RESEARCH ARTICLE

Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb

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Abstract We investigated how volitional contractions affect interhemispheric inhibition (IHI) from the active to the passive hemisphere. Younger and older adults isometrically contracted their dominant thumb (abductor pollicis brevis, APB) to various force targets. In ballistic contraction trials, transcranial magnetic stimulation (TMS) was administered very shortly after the onset of APB activity. In tonic contraction trials, TMS was delivered while the target force was maintained. In control trials both thumbs remained quiescent. In all trials, a test stimulus (TS) was directed to the APB hotspot in the non-dominant hemisphere (130% left APB resting motor threshold, RMT). In half the trials, a conditioning stimulus (130% right APB RMT) was applied to the APB hotspot in the dominant hemisphere 10 ms prior to the TS. Targeted ballistic contractions of the right APB were found to modulate (increase) IHI measured in the left APB, as previously reported for tonic contractions. Furthermore, the extent of the IHI increase was found to scale with the strength of the contralateral ballistic or tonic contraction. Less pronounced, but statistically significant, IHI increases were also observed in the left abductor digiti minimi and extensor carpi radialis during right APB contraction. For these muscles, however, the extent of the IHI modulation was *independent* of APB contraction strength. The capacity to modulate inhibition during contractions was unaffected by advancing age. During volitional actions, the ability to modulate IHI most adaptively in the homologous muscle of the resting limb may contribute to the prevention of mirror movements.

Introduction

The corpus callosum (CC) is the primary link between the two cortices and plays an important role in transferring perceptual, sensory and motor information between the cortices (see Gazzaniga 2005 for a review). In young children, unimanual movements present some difficulty-bilateral muscle activity and movements of the contralateral limb are considered as normal. However, the bilateral response decreases as infants develop (Mayston et al. 1999) and is closely linked with the development (myelination) of the CC. As such it is believed that the ability to suppress, or inhibit, the bilateral response is mediated by the transcallosal fibres of the CC (Muller et al. 1997) through a mechanism known as interhemispheric inhibition (IHI). IHI can be examined non-invasively in humans using a transcranial magnetic stimulation (TMS) paradigm in which a conditioning stimulus (CS) is applied to one ('conditioned') hemisphere followed by a test stimulus (TS) to the other ('test') hemisphere (Ferbert et al. 1992). Inhibition, i.e. lower amplitude motor-evoked potentials (MEPs) in the target muscle following paired-pulse stimulation compared to MEPs amplitudes as a result of test pulses alone, was observed when the CS preceded the TS by 6–15 ms.

Recent studies have begun to explore the interesting question of how IHI may be modulated in preparation for, or during, voluntary movements. Perez and Cohen (2008)

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investigated IHI changes during ongoing (tonic) voluntary contractions. They concluded that (when the intensity of the conditioning stimuli were adjusted to standardise MEP sizes—see Chen 2004) tonic contractions of the right wrist decreased IHI measured in the resting left wrist compared to when both limbs were at rest. Vercauteren et al. (2008) found increased IHI in the left wrist during low force tonic contractions of the right wrist, compared to when both limbs were at rest. The results of Vercauteren et al. (2008) are consistent with the initial observations of Ferbert et al. (1992) who reported that tonic contraction of the left wrist resulted in a small, but statistically significant, increase in the IHI measured in the right wrist. Interestingly, Perez and Cohen (2008) alluded to the fact that when stimulations intensities were *not adjusted*, IHI in the left wrist *increased* during right wrist contraction, a finding consistent with other studies (Vercauteren et al. 2008; Ferbert et al. 1992; Talelli et al. 2008).

During later life, an increase in the degree of mirror activity during unimanual tasks is observed (see Hoy et al. 2004 for a review), and recent imaging studies suggest this is a result of greater bi-hemispheric activation of the motor cortices during unimanual tasks. (Ward and Frackowiak 2003; for a review, see Ward 2006). Talelli et al. (2008) recently provided neurophysiological evidence to suggest that the less-lateralised motor cortical activation found in older adults during unimanual tasks may be a result of a breakdown in specific interhemispheric inhibitory mechanisms. Participants of varying ages were asked to produce a sustained (low level) contraction with the right index finger, while IHI was measured in the left index finger. IHI at a short (10-ms) inter-stimulus interval (IHI10) was found to increase (though not significantly) during the contractions, compared to the resting condition (i.e. both hands at rest), but this was unaffected by age. In contrast, at a long (40-ms) interstimulus interval, younger adults tended to increase the extent of interhemispheric inhibition during contractions, whereas for older adults this increase was less pronounced, or reversed, such that disinhibition sometimes occurred.

The extant literature, as reviewed briefly earlier, has investigated how cortical interactions can result in changes in IHI during ongoing, contractions, and how this may be affected by age. Relatively little is known, however, about how the cortices interact in the milliseconds following the initiation of a targeted ballistic contraction. This is an important issue because, compared to tonic activations, targeted ballistic contractions resemble more closely everyday movement tasks such as reaching and grasping in which bursts of muscle activation at precise force levels are required. In a recent study (Hinder et al. 2010), we began to investigate whether the cortical interactions evoked by targeted ballistic contractions can alter the neural excitability of the ipsilateral cortex. Specifically, TMS was used

to measure excitability, short-interval intracortical inhibition (SICI) and silent period duration in the left cortex (muscles of the right hand) *immediately following* the onset of EMG activity related to a targeted ballistic contraction of the left thumb. We found increased excitability of the ipsilateral (left) homologous muscle during contraction of the right hand, together with a reduction in silent period duration but no change in the circuits mediating SICI (Hinder et al. 2010).

In the present study, we aimed to increase our understanding of the interaction between the motor cortices *immediately* following targeted ballistic contractions. Specifically, we were interested in evaluating interhemispheric inhibition from the active to the passive (ipsilateral) cortex in the period immediately following volitional contractions. Regulation of this mechanism could contribute to the prevention of undesired movement/activation (mirror activation) in the contralateral limb. Whether age-related decline affects the ability to modulate IHI during these functional ballistic tasks, where one would assume that adaptive IHI modulation immediately following the onset of the EMG burst would be imperative in preventing mirror movements, is an important consideration for movement control in the aged population. Indeed, as alluded to previously, older adults exhibit greater motor overflow than their younger counterparts (Hoy et al. 2004). While Talelli et al. (2008) found that older adults maintained the ability to modulate IHI during sustained contractions, it is feasible that a deterioration in the ability to modulate IHI *rapidly* at the onset of a ballistic contraction may occur, which could explain the observation of increased mirror activity in older adults in dynamic tasks.

We had four specific aims in the present study: to determine (1) whether IHI (from the contralateral to ipsilateral cortex) is modulated at the onset of self-paced volitional ballistic contractions in a similar manner to that reported during ongoing tonic contractions; (2) whether the forcefulness of the contractions affected any manifested modulation of IHI; (3) whether changes in IHI were apparent only in the homologous muscle in the contralateral limb or were more generalised and (4) whether older adults exhibit IHI modulation that is comparable to that exhibited by the younger adults in the ballistic and tonic tasks, and across a range of target force levels.

Methods

Participants

Twenty adults were recruited into one of two equally sized groups based on age: younger group (mean ± SD) 25.9 ± 3.4 years, range 23–32; older group 66.4 ± 4.0 years,

range 62–75 years. There were 5 women in each group. All participants were self-reported right-handers. The study received ethical approval from the University of Tasmania's Human Research Ethics committee. Participants gave (written) informed consent prior to beginning the experiment, did not have any contra-indications to TMS, had normal or corrected-to-normal vision, and were free from neurological and neuromuscular disorders.

Experimental set-up

While seated, participants placed their forearms in a pronated position (palms down) on supports, with elbows bent at approximately 120°. Their thumbs rested on custom-made platforms fitted with single degree of freedom force transducers aligned to measure downward force as a result of activating the abductor pollicis brevis (APB) muscle (thumb abductor). A computer screen was placed approximately 60 cm in front of them and provided feedback of forces during each trial.

Maximum voluntary contraction (MVC)

To determine the MVC of each participant's right (dominant) APB muscle, participants were asked to press down as hard as possible with their right thumb on the force transducer for approximately 2 s within a 5 s recording period. They received visual feedback on the computer screen and were encouraged to move the trace as high as possible on the screen (maximise force), using only the thumb muscle. Three trials were conducted with 30 s rest between each trial. The mean peak value of the three trials was calculated and used to establish the target force levels for the movement task.

Movement task

Each 5 s trial began with both thumbs relaxed, with forearms and thumbs in the posture described earlier. Visual feedback of right thumb force was provided in real time in the form of a trace that ran across the screen. Pushing down on the platform resulted in the force feedback line moving up the screen. Horizontal cursors provided a target force zone: these cursors were located 5% APB MVC above and below the target force. In all trials, the left thumb remained quiescent. However, it was placed on the small platform to standardise the posture for both limbs.

Ballistic contraction trials

In ballistic contraction trials, participants attempted to produce a ballistic force pulse of ~100–200 ms duration with the right thumb. They were instructed that the aim was to produce a peak force magnitude that was within the target zone. Three force levels were used: 5, 15 and 30% of the predetermined APB MVC. The word 'relax' (generated within the data collection software) was heard 1.5 s into the trial and instructed participants to fully relax both limbs. The word 'ready' (again, generated within the data collection software) was heard at 3.5 s and indicated that participants should, at any time between that point and the end of the trial (i.e. a self-paced action within the next 1.5 s), produce a *ballistic* force pulse with their right APB while maintaining quiescence in the left hand and arm. Any trial in which EMG activity was apparent (RMS EMG > 0.015 mV) in the right APB prior to 3.5 s (i.e. activity not associated with the volitional ballistic EMG burst) was not recorded and was repeated.

Tonic contraction trials

In this condition, the word 'push' (heard at 1.5 s) replaced 'relax', indicating that participants should push down on the instrumented force platform positioned under the right thumb and keep the force within the target zone until the end of the trial (i.e. they maintained the force for ~3.5 s). No other commands were heard. As with the ballistic trials, 5, 15 and 30% MVC force levels were used and the left thumb remained quiescent.

Control trials

We conducted control trials in which both the left and right thumbs remained quiescent. The word 'relax' was heard at 1.5 s indicating that both thumbs should be relaxed and be kept relaxed until the end of the trial. A comparison of tonic and ballistic trials to these control trials would elucidate if contraction of the right APB modulated IHI from the dominant to non-dominant hemisphere, compared to when IHI was determined in the resting state.

Training

Prior to the experimental trials, participants practiced producing tonic and ballistic force pulses with the right APB of the desired duration and force magnitudes, while the left APB was quiescent. The training lasted approximately 10 min and did not involve any TMS. Training trials were not recorded or analysed.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was delivered to the left ('conditioned') and right ('test') cortices using two Magstim 200 units (Magstim Company, Dyfed, UK) and two 'branding iron' style figure of eight coils (with a diameter

of 50 mm for each wing). One experimenter was responsible for holding each coil. Branding iron coils were chosen as one coil could be placed on each cortex without compromising either coil's positioning relative to the respective motor hotspots.

Optimal coil positions for eliciting MEPs from the left and right APB (with posterior to anterior current direction, i.e. coils at ∼45 degrees to the midline) were determined and marked on the scalp. Resting motor thresholds (RMT), from which the stimulation intensities were derived, were determined as the minimum intensities required to elicit MEPs > 50 μV in the right and left APB muscles in three out of five consecutive trials when stimulating at the predetermined hotspots (Garry et al. 2005; Garry and Thomson 2009; Rogasch et al. 2009). Of the 20–24 trials conducted in each condition, half involved a single 'test' stimulus (TS) applied at the motor hotspot for the non-dominant (resting) left APB muscle (i.e. right cortex) at 130% left APB RMT. In the other trials, a conditioning stimulus (CS) was delivered at the motor hotspot for the dominant APB muscle (i.e. left cortex) at 130% of the right APB RMT 10 ms prior to the TS. These trials were designed to investigate interhemispheric inhibitory processes (Ferbert et al. 1992). We chose an ISI of 10 ms to allow direct comparison between our results and the majority of the previous task-related IHI studies (e.g. Duque et al. 2005, 2007; Perez and Cohen 2008; Vercauteren et al. 2008). Furthermore, our pilot work suggested IHI at 10-ms ISI was both strong and consistent (c.f. Ferbert et al. 1992; Gerloff et al. 1998), possibly because this ISI is consistent with estimates of transcallosal conduction time (see De Gennaro et al. 2004; also Aboitiz et al. 1992; Cracco et al. 1989; Rossini et al. 1985), whereas IHI with an ISI of 40 ms was often difficult to attain (c.f. De Gennaro et al. 2004).

In the ballistic contraction trials, TMS was administered based on the detection of EMG activity in the right APB. We used custom-written software (Signal 3.08) that allowed us to reliably detect EMG onset within 2.5 ms of the first perceptible occurrence of right APB EMG above background (noise) levels (Hinder et al. 2010). We administered TMS at two specific points relative to the detection of the EMG onset. First, we triggered as soon as possible following EMG onset. In this condition (referred to as the ballistic condition), the CS (when applied) was administered at the detected EMG onset. The TS was applied (to the other cortex) 10 ms later. In the single-pulse trials, TS was administered 10 ms after the detected onset of EMG. In this manner, we standardised the timing of the test pulse, with respect to the EMG burst onset, in single- and paired-pulse trials. In a second ballistic condition, we imposed a delay between EMG detection and administering TMS in an attempt to stimulate concurrently with the maximum cortical outflow to the APB muscle. In this condition ('ballistic-delay' condition), we estimated each participant's average EMG pulse width during the ballistic condition, and imposed a delay of half this value less 20 ms (i.e. equivalent to the conduction time from the motor command leaving the cortex to the occurrence of EMG at the muscle). On the assumption that the maximum EMG activity occurred in the centre of the burst, we anticipated that this delay would enable us to stimulate the motor cortex at the time of maximum cortical outflow. In the paired-pulse trials, participants were told that they should ignore, as much as possible, the transient effect of the conditioning stimuli that would somewhat perturb their ballistic force pulse.

In the tonic contraction condition, TMS were triggered by the computer (after 3.5 s) while participants maintained a steady force. Participants were asked to maintain the tonic force within the target cursors until the end of the trial, i.e. they should not relax upon sensing the TMS. However, they were told that they should ignore, as much as possible, the transient force perturbation to the right thumb that occurred as a result of the conditioning stimuli. In the control condition, as with tonic contraction condition, TMS was administered following 3.5 s. Participants were instructed to keep both limbs relaxed.

In each contraction type (tonic, ballistic and ballistic delay) and at each force level, 20–24 trials (each 5 s long) were conducted. Consecutive pairs of trials consisted of one single-pulse and one paired-pulse trial. Conditions were presented in a pseudorandomised order (the ballistic-delay condition always had to occur following the ballistic condition as we had to establish the delay based on the EMG pulse width). The force levels within each condition were conducted in a random order.

The procedure, including set-up and training, lasted approximately 60 min.

Data recording, reduction and analysis

MEP responses were recorded in the (resting) left APB, left abductor digiti minimi (ADM) and left extensor carpi radialis (ECR) muscles at 10 kHz. Muscle activity in the right APB (triggering muscle) was also recorded (at 10 kHz), as was the force produced by the right thumb. Data were stored on a computer for offline analysis. Each trial was visually inspected to ensure participants had achieved the correct force level with the right thumb, while keeping the left thumb relaxed. In ballistic force trials, we also checked that right APB EMG pulses were of the correct duration (∼100–200 ms). In tonic trials, we checked that the desired force produced by the right hand had been maintained throughout the trial. Any trial in which the desired force fell outside the permitted

bandwidth (i.e. >5% APB MVC from the target force) was rejected from analyses. Furthermore, trials in which EMG activity in the muscles of the left hand or arm was present (RMS EMG > 0.015 mV) prior to the MEP were discarded. MEP amplitudes in the left hand (APB, ADM) and arm (ECR) muscles were calculated for the remaining trials and averaged across single-pulse trials and paired-pulse trials in each condition. MEPs in the active conditions were normalised to the corresponding control (resting) MEP condition (nMEP). This permitted a fully factorial ANOVA to be conducted (with stimulation type [single-pulse, paired-pulse], muscle [APB, ADM, ECR], condition [tonic, ballistic, ballistic-delay] and contraction strength [5, 15, 30% right APB MVC] as within-subjects factors, and age [younger, older] as the between-subjects factors). By normalising MEPs, as well as investigating the main effects and interactions relating to our independent variables, we were able to determine within the ANOVA if, averaged over all conditions, potentiation of MEPs occurred relative to their respective resting state values (i.e. if nMEP > 1). For each participant, the ratio of the average MEP amplitude in the paired-pulse trials to the average MEP amplitude in the single-pulse trials was calculated to give the IHI ratio for each muscle in each condition (IHI < 1 indicates inhibition; the smaller the value, the greater the inhibition). We shall refer to these ratios as IHIc (IHI ratio in the control condition) and IHIa (IHI ratio in the active conditions, i.e. tonic, ballistic and ballistic-delay conditions). Using single sample t-tests, we assessed whether significant inhibition (IHI < 1) was attained in active and control conditions. For each participant we then computed the ratio of IHIa to IHIc as an indication of how IHI was influenced by the volitional contractions. This ratio is referred to as IHIa/c: IHIa/c > 1 indicates greater inhibition was observed in the control condition relative to the specific active condition (task-related decrease in inhibition) whereas IHIa/c < 1 indicates greater inhibition in the active condition compared to control (task-related increase in inhibition). We log-transformed all IHIa/c ratios (Sinclair and Hammond 2009) before undertaking mixed-factorial ANOVA with muscle,

condition and contraction strength as within-subjects factors and age as a between-subjects factor. Subsequent analyses were undertaken to investigate any main effect or interactions of interest. For both ANOVAs, Huynh–Feldt corrections were applied if the assumption of sphericity was violated ($\varepsilon < 0.7$). The a priori alpha level was set at 0.05 when determining statistical significance. Partial eta-squared is presented as a measure of effect size to aid the interpretation of the tests of significance. For presentation of data in figures, IHI ratios are presented as geometric means ($\pm$95% confidence intervals) within each condition (i.e. back-transformed log-ratios, see Sinclair and Hammond 2009) while average (arithmetic mean) MEP amplitudes ($\pm$95% confidence intervals) are presented.

Results

All participants were able to conduct the ballistic and tonic contraction tasks at all the desired force levels relatively accurately. However, two participants, one from each group, exhibited very small MEPs which were sometimes indeterminable from background (resting muscle) EMG signals. Accordingly, data from these participants were excluded and further data analysis and statistics were performed on two groups of nine participants. A total of 10.3% of trials (across all conditions and participants) were rejected for high background EMG activity and/or inaccurate force production (magnitude or duration), with no participant exhibiting a particularly high rejection rate in any condition. Table 1 shows average ($\pm$SD) age, MVC, RMTs associated with the magnetic stimulation and trigger delays for the younger and older groups, together with t-scores and P values associated with inter-group (independent samples) t-tests. These analyses failed to show any significant difference between the MVCs of the two groups. No significant inter-group difference was found between the RMT of the left, or right, cortex, nor did RMT of the left and right cortex differ within each group. The trigger delay, which was imposed based on the estimated

Table 1 Comparisons (mean $\pm$ SD) of ages, forces and TMS parameters for the two participant groups

	Age	Max force	RMT left hemisphere (% MSO)	RMT right hemisphere (% MSO)	Trigger delay (ms)
Younger group	25.9 ± 3.4	1.54 ± 0.47	41.8 ± 5.0	43.2 ± 6.2	55.0 ± 11.2
Older group	66.4 ± 4.0	1.51 ± 0.50	44.7 ± 8.1	44.7 ± 5.2	52.8 ± 13.3
T-score	23.04	0.12	0.91	0.53	0.38
df	16	16	16	16	16
P value	**<0.0001**	0.90	0.38	0.61	0.71

No significant differences (independent samples t-test) were found between groups for maximum force, RMT (measured as a percentage of maximum stimulator output, MSO) of either hemisphere or trigger delay. Furthermore, no difference was found (paired sample t-tests) between RMT of the left and right hemisphere for the younger ($t_{16} = 0.63$, $P = 0.54$) or older ($t_{16} = 0.00$, $P = 1.00$) groups
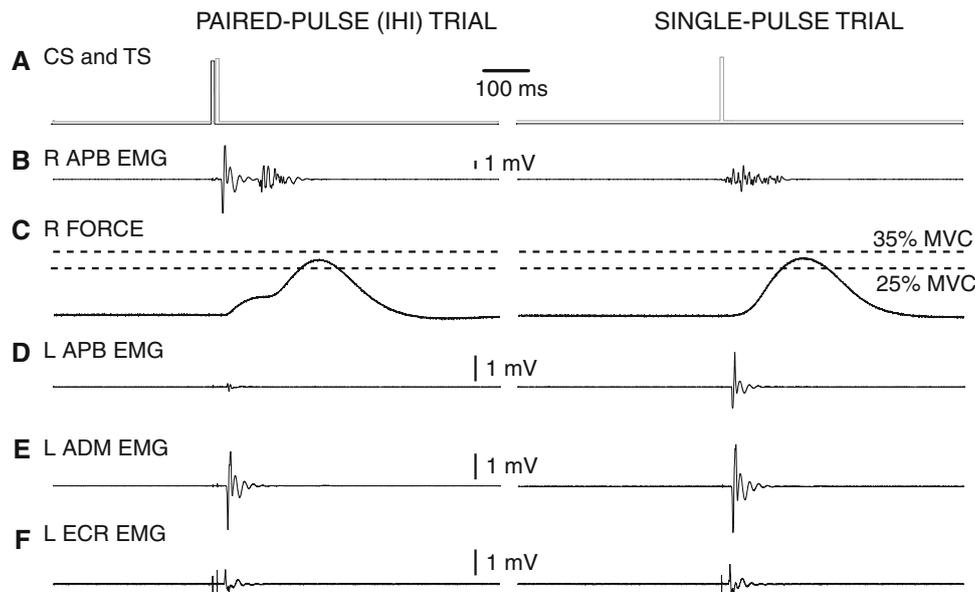
Fig. 1 Example of paired-pulse (*left-hand panels*) and single-pulse (*right-hand panels*) in the 30% MVC ballistic (immediate triggering) condition. **a** The CS (*black trace*) and TS (*grey*) pulses were triggered as soon as possible following EMG onset in the right APB (**b**). In the paired-pulse trial, note the MEP and subsequent silent period as a result of the CS in the right APB EMG. **c** Force measured by the force transducer as a result of the right APB contraction. The *horizontal dotted bars* indicate the target zone (30% MVC ± 5% in this case).

The CS causes a transient perturbation of the force profile in the paired-pulse trial. MEPs as a result of the TS are shown for the left APB (**d**), left ADM (**e**) and left ECR (**f**). It is apparent that IHI is more pronounced for the APB than for the ADM and ECR. All panels are plotted on the same time scale (see *bar* in the *top panel*). The voltage scales for the EMG channels are shown individually for panels **b**, **d**, **e** and **f**

pulse width during ballistic trials (see "Methods"), was not significantly different between groups.

Figure 1 shows a typical paired-pulse (IHI) trial (left panels) and single-pulse trial (right panels) in which the participant made a ballistic contraction of the right thumb and TMS was triggered immediately upon detection of the EMG activity in the right APB.

Figure 2 (upper left panels of a–e) and Table 2 show the average MEP size observed in the single and paired-pulse trials in each muscle and each trial condition, for both the younger (left hand column) and older (right-hand column) participants. Group-average MEP sizes in single-pulse trials ranged from 0.6 to 1.9 mV for both age groups, and all conditions and muscles. MEPs elicited following the paired-pulse paradigm were generally, as expected in an IHI paradigm, smaller than those observed following single-pulse stimulation in the equivalent muscle/condition, and were in the range 0.3–1.1 mV (see Fig. 2). Figure 2 indicates that contraction of the right APB led to a qualitative increase (relative to the rest condition) in the size of the MEP elicited by the single-pulse trials (black diamonds) in the left APB (top panels), and (to a lesser extent) in the left ADM and left ECR (middle and lower panels, respectively). The influence of the right APB contraction on the size of the MEPs elicited from the paired-pulse trials (Fig. 2, grey triangles) was less pronounced with MEP

amplitudes in all active conditions similar to control. To investigate how contractions of varying strength and type (tonic/ballistic/ballistic delay) of the right APB affected MEP amplitudes in the left APB, ADM and ECR, relative to control (i.e. when the right limb was quiescent) we conducted ANOVA of normalised MEP size in each active condition relative to the control (i.e. nMEP, see "Data reduction and analysis"). Averaged across all factors, nMEP was significantly larger than 1 ($F_{(1,17)} = 8.36$, $P = 0.01$, $\eta_p^2 = 0.33$) indicating potentiation of MEPs in the active conditions, relative to their respective control. nMEPs were larger in the single-pulse trials than in the paired-pulse trials (stimulation type main effect $F_{(1,16)} = 20.30$, $P < 0.001$, $\eta_p^2 = 0.56$) while the significant main effect of contraction strength ($F_{(2,16)} = 14.99$, $P = 0.02$, $\eta_p^2 = 0.26$) indicates that more forceful contractions resulted in greater potentiation of MEP amplitudes relative to the control condition than lower strength contractions. The main effect of muscle was not significant ($F_{(2,32)} = 1.84$, $P = 0.18$, $\eta_p^2 = 0.10$). Furthermore, the main effect of age and all interactions with age as a factor were not significant ($Ps > 0.2$).

While the omnibus ANOVA detailed earlier indicates overall potentiation of MEPs in the active conditions, relative to control, it does not allow us to tell whether the MEPs measured in response to paired-pulse *and*
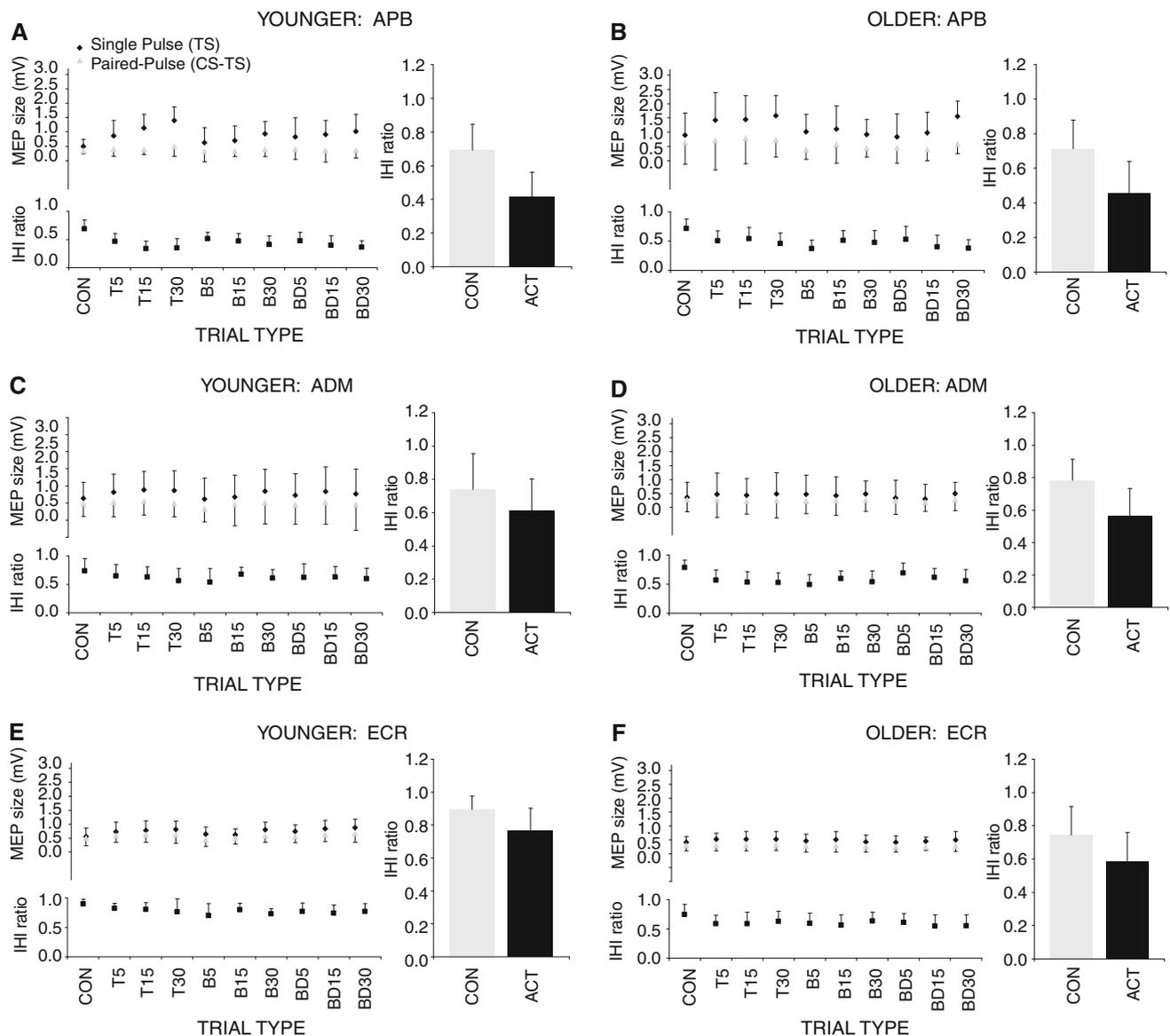
Fig. 2 Averaged MEP amplitudes and geometric means of IHI for **a** younger group APB, **b** older group APB, **c** younger group ADM, **d** older group ADM, **e** younger group ECR and **f** older group ECR. For each group/muscle, the *top left* panels show average MEP amplitudes in the single-pulse (*black diamonds*) and paired-pulse (*grey triangles*) trials, in each of the 10 conditions (*CON* Control, *T* tonic, *B* ballistic, *BD* ballistic delay; 5, 15 and 30 indicate R APB contractions of 5, 15 or 30% of right APB MVC). The *bottom left* panels display IHI ratios (geometric mean) for each of the 10 conditions. The *right-hand panels* show IHI for the control condition (CON, *grey bars*) and averaged across all 9 active conditions (ACT, *black bars*). All error bars represent 95% confidence intervals in all plots

single-pulse stimulations were *both* potentiated in active contraction trials relative to their respective control, rather it indicates that averaged over both stimulation types (and all contraction types and contraction levels), MEPs were potentiated. We therefore conducted two additional ANOVAs (again, using normalised MEPs as the dependent variable) for single-pulse trials and paired-pulse trials *separately*. For single-pulse stimulations, MEPs in the active conditions were significantly potentiated with respect to control trials ($F_{(1,17)} = 13.59$, $P = 0.002$,

$\eta_p^2 = 0.46$), with the stronger contractions causing greater potentiation (contraction strength main effect $F_{(2,32)} = 8.28$, $P = 0.008$, $\eta_p^2 = 0.26$). This finding is consistent with previous research indicating increased excitability of the limb contralateral to a tonic (Hess et al. 1986; Muellbacher et al. 2000) or ballistic isometric contraction similar to that used in the present task (Hinder et al. 2010). In contrast, the MEPs measured in response to the paired-pulse (IHI) stimulations were not reliably different from control ($F_{(1,17)} = 2.70$ $P = 0.12$, $\eta_p^2 = 0.15$).

Table 2 Comparisons (mean ± SD) of MEP sizes for the two participant groups in each muscle of the left hand for each experimental condition

Muscle	Condition	Unconditioned MEP size		Conditioned MEP size	
		Younger	Older	Younger	Older
APB	CON	0.58 ± 0.38	1.31 ± 1.18	0.39 ± 0.17	1.10 ± 1.17
	T5	1.08 ± 0.82	1.79 ± 1.48	0.51 ± 0.38	1.23 ± 1.59
	T15	1.32 ± 0.73	1.75 ± 1.28	0.46 ± 0.27	1.22 ± 1.37
	T30	1.53 ± 0.71	1.85 ± 1.09	0.68 ± 0.53	1.09 ± 0.9
	B5	0.90 ± 0.79	1.35 ± 0.94	0.52 ± 0.56	0.63 ± 0.5
	B15	0.92 ± 0.77	1.72 ± 1.24	0.42 ± 0.29	1.03 ± 1.00
	B30	1.08 ± 0.66	1.36 ± 0.8	0.50 ± 0.39	0.73 ± 0.48
	BD5	1.18 ± 1.01	1.40 ± 1.22	0.68 ± 0.54	0.89 ± 0.81
	BD15	1.13 ± 0.74	1.43 ± 1.10	0.57 ± 0.63	0.76 ± 0.59
	BD30	1.29 ± 0.9	1.76 ± 0.82	0.52 ± 0.43	0.81 ± 0.51
ADM	CON	0.83 ± 0.71	0.67 ± 0.83	0.66 ± 0.55	0.51 ± 0.67
	T5	1.09 ± 0.81	0.90 ± 1.17	0.76 ± 0.65	0.64 ± 0.96
	T15	1.19 ± 0.83	0.76 ± 0.93	0.77 ± 0.62	0.50 ± 0.71
	T30	1.20 ± 0.89	0.91 ± 1.16	0.75 ± 0.59	0.61 ± 0.96
	B5	0.96 ± 0.94	0.94 ± 1.06	0.60 ± 0.59	0.57 ± 0.71
	B15	0.98 ± 0.98	0.85 ± 1.02	0.76 ± 0.96	0.61 ± 0.84
	B30	1.14 ± 0.99	0.77 ± 0.71	0.80 ± 0.96	0.56 ± 0.62
	BD5	1.06 ± 0.97	0.78 ± 0.97	0.77 ± 0.88	0.58 ± 0.75
	BD15	1.17 ± 1.11	0.61 ± 0.79	0.85 ± 0.99	0.40 ± 0.51
	BD30	1.12 ± 1.11	0.71 ± 0.62	0.86 ± 1.16	0.50 ± 0.6
ECR	CON	0.65 ± 0.48	0.48 ± 0.32	0.58 ± 0.41	0.40 ± 0.31
	T5	0.83 ± 0.52	0.60 ± 0.35	0.67 ± 0.38	0.37 ± 0.3
	T15	0.89 ± 0.52	0.62 ± 0.45	0.72 ± 0.43	0.39 ± 0.3
	T30	0.92 ± 0.45	0.63 ± 0.44	0.76 ± 0.47	0.41 ± 0.32
	B5	0.73 ± 0.41	0.56 ± 0.38	0.55 ± 0.38	0.37 ± 0.33
	B15	0.70 ± 0.33	0.62 ± 0.45	0.58 ± 0.31	0.41 ± 0.36
	B30	0.89 ± 0.42	0.54 ± 0.39	0.67 ± 0.36	0.39 ± 0.33
	BD5	0.81 ± 0.36	0.51 ± 0.35	0.65 ± 0.35	0.35 ± 0.30
	BD15	0.93 ± 0.44	0.50 ± 0.23	0.71 ± 0.38	0.31 ± 0.19
	BD30	0.98 ± 0.48	0.61 ± 0.49	0.80 ± 0.49	0.37 ± 0.30

CON control; *T* tonic contraction, *B* ballistic contraction, *BD* ballistic delay; 5, 15 and 30 refer to the contraction strength as % MVC

IHI ratios for each condition (control and active) are shown in the lower left panels of Fig. 2a–f. IHI for each muscle, condition and group (younger and older) was significantly less than 1 (single sample *t*-tests *P*s < 0.005), indicating that the paired-pulse paradigm successfully resulted in inhibitory interhemispheric interactions in *all* muscles and *all* task conditions. To investigate whether active contraction of the right APB resulted in a change in the *extent* of the IHI measured in the muscles of left limb, we calculated the ratio of IHI in each active condition to IHI in the control condition (IHIa/c, see Data reduction and analysis). ANOVA revealed that averaged across all conditions, all three muscles and both participant groups, active contraction increased IHI compared to the control condition (i.e. average IHIa/c ratio < 1: $F_{(1,16)} = 32.23$, $P < 0.001$, $\eta_p^2 = 0.69$). This finding is depicted in the right-hand panels of Fig. 2a–f, where IHI in the control condition (CON) is

compared to average IHI across the 9 active conditions (ACT). There was also a significant main effect of muscle ($F_{(2, 32)} = 5.55$, $P < 0.01$, $\eta_p^2 = 0.26$) with subsequent pairwise comparisons revealing that IHIa/c was lower (indicating a greater increase in inhibition in the active conditions compared to rest) for the APB than both the ADM and ECR (Ps < 0.05). The contraction type ($F_{(2, 32)} = 0.02$, $P = 0.98$, $\eta_p^2 = 0.01$) and contraction strength ($F_{(2, 32)} = 1.47$, $P = 0.25$, $\eta_p^2 = 0.08$) main effects were not significant. None of the two- and three-way interactions were statistically significant, although the muscle by strength ($F_{(4, 64)} = 2.09$, $P = 0.11$, $\eta_p^2 = 0.12$) and condition x strength ($F_{(4, 64)} = 2.27$, $P = 0.09$, $\eta_p^2 = 0.12$) interactions were marginal. The between-subjects effect of age was not significant ($F_{(1,16)} = 0.20$ $P = 0.66$, $\eta_p^2 = 0.01$).

As stated earlier, the omnibus ANOVA revealed a significant main effect of muscle, with the largest change in

IHI as a result of the voluntary contractions exhibited for the APB (Fig. 2). However, such a result does not unambiguously indicate whether IHI was significantly altered (relative to control) in all three muscles of the left limb as a result of the voluntary contractions of the right thumb. To address this issue, ANOVAs (with contraction type and contraction strength as within-subject factors and age as a between-subject factor) were conducted for each muscle *separately*. For all three muscles IHIa/c was significantly less than 1 (APB: IHIa/c $= 0.62$, $F_{(1,16)} = 35.42$, $P < 0.001$, $\eta_p^2 = 0.69$; ADM: IHIa/c $= 0.77$, $F_{(1,16)} = 11.43$, $P = 0.004$, $\eta_p^2 = 0.42$; ECR: IHIa/c $= 0.82$, $F_{(1,16)} = 8.92$, $P = 0.009$, $\eta_p^2 = 0.36$), signifying a generalised increase in IHI in the muscles of the left limb as a result of focal contractions of the right thumb. However, as can be seen from the average IHIa/c for each muscle (geometric mean of IHIa/c $= 0.62$, 0.77 and 0.82 for the APB, ADM and ECR, respectively) as well as the magnitude of the effect sizes ($\eta_p^2 = 0.69$, 0.42 and 0.36 for the APB, ADM and ECR, respectively), the modulation (increase) in IHI was most pronounced for the APB (smallest IHIa/c and largest effect size), followed by ADM, with ECR exhibiting the smallest increase in IHI (as indicated by a larger IHIa/c and smaller effect size compared to the other muscles). Furthermore, for the APB, the main effect of contraction strength was significant ($F_{(2,32)} = 3.39$, $P < 0.05$, $\eta_p^2 = 0.18$); the more forceful contractions of the APB resulted in more pronounced increases in IHI than the weaker contractions (Fig. 2a, b). Conversely, for the ADM and ECR, contraction strength did not affect the extent of the IHI modulation (ADM: $F_{(2,32)} = 0.83$, $P = 0.45$, $\eta_p^2 = 0.167$; ECR: $F_{(2,32)} = 0.08$, $P = 0.92$, $\eta_p^2 = 0.01$). The main effects of contraction type and age, and all two- and three-way interactions were not significant for any muscle ($Ps > 0.20$). In summary, the findings from the ANOVAs conducted on each muscle separately suggest that greater IHI modulation in the homologous APB muscle occurs compared to the modulation observed in the non-homologous muscles. Furthermore, IHI modulation in the left APB was sensitive to the strength of contraction of the right APB whereas modulation of IHI in the non-homologous left limb muscles (ADM, ECR) was unaffected by the strength of the right APB contraction.

Discussion

This study was designed to investigate how isometric contractions of the dominant thumb affect interhemispheric inhibition from the dominant (active) to non-dominant (quiescent) motor cortex, in both younger and older adults. While a number of recent studies have investigated the effect of tonic contractions on IHI from the active to resting hemisphere, to our knowledge the effects of targeted ballistic contractions, which more closely resemble the finely controlled, goal-directed movements we use in daily living, have not been examined. To this end, participants made targeted isometric and ballistic contractions of the right APB to various predetermined force targets. Single and paired-pulse TMS was administered during these contractions to assess IHI in the muscles of the contralateral limb. We measured IHI (at an ISI of 10 ms) in the homologous muscle (APB), a non-homologous intrinsic hand muscle (ADM) and a forearm extensor (ECR) to determine the specificity or generalisation of any modulation of inhibition. In this experiment, we followed the protocol adopted by Talelli et al. (2008) and did not to adjust either CS or TS intensities in our active conditions. Arguments exist for normalising MEP amplitudes in response to the CS (i.e. in the 'conditioned limb') and TS (i.e. in the test limb) across all conditions of an experiment by adjusting stimulation intensities (see Chen 2004; also see Lee et al. 2007). However, it has also been argued that not adjusting (the intensity of the conditioning pulse) may permit a "true indication" of how changes in the cortex contralateral to a voluntary action may influence interhemispheric effects originating in the contralateral cortex (Perez and Cohen 2008).

We observed increased IHI in the left APB as a result of tonic contractions of the right APB, consistent with the findings of Ferbert et al. (1992), Vercauteren et al. (2008) and Talelli et al. (2008). For the first time, we have also shown that self-paced, ballistic contractions of the right APB (with the aim of producing a predetermined force level) also increase IHI measured in the left APB. Interestingly, the volitional actions used in the present experiment, unlike the tasks employed by Duque et al. (2005, 2007) in which participants reacted as quickly as possible to external signals, were *self-paced*. Accordingly, the finding of task-related modulation at the very onset of ballistic actions in the present study indicates that IHI modulation is not dependent upon external triggers but occurs as a result of internally generated commands related to movement preparation/initiation.

The increases in IHI measured in the left APB were observed at all contraction strengths (i.e. 5, 15 or 30% MVC contraction of the right APB) in tonic and ballistic contractions. Moreover, we found that IHI modulation for the left APB muscle was most pronounced at the higher levels of force production in the right APB, in both ballistic and tonic contractions. IHI modulation was also observed in the left ADM and ECR, although the increase was less than that observed in the APB, and did not vary as a function of right APB force. While it could be argued that covert activation of the right ADM (and ECR) (during intended focal activation of the right APB) may have

resulted in the IHI modulation in the left ADM (and ECR) we believe this alternative view is unlikely. Hardware limitations did not permit us to record EMG from right ADM (and ECR) during the main experiment, but a subsequent recording did not reveal any evidence for concomitant activity in the right ADM or right ECR across the range of tonic or ballistic APB contractions (5–30% MVC) investigated in the main experiment. Accordingly, our findings support the proposition that during volitional contractions the motor system inhibits most strongly, and most adaptively, the mirror movement with a less pronounced, generalised inhibition of neighbouring muscles.

Interestingly, for all muscles in the left limb in which we measured IHI, the extent of the IHI modulation at a particular contraction strength was not affected by whether IHI was examined as early as possible during the ballistic task (ballistic condition), at the approximate time of peak motor outflow from the motor cortex (i.e. just prior to the centre of the EMG burst) during the ballistic task (ballistic-delay condition), or during an ongoing, tonic, contraction of the same force magnitude (tonic condition). This particular finding is consistent with that notion that IHI is modulated in preparation for a ballistic movement (Duque et al. 2005, 2007). It also expands our understanding of IHI modulation by demonstrating that further modulation (increase) of IHI does not occur during the later (force-production) stages of a ballistic or tonic contraction. For the APB muscle, the fact that IHI modulation was dependent on the level of contraction in the right APB indicates that the inhibitory networks had access to a feedforward prediction of the level of force production in the contralateral APB muscle and tailored the degree on IHI modulation accordingly.

Analyses conducted on MEP amplitudes indicate that when the right thumb was contracted (active trials), potentiation of ipsilateral MEPs in response to the single-pulse trials occurred, but no change in the size of MEPs in response to paired stimulations was observed. The increase in ipsilateral excitability in the single-pulse trials in the present study (in tonic, ballistic and ballistic-delay conditions; Fig. 2) is consistent with the result found in our previous study, in which we considered the effect of similar ballistic thumb contractions on the excitability of the ipsilateral cortex (Hinder et al. 2010). It is also consistent with the results of Muellbacher et al. (2000) and Hess et al. (1986) who found increased excitability in the ipsilateral cortex in response to tonic contraction. Other studies have reported no change in ipsilateral excitability (Duque et al. 2007; Murase et al. 2004) or even a decrease (Sohn et al. 2003), but these differences can probably be reconciled by differences in the dynamics of the task and timing of the cortical stimulations with respect to the contraction: the former two of these aforementioned studies considered IHI

prior to movement onset (i.e. in a reaction-time period following an external stimulus) while the latter stimulated 13–2,000 ms following generation of the target force.

As alluded to in the introduction, Talelli et al. (2008) reported that IHI measured in the left index finger (using 10 and 40 ms ISI, IHI10 and IHI40, respectively) tended to increase during low force contractions of the right index finger, compared to when both fingers were at rest. However, the overall effect (increase relative to rest) was *not* significant and showed high variability (i.e. some participants showed increased IHI while others showed decreased IHI). Interestingly, there was no age effect for IHI10, but for IHI40 regression analysis suggested that younger adults increased IHI, while older adults tended to decrease IHI. The present data suggest that IHI10 can be modulated (increased) by younger *and* older adults at a variety (5, 15 and 30% of MVC) of tonic force levels. This finding is not incompatible with the results of Talelli et al. (2008) for IHI10: the fact that they did not measure statistically significant increases in IHI during contraction may simply have been due to substantial inter-subject variability. Moreover, the present study expands on the work of Talelli et al. (2008) and indicates that older adults are also on a par with their younger counterparts with respect to the ability to modulate IHI10 in the period immediately following the onset of a ballistic contraction, as well as during ongoing contractions. Furthermore, the older adults in our study exhibited a pattern similar to the younger adults across the different muscles investigated, i.e. force-dependent modulation of IHI in the homologous (APB) muscle, with a less pronounced, force-independent modulation of IHI in the non-homologous muscles. Accordingly, we have shown that the mechanisms mediating IHI10, and the ability to modulate IHI10 over a range of contraction types and strengths, appear unaffected by advancing age. The present findings suggest that increased motor overflow in dynamic tasks that often occurs with increasing age (see Hoy et al. 2004 for a review) is not a result of deterioration in the ability to modulate IHI at 10-ms ISI in the first few milliseconds following the onset of ballistic muscle activation.

While IHI10 and IHI40 are both believed to be mediated via excitatory callosal neurons (Lee et al. 2007), the connections with the inhibitory interneurons in the contralateral cortex may differ (Chen 2004), and it has been hypothesised that IHI at 40 ms may be related to ipsilateral silent period (Chen et al. 2003). Further work investigating whether older participants are able to modulate IHI40 (or ipsilateral silent period) across a range of contraction types and strengths will determine whether the age effects noted by Talelli et al. (2008) are apparent across different task conditions. Moreover, determining how any deficiencies in specific inhibitory mechanisms may affect movement

control, or can be adequately compensated for, is an important question in ageing research.

In conclusion, we found that both tonic and ballistic activations of the right thumb result in a modulation (increase) in IHI from the active to passive cortex. The modulation was observed at the very onset of the ballistic contraction and was most pronounced in the homologous hand muscle, but also apparent in other left limb muscles. It appears therefore that the mechanisms mediating the alteration in IHI affect an extended region of the cortex, rather than being restricted to the networks controlling the activated muscle and its homologue. Age did not affect the ability to modulate short-interval interhemispheric inhibition in the period immediately following onset of ballistic actions as well as during tonic contractions. As such, the breakdown of inhibition that is sometimes associated with normal ageing (leading to less-lateralised cortical activations—see Ward 2006) is not due to a breakdown of the inhibitory mechanisms mediating changes in short-interval IHI in response to either ballistic, or tonic, volitional contractions.

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