.30	1.51
Right hand	1.84	0.50	**0.043**	0.63	140.78	15.32	**0.034**	0.66		
Older group										
BL (left hand)	0.83	0.30			156.92	7.93				
IPS_ISO	0.91	0.38	0.430	0.23	150.67	13.21	0.166	0.41	20.67	3.26
IPS_N-ISO	0.87	0.30	0.557	0.17	148.69	14.04	0.056	0.59	31.35	3.45
CNT_ISO	0.94	0.37	0.295	0.30	151.12	11.76	0.120	0.46	20.77	1.63
CNT_N-ISO	0.97	0.39	0.203	0.37	147.63	13.45	0.085	0.52	23.84	1.95
Right hand	0.87	0.29	0.331	0.28	146.65	10.62	**0.048**	0.61		

Key: BL, baseline; CI, confidence interval; CNT_ISO, contralateral isodirectional; CNT_N-ISO, contralateral nonisodirectional; ECR, extensor carpi radialis; IPS_ISO, ipsilateral isodirectional; IPS_N-ISO, ipsilateral nonisodirectional; M, mean; MEP, motor evoked potentials; RP, relative phase; SP, silent period. Significant *p* values shown in bold.

differ between the older (44.31 ± 3.70% stimulator output) and younger (42.46 ± 3.43%) adults.

3.2.1.3. Modulation of MEP amplitude and SP duration. The modulation of MEP amplitude and SP duration from the baseline left hand isometric contraction condition was investigated using pairwise comparisons between the baseline condition (in which the left hand maintained a static contraction) and each of the other conditions (IPS_ISO, IPS_N-ISO, CNT_ISO, CNT_N-ISO, right hand phasic). Table 2 shows nonnormalized MEP amplitude and SP duration in each condition with statistical comparisons with the baseline (left hand isometric contraction only).

3.2.1.4. MEP amplitude. Younger adults showed significantly higher nonnormalized baseline MEP amplitude than older adults (see Table 2), $t(24) = 2.71$, $p = 0.01$, $d = 1.08$, which is consistent with the finding that the younger adults exhibited greater EMG in this muscle. For both groups, EMG amplitude in the majority of the conditions did not vary significantly from baseline. However, for the young group, the marginal significance levels and medium effect sizes indicate that, in general, MEP amplitudes of lECR tended to increase whenever the rECR was active relative to baseline (when the rECR was quiescent). Although the tendency for increased MEP amplitudes relative to baseline was also observed in older adults, none of the pairwise comparisons approached significance. For normalized MEP amplitude of the left ECR, none of the main effects ($ps > 0.37$) or interactions reached the conventional significance level ($ps > 0.12$).

3.2.1.5. Silent period. The nonnormalized baseline SP durations for left ECR were comparable between younger and older adults ($p = 0.48$, see Table 2). Marginal significance levels and the effect sizes suggested that SP durations of lECR in the coordination of right hand and left or right foot conditions were shortened relative to the baseline in older adults. For normalized SP of left ECR, there was a significant GROUP × LC × CM interaction, $F(1,24) = 4.47$, $p = 0.04$, $\eta p^2 = 0.16$. As illustrated in Fig. 5, in younger adults, SP duration in the IPS_N-ISO was significantly longer than other conditions ($p < 0.01$) which did not differ from each other ($p > 0.16$). In contrast, older adults showed comparable SP durations across conditions ($ps > 0.41$).

3.2.1.6. Behavioral results (SD of RP). Stability of performance was found to be similar to the results of Exp1. A main effect of GROUP, $F(1,24) = 13.59$, $p = 0.001$, $\eta p^2 = 0.36$, indicated that performance was less stable in older adults (24.16 ± 3.53°) than in younger adults (19.55 ± 2.20°). Coordination of ipsilateral limbs was also less stable (23.13 ± 3.87°) than the coordination of contralateral limbs (20.58 ± 3.94°) $F(1,24) = 11.02$, $p = 0.003$, $\eta p^2 = 0.31$.

As in Exp1, there was a significant interaction of GROUP × CM, $F(1,24) = 15.35$, $p < 0.001$, $\eta p^2 = 0.42$. The effect of aging was more prominent in nonisodirectional conditions where older adults (27.59 ± 3.45°) exhibited less stability than younger adults (19.99 ± 2.52°) ($p < 0.01$). Furthermore, the nonisodirectional mode was less stable than isodirectional mode (20.72 ± 2.37°) in older ($p < 0.01$), but not younger adults (ISO: 19.11 ± 2.03°, $p = 0.73$) ($p = 0.87$). Unlike Exp1, the interaction of between group and limb combination was not significant, $F(1,24) = 1.77$, $p = 0.20$, $\eta p^2 = 0.07$.

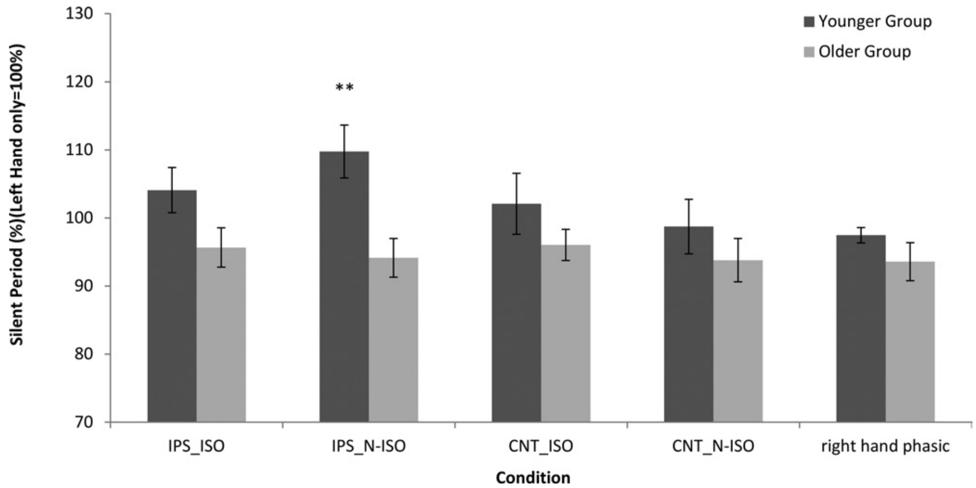

Fig. 5. Mean left extensor carpi radialis (ECR) silent period duration relative to the baseline (hand only) for younger and older groups in experiment 2 (Exp2). Asterisks indicate statistically significant differences between conditions (** $p < 0.01$). Abbreviations: CNT_ISO, contralateral isodirectional; CNT_N-ISO, contralateral nonisodirectional; IPS_ISO, ipsilateral isodirectional; IPS_N-ISO, ipsilateral nonisodirectional. Error bars indicate 95% confidence intervals.

3.2.1.7. Relationship between motor performance and inhibitory function in Exp2. As in Exp1, the relationship between SP duration and SD of RP in the IPS_N-ISO condition was examined in younger and older adults. Neither group showed significant correlations between coordination performance (SD of RP) and inhibitory function (SP duration) (young, $r = 0.007$, $p = 0.98$; older, $r = 0.05$, $p = 0.871$). Older adults again showed a bimodal distribution in the SD of RP data and were grouped into higher performing ($n = 7$, M = 26.70 ± 1.68°) and lower performing ($n = 6$, M = 37.49 ± 7.38°) subgroups, $t(11) = 4.33$, $p = 0.005$, $d = 3.50$. A comparison between the lECR SP durations of the higher (93.42 ± 7.76%) and lower performers (94.98 ± 8.72%), however, was not significant, $t(11) = 0.06$, $p = 0.96$, $d = 0.03$. Similar to older adults, although higher performing ($n = 7$, M = 18.88 ± 1.03°) and lower performing ($n = 6$, M = 26.30 ± 1.18°) younger adults showed significant performance differences $t(11) = 4.16$, $p = 0.002$, $d = 2.32$, there was no difference in SP duration between the 2 subgroups (higher performing, M = 1.03 ± 0.09; lower performing, M = 1.18 ± 0.20), $t(11) = 1.42$, $p = 0.18$, $d = 0.77$.

4. Discussion

The present study examined age-related differences in performance, corticospinal excitation, and inhibition during interlimb coordination. Kinematic measures of interlimb coordination performance replicated previous studies (Fujiyama et al., 2009; Heuninckx et al., 2005; Serrien et al., 2000). As expected, in both experiments younger adults were able to produce isodirectional and nonisodirectional movement patterns with limbs on either the same side (ipsilateral) or opposite sides (contralateral) of the body with high levels of accuracy and stability (e.g., SD of RP less than 30°; Fujiyama et al., 2009; Heuninckx et al., 2004). In contrast, while older adults performed the contralateral limb patterns and the isodirectional pattern with ipsilateral limbs as well as young adults, they had difficulty in performing the nonisodirectional pattern with ipsilateral limbs. These results are consistent with previous research showing reduced performance in nonisodirectional patterns, but preserved capability to perform isodirectional patterns in older adults (Greene and Williams, 1996; Heuninckx et al., 2005; Serrien et al., 2000). We chose SP as an index of corticospinal inhibition because previous studies have consistently reported a reduced SP duration in older adults (Eisen et al., 1996; Hinder et al., 2010; Oliviero et al., 2006; Prout and Eisen, 1994; Sale and Semmler, 2005). The aim of the present study was to determine whether this relatively robust age-related reduction of silent period duration was related to age-related changes in motor performance. In contrast, the effect of aging on short interval intracortical inhibition (SICI), measured using a paired-pulse TMS protocol, appears equivocal; some studies report no difference between young and older adults (Fujiyama et al., 2011; Hinder et al., 2010; Oliviero et al., 2006; Wassermann, 2002), while others found increases (Kossev et al., 2002; McGinley et al., 2010) or decreases (Peinemann et al., 2001) in SICI in older adults. Furthermore, unlike SICI, the SP protocol enabled us to investigate corticospinal inhibitory processes in active muscles which are activated to different levels. It has been demonstrated in a number of studies that background EMG has a minor effect on the duration of the silent period (Säisänen et al., 2008; Taylor et al., 1997; Terao and Ugawa, 2002). In contrast, it appears that the degree of SICI is related to the intensity of muscle contraction in the target muscle (Ortu et al., 2008).

Of particular interest in the present study was the extent to which corticospinal excitability and inhibitory processes contribute to the kinematic differences between younger and older adults during interlimb coordination. A consistent potentiation of MEP amplitude was observed across all coordination modes suggesting that net corticospinal excitability of both ipsilateral and contralateral projections is not affected by the specific coordination pattern that is undertaken. In contrast to MEP amplitude, SP durations were modulated between conditions for both younger and older adults in experiment 1. In experiment 2 younger adults showed SP duration increases in the ipsilateral M1 in all coordination conditions relative to the baseline condition (not all comparisons were significant; see Table 2), except in the nonisodirectional coordination mode using contralateral limbs (Fig. 5). It is worth noting that a control experiment was conducted in which we obtained MEP amplitudes and SP from the right ECR which maintained a tonic contraction without activation of any other limbs, or in conjunction with phasic oscillations of the left or right foot. MEP amplitudes and SP durations did not vary reliably across these conditions (MEP amplitude, $p > 0.290$; SP duration, $p > 0.10$). Accordingly, the modulation of SP we observed in Exp1 and Exp2 appears to be due to coordinated movements of hand and foot, and not due to remote effects of foot movement measured at the hand (e.g., surround inhibition).

Thus, in general, younger adults exhibited increased corticospinal inhibition in ipsilateral M1 during the coordination tasks compared with when the left hand maintained an isometric contraction. In contrast, a release of corticospinal inhibition was generally observed in older adults during the coordination tasks. Thus, the pattern of MEP amplitudes and SP durations across conditions suggests that corticospinal excitability and inhibitory pathways are modulated independently during interlimb coordination by different regulating mechanisms (Wu et al., 2002). We note that SP durations were comparable across the 3 hand angles in both younger and older adults (experiment 1). This particular finding indicates that the observed SP modulation cannot be explained by differences in the position of the hand across conditions; rather the data are consistent with the view that modulation of SP duration is a result of mechanisms that specifically accommodate the spatial and behavioral constraints relating to specific hand-foot coordination patterns.

4.1. *Reduced corticospinal inhibition during nonisodirectional coordination mode using ipsilateral limbs in older adults*

Older adults showed shorter SP duration in the most demanding coordination mode (nonisodirectional with ipsilateral limbs), indicating that their more unstable interlimb coordination in this mode was accompanied by a reduced corticospinal inhibition. In experiment 1, both groups showed comparable MEP amplitudes and SP durations when the coordinated limbs (contralateral) involved right hand and left foot. However, age-related differences in SP duration were evident in the ipsilateral limb combinations. Previous research has shown that intracortical inhibition in a resting arm muscle is selectively reduced during dorsiflexion compared with plantarflexion movement of the ipsilateral lower limb suggesting that lower excitability of M1 inhibitory circuit during dorsiflexion may facilitate isodirectional movements between hand and foot (Byblow et al., 2007). Thus, successful performance of the nonisodirectional pattern may require the suppression of intracortical connections favoring isodirectional coupling between hand-foot areas.

The analysis of higher and lower performing adults allowed us to directly investigate the role of inhibitory mechanisms in maintaining stable coordination behavior. We restricted this analysis to the most difficult IPS_N-ISO coordination mode as we hypothesized that in this coordination mode the motor system would be under most "strain" and as such differences in performance, and thus differences in inhibitory control, between higher and lower performers would be most apparent. The analysis showed that those older adults with the lowest behavioral performance exhibited significantly shorter SP duration than those older adults with significantly more stable performance (i.e., higher performers). These findings suggest for the first time a direct link between changes in the corticospinal inhibitory processes mediating silent period (i.e., $GABA_B$-ergic circuits) and interlimb coordination in older adults.

The difference between high and lower performers is consistent with the view that corticospinal inhibitory control/modulation plays a prominent role in permitting successful execution of the more difficult interlimb coordination patterns that require suppression of the more inherently stable modes (Classen et al., 1998; Garry et al., 2004).

4.2. *The motor cortex ipsilateral to the moving hand during interlimb coordination*

In the second part of the current study (experiment 2), the primary motor cortex ipsilateral to the moving hand was examined by measuring MEP amplitude and SP duration from the left ECR during the coordination tasks. Previous studies have reported shortened SP durations accompanying the activation of the contralateral homologous hand muscle (Hinder et al., 2010; Sohn et al., 2003). The present study investigated whether this effect was also apparent when rhythmic coordination was undertaken. Consistent with previous studies (Hinder et al., 2010; Sohn et al., 2003), both younger and older adults showed shortened SP durations in the tonically contracted left ECR when the right hand was moving relative to the baseline condition in which only left hand was tonically contracted (see Table 2). Furthermore, the younger group exhibited greater MEP amplitude during the right hand movement relative to the baseline condition (see Table 2) which is in line with previous studies showing that activation of the muscles on one side of the body can result in an increase in the excitability of the contralateral homologous motor pathway (e.g., Carson et al., 2004).

Interestingly, changes in SP duration as a function of coordination pattern evident in the left ECR (experiment 2) were similar to changes in SP duration exhibited in the right ECR (experiment 1). That is, corticospinal inhibition in both hemispheres was higher during the performance of ipsilateral limb combinations compared with contralateral limb combinations. The elevated corticospinal inhibition during movements with ipsilateral limbs relative to movements with contralateral limbs does not seem to be a functional modulation to suppress irrelevant left hand movements because the SP modulation patterns did not correspond to the changes in the left ECR EMG activity accompanying contraction of the homologous right ECR contraction (experiment 1, see Fig. 3).

The bilateral changes in cortical activity observed in the current study are in line with the previous findings showing that movements of one side of the body increase corticospinal excitability of the contralateral M1 (Martin et al., 2006; Rothwell et al., 1991; Taylor et al., 1997) as well as the ipsilateral cortex (Carson et al., 2004; Hess et al., 1986; Hortobágyi et al., 2003; Muellbacher et al., 2000; Perez and Cohen, 2008, 2009; Stinear et al., 2001; van den Berg et al., 2011). Furthermore, using a motor learning paradigm, Hinder and colleagues (Hinder et al., 2011) found that, after ballistic finger acceleration training, a decrease of corticospinal inhibition in the M1 contralateral to the hand was accompanied by the reduction of corticospinal inhibition in the M1 ipsilateral to the trained hand. Thus, it is possible that modulation of the intracortical inhibitory pathways in the ipsilateral M1 is linked to the modulation within the contralateral M1, possibly through interhemispheric inhibitory pathways (Hinder et al., 2011).

4.3. Conclusions

In summary, younger adults exhibited longer SPs, reflecting increased corticospinal inhibition, during ipsilateral limb coordination than during coordination of contralateral limbs, consistent with the findings of Fujiyama et al. (2009). Older adults showed a different pattern with lower performance in the most difficult ipsilateral nonisodirectional condition accompanied by a significantly reduced level of corticospinal inhibition. Furthermore, experiment 2 revealed that in younger adults coordination of ipsilateral limbs was also accompanied by increased inhibition in the nonoscillating hand compared with coordination of contralateral limbs. Thus, coordination of upper and lower limbs induces a bilateral modulation of intracortical inhibitory circuits in the left and right M1 in younger adults. Older adults, in contrast, showed no modulation of SP across conditions except when the nonisodirectional pattern was performed by the ipsilateral hand and foot. Of particular importance was that differences in the level of corticospinal inhibition in this condition distinguished between high and lower performing older adults. Thus, this study represents, for the first time, direct evidence supporting the postulation that, for older adults, the reduced ability to coordinate upper and lower limbs is associated with a decreased ability to control corticospinal inhibition.

Disclosure statement

The authors disclose no conflicts of interest.

Subjects provided written informed consent prior to participation in the study. Ethics approval was obtained from the Human Research Ethics Committee (Tas) Network.

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References

Baldissera, F., Cavallari, P., Civaschi, P., 1982. Preferential Coupling between Voluntary Movements of Ipsilateral Limbs. Neurosci. Lett. 34, 95–100.

Baldissera, F., Esposti, R., 2005. Postural constraints to coupling of ipsilateral hand-foot movements. Neuroreport 16, 1615–1619.

Borroni, P., Cerri, G., Baldissera, F., 2004. Excitability changes in resting forearm muscles during voluntary foot movements depend on hand position: a neural substrate for hand-foot isodirectional coupling. Brain Res. 1022, 117–125.

Byblow, W.D., Coxon, J.P., Stinear, C.M., Fleming, M.K., Williams, G., Müller, J.F., Ziemann, U., 2007. Functional connectivity between secondary and primary motor areas underlying hand-foot coordination. J. Neurophysiol. 98, 414–422.

Carson, R.G., Riek, S., Mackey, D.C., Meichenbaum, D.P., Willms, K., Forner, M., Byblow, W.D., 2004. Excitability changes in human forearm corticospinal projections and spinal reflex pathways during rhythmic voluntary movement of the opposite limb. J. Physiol. 560, 929–940.

Chen, R., Lozano, A.M., Ashby, P., 1999. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. Exp. Brain Res. 128, 539–542.

Classen, J., Liepert, J., Wise, S.P., Hallett, M., Cohen, L.G., 1998. Rapid plasticity of human cortical movement representation induced by practice. J. Neurophysiol. 79, 1117–1123.

de Rekeneire, N., Visser, M., Peila, R., Nevitt, M.C., Cauley, J.A., Tylavsky, F.A., Simonsick, E.M., Harris, T.B., 2003. Is a fall just a fall: Correlates of falling in healthy older persons. The health, aging and body composition study. J. Am. Geriatr. Soc. 51, 841–846.

Dick, J.P.R., Guiloff, R.J., Stewart, A., Blackstock, J., Bielawska, C., Paul, E.A., Marsden, C.D., 1984. Mini-mental state examination in neurological patients. J. Neurol. Neurosurg. Psychiatry 47, 496–499.

Eisen, A., Entezari-Taher, M., Stewart, H., 1996. Cortical projections to spinal motoneurons: Changes with aging and amyotrophic lateral sclerosis. Neurology 46, 1396–1404.

Fuhr, P., Agostino, R., Hallett, M., 1991. Spinal motor neuron excitability during the silent period after cortical stimulation. Electroencephalogr. Clin. Neurophysiol. 81, 257–262.

Fujiyama, H., Garry, M.I., Levin, O., Swinnen, S.P., Summers, J.J., 2009. Age-related differences in inhibitory processes during interlimb coordination. Brain Res. 1262, 38–47.

Fujiyama, H., Tandonnet, C., Summers, J.J., 2011. Age-related differences in corticospinal excitability during a Go/NoGo task. Psychophysiology 1148, 1448–1455.

Garry, M.I., Kamen, G., Nordstrom, M.A., 2004. Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning. J. Neurophysiol. 91, 1570–1578.

Garry, M.I., van Steenis, R.E., Summers, J.J., 2005. Interlimb coordination following stroke. Hum. Mov. Sci. 24, 849–864.

Greene, L.S., Williams, H.G., 1996. Aging and coordination from the dynamic pattern perspective, in: Ferrandez, A.M., Teasdale, N. (Eds.), Change in Sensorimotor Behavior in Aging. Elsevier Science B.V., Holland, pp. 89–131.

Hess, C.W., Mills, K.R., Murray, N.M., 1986. Magnetic stimulation of the human brain: Facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. Neurosci. Lett. 71, 235–240.

Heuninckx, S., Debaere, F., Wenderoth, N., Verschueren, S., Swinnen, S.P., 2004. Ipsilateral coordination deficits and central processing requirements associated with coordination as a function of aging. J. Gerontol. B Psychol. Sci. Soc. Sci. 59, 225–232.

Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., Swinnen, S.P., 2005. Neural basis of aging: The penetration of cognition into action control. J. Neurosci. 25, 6787–6796.

Hinder, M.R., Schmidt, M.W., Garry, M.I., Carroll, T.J., Summers, J.J., 2011. Absence of cross-limb transfer of performance gains following ballistic motor practice in older adults. J. Appl. Physiol. 110, 166–175.

Hinder, M.R., Schmidt, M.W., Garry, M.I., Summers, J.J., 2010. The effect of ballistic thumb contractions on the excitability of the ipsilateral motor cortex. Exp. Brain Res. 201, 229–238.

Hiraga, C.Y., Summers, J.J., Temprado, J.J., 2004. Attentional costs of coordinating homologous and non-homologous limbs. Hum. Mov. Sci. 23, 415–430.

Hiraga, C.Y., Summers, J.J., Temprado, J.J., 2005. Effects of attentional prioritisation on the temporal and spatial components of an interlimb circle-drawing task. Hum. Mov. Sci. 24, 815–832.

Hortobágyi, T., Taylor, J.L., Petersen, N.T., Russell, G., Gandevia, S.C., 2003. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. J. Neurophysiol. 90, 2451–2459.

Kelso, J.A., Jeka, J.J., 1992. Symmetry breaking dynamics of human multilimb coordination. J. Exp. Psychol. Hum. Percept. Perform. 18, 645–668.

Kido, A., Tanaka, N., Stein, R.B., 2004. Spinal excitation and inhibition decrease as humans age. Can. J. Physiol. Pharmacol. 82, 238–248.

Kossev, A.R., Schrader, C., Däuper, J., Dengler, R., Rollnik, J.D., 2002. Increased intracortical inhibition in middle-aged humans; a study using paired-pulse transcranial magnetic stimulation. Neurosci. Lett. 333, 83–86.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P., Marsden, C.D., 1993. Corticocortical inhibition in human motor cortex. J. Physiol. 471, 501–519.

Mardia, K.V., 1972. Statistics of Directional Data. Academic Press, London.

Martin, P.G., Gandevia, S.C., Taylor, J.L., 2006. Output of human motoneuron pools to corticospinal inputs during voluntary contractions. J. Neurophysiol. 95, 3512–3518.

Mattay, V.S., Fera, F., Tessitore, A., Hariri, A.R., Das, S., Callicott, J.H., Weinberger, D.R., 2002. Neurophysiological correlates of age-related changes in human motor function. Neurology 58, 630–635.

McGinley, M., Hoffman, R.L., Russ, D.W., Thomas, J.S., Clark, B.C., 2010. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. Exp. Gerontol. 45, 671–678.

Meesen, R.L., Wenderoth, N., Swinnen, S.P., 2005. The role of directional compatibility in assembling coordination patterns involving the upper and lower limb girdles and the head. Behav. Brain Res. 165, 262–270.

Muellbacher, W., Facchini, S., Boroojerdi, B., Hallett, M., 2000. Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. Clin. Neurophysiol. 111, 344–349.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Oliviero, A., Profice, P., Tonali, P.A., Pilato, F., Saturno, E., Dileone, M., Ranieri, F., Di Lazzaro, V., 2006. Effects of aging on motor cortex excitability. Neurosci. Res. 55, 74–77.

Ortu, E., Deriu, F., Suppa, A., Tolu, E., Rothwell, J.C., 2008. Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. J. Physiol. 86, 5147–5159.

Peinemann, A., Lehner, C., Conrad, B., Siebner, H.R., 2001. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci. Lett. 313, 33–36.

Perez, M.A., Cohen, L.G., 2008. Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J. Neurosci. 28, 5631–5640.

Perez, M.A., Cohen, L.G., 2009. Scaling of motor cortical excitability during unimanual force generation. Cortex 45, 1065–1071.

Prout, A.J., Eisen, A.A., 1994. The cortical silent period and amyotrophic lateral sclerosis. Muscle Nerve 17, 217–223.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Safety of TMS Consensus Group, 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 120, 2008–2039.

Rothwell, J.C., Thompson, P.D., Day, B.L., Boyd, S., Marsden, C.D., 1991. Stimulation of the Human Motor Cortex through the Scalp. Exp. Physiol. 76, 159–200.

Säisänen, L., Pirinen, E., Teitti, S., Könönen, M., Julkunen, P., Määttä, S., Karhu, J., 2008. Factors influencing cortical silent period: Optimized stimulus location, intensity and muscle contraction. J. Neurosci. Methods 169, 231–238.

Sale, M.V., Semmler, J.G., 2005. Age-related differences in corticospinal control during functional isometric contractions in left and right hands. J. Appl. Physiol. 99, 1483–1493.

Serrien, D.J., Swinnen, S.P., 1997. Coordination constraints induced by effecter combination under isofrequency and multifrequency conditions. J. Exp. Psychol. Hum. Percept. Perform. 23, 1493–1510.

Serrien, D.J., Swinnen, S.P., Stelmach, G.E., 2000. Age-related deterioration of coordinated interlimb behavior. J. Gerontol. B Psychol. Sci. Soc. Sci. 55B, 295–303.

Sink, C.A., Stroh, H.R., 2006. Practical Significance: The Use of Effect Sizes in School Counseling Research. Prof. Sch. Couns. 9, 401–411.

Sohn, Y.H., Jung, H.Y., Kaelin-Lang, A., Hallett, M., 2003. Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. Exp. Brain Res. 148, 176–185.

Sohn, Y.H., Kang, S.Y., Hallett, M., 2005. Corticospinal disinhibition during dual action. Exp. Brain Res. 162, 95–99.

Spirduso, W.W., Choi, Y., 1993. Age and practice effects on force control of the thumb and index fingers in precision pinch and bilateral digit coordination, in: Stelmach, G.E., Hömberg, V. (Eds.), Sensory-Motor Impairments in the Elderly. Kluwer Academic Publishers, Boston, pp. 393–412.

Stinear, C.M., Walker, K.S., Byblow, W.D., 2001. Symmetric facilitation between motor cortices during contraction of ipsilateral hand muscles. Exp. Brain Res. 139, 101–105.

Swinnen, S.P., 2002. Intermanual coordination: From behavioural principles to neural-network interactions. Nat. Rev. Neurosci. 3, 350–361.

Swinnen, S.P., Dounskaia, N., Verschueren, S., Serrien, D.J., Daelman, A., 1995. Relative phase destabilization during interlimb coordination: The disruptive role of kinesthetic afferences induced by passive movement. Exp. Brain Res. 105, 439–454.

Taylor, J.L., Allen, G.M., Butler, J.E., Gandevia, S.C., 1997. Effect of contraction strength on responses in biceps brachii and adductor pollicis to transcranial magnetic stimulation. Exp. Brain Res. 117, 472–478.

Tazoe, T., Endoh, T., Nakajima, T., Sakamoto, M., Komiyama, T., 2007. Disinhibition of upper limb motor area by voluntary contraction of the lower limb muscle. Exp. Brain Res. 177, 419–430.

Terao, Y., Ugawa, Y., 2002. Basic mechanisms of TMS. J. Clin. Neurophysiol. 19, 322–343.

van den Berg, F.E., Swinnen, S.P., Wenderoth, N., 2011. Excitability of the motor cortex ipsilateral to the moving body side depends on spatio-temporal task complexity and hemispheric specialization. PLoS One 6.

Wassermann, E.M., 2002. Variation in the response to transcranial magnetic brain stimulation in the general population. Clin. Neurophysiol. 113, 1165–1171.

Wenderoth, N., Debaere, F., Swinnen, S.P., 2004. Neural networks involved in cyclical interlimb coordination as revealed by medical imaging techniques, in: Swinnen, S.P., Duysens, J.E.J. (Eds.), Neurobehavioral Determinants of Interlimb Coordination: a Multidisciplinary Approach. Kluwer Academic, Boston, pp. 187–222.

Wu, L., Goto, Y., Taniwaki, T., Kinukawa, N., Tobimatsu, S., 2002. Different patterns of excitation and inhibition of the small hand and forearm muscles from magnetic brain stimulation in humans. Clin. Neurophysiol. 113, 1286–1294.

Zehr, E.P., Collins, D.F., Frigon, A., Hoogenboom, N., 2003. Neural control of rhythmic human arm movement: Phase dependence and task modulation of Hoffmann reflexes in forearm muscles. J. Neurophysiol. 89, 12–21.