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RESEARCH ARTICLE

The effect of ballistic thumb contractions on the excitability of the ipsilateral motor cortex

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Abstract We investigated how ballistic contractions of the left thumb affect the excitability of the ipsilateral motor cortex using transcranial magnetic stimulation (TMS). TMS was applied at the motor hotspot for the right abductor pollicis brevis (APB) muscle. In 'self-triggered' trials, participants made targeted, isometric, contractions of the left APB. The right APB was either relaxed or maintained a tonic contraction. TMS was administered as soon as possible after electromyographic onset in the left APB. In 'control' trials, the left thumb remained quiescent and TMS was triggered by the computer. In each condition, 20–24 trials were conducted. Half these trials involved a single test stimulus, TS (130% APB resting motor threshold, RMT). In the other trials, short-interval intracortical inhibition (SICI) was investigated by applying a conditioning stimulus (70% APB RMT) 3 ms prior to the TS. SICI ratios were not significantly different in self-triggered and control trials. However, when the right APB was active, significantly shorter silent periods (SPs) were observed in self-triggered trials when compared with control trials. Our results support the view that SICI and SP are mediated by different inhibitory circuits, and that ipsilateral $GABA_B$-ergic circuits (assessed by SP), but not $GABA_A$-ergic circuits (assessed by SICI), are affected in the period immediately following voluntary ballistic contractions.

Keywords SICI · Inhibition · Movement · Silent period

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Introduction

It is well known that cortical regions in the two hemispheres frequently interact and that the principal pathway for the transfer of perceptual, sensory and motor information is the corpus callosum. Interaction between the two motor areas underlies our ability to accomplish tasks such opening a jar, typing, or playing a piano, in which both hands simultaneously undertake different actions, or tasks in which one hand remains quiescent while the other moves. The nature of the signals transmitted by the corpus callosum, and the effect on the contralateral hemisphere are, however, not fully understood.

Using transcranial magnetic stimulation (TMS), it is possible to non-invasively assess the net level of excitability and to more specifically assess the inhibitory circuits (via short-interval intracortical inhibition (SICI), Kujirai et al. 1993, and silent period (SP) durations) within a cortex. How volitional unilateral actions of one limb affect these measures of excitability and inhibition within the cortex ipsilateral to the action can help us to understand how the two cortices interact to enable fine motor control.

Isometric contractions of the hand and arm have been shown to facilitate motor-evoked potentials (MEPs) recorded in the quiescent homologous muscle of the opposite limb (e.g., Hess et al. 1986; Muellbacher et al. 2000). Although a considerable proportion of the observed increase in MEP size would be expected to be mediated at the level of the spinal cord, Muellbacher et al. (2000) found that during maximal isometric abductions of the right thumb, SICI in the right cortex was reduced. This finding implies that changes at the cortical level could, at least to some degree, contribute to the observed changes in MEP size.

In contrast to the above studies, low-force contractions have been shown to inhibit the ipsilateral cortex. For example, Liepert et al. (2001) reported that low-force phasic pinches of ~200-ms duration and 1–2% MVC of the first dorsal interosseus (FDI) muscle reduced the amplitude of MEPs recorded in the homologous (FDI) muscle in the resting hand up to 100 ms after the target force was attained. This is consistent with the notion that the net excitability of the resting hand was reduced by interhemispheric (trans-callosal) mechanisms. Phasic pinches of 5% MVC or greater did not significantly alter MEP size relative to control (rest). Liepert et al. also showed that tonic pinches of 40% MVC resulted in larger MEPs (i.e., potentiation) in the resting FDI muscle when compared with control (both hands at rest), a result consistent with Hess et al. (1986) and Muellbacher et al. (2000). Sohn et al. (2003) investigated the effects of low-force ballistic movements on the excitability of the ipsilateral motor cortex. TMS was applied to the right cortex 13–2,000 ms following the onset of muscle activity in specific muscles of the right hand. Single TMS pulses revealed a general (i.e., apparent in both homologous and non-homologous muscles of the left upper limb) reduction in the net excitability of the ipsilateral cortex when TMS was administered 35–70 ms following contraction of muscles of the right index finger. In paired-pulse trials, an increase in intracortical facilitation (ICF) was reported, but only in the homologous muscle. Although no change in SICI was observed, ballistic movements caused a reduction in the duration of the silent period when the homologous muscle (in the left hand) maintained a tonic (isometric) contraction.

The present study aimed to expand on previous research (Muellbacher et al. 2000; Liepert et al. 2001; Sohn et al. 2003) indicating that the effects of voluntary actions on excitability of the ipsilateral motor cortex are influenced not only by contraction strength, but also by the dynamics of task (i.e., tonic or phasic/ballistic contractions) and the delay between the onset of muscular activity in the moving hand and the TMS pulse to the ipsilateral cortex. Specifically, Sohn et al. found that the net excitability of the ipsilateral cortex (as indicated by MEPs from single pulse TMS pulses) was not significantly affected by ballistic contractions until 35 ms after electromyographic (EMG) onset in the active muscle. The possibility exists, however, that changes closer to the onset of the EMG (i.e., <35 ms) may have occurred in the inhibitory circuits that were masked by reciprocal changes in excitatory circuits such that net excitability appeared unaffected. Accordingly, our principal aim was to apply TMS as soon as possible following the onset of EMG in a volitional ballistic contraction and measure the influence of this contraction on both net excitability and inhibitory circuits within the ipsilateral cortex. By studying a range of ballistic force levels, we aimed to elucidate whether the force-dependent changes in the ipsilateral cortex found for phasic activations when TMS was delivered after the acquisition of the target force (Liepert et al. 2001) are also apparent at the onset of the targeted force pulse. We investigated if changes in the ipsilateral cortex were observed when the homologous muscle was quiescent or maintained different levels of activation. Furthermore, we investigated if any effects were muscle-specific by also recording responses in non-homologous muscles. By comparing and contrasting our results with extant studies, we hoped to broaden the understanding of the effects of timing and force on the ipsilateral effects of unimanual volitional actions.

Methods

Participants

Nine self-reported right-handed participants (6 males), with an average age of 26.7 years (range 23–35) took part in this study, which had received ethical approval from the University of Tasmania's Human Research Ethics committee. Participants gave informed consent prior to beginning the experiment, and did not have any contraindications to TMS, had normal or corrected to normal vision, and were free from neurological and neuromuscular disorders.

Experimental set-up

In a seated position, 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 vertically 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 (see below).

Maximum voluntary contraction

To determine APB maximum voluntary contraction (MVC) participants were asked to press down as hard as possible on the force transducer for approximately 2 s within a 5-s trial. They received force feedback on the computer screen and were encouraged to move the force trace as high as possible on the screen (maximise force), while attempting to isolate the thumb muscle. Three trials were conducted for the left and right thumbs, with 30-s rest between each trial. The averaged peak value for each thumb was calculated and used to establish the target force levels for the movement task (see below).

Movement task

Each 5-s trial began with both thumbs relaxed, with forearms and thumbs in the posture described above. Visual feedback of both the left and right vertical forces was provided in real time in the form of traces that ran across the screen. Pushing down on the platforms resulted in the force feedback lines moving up the screen. Horizontal cursors provided a target force 'zone' for the ballistic force pulse of the left thumb and the tonic force level for the right thumb: these cursors were located at ±5% of the target proportion of each participant's MVC. There were 15 experimental conditions that consisted of different combinations of left and right force levels (see "Self-triggered trials" and "Control trials"). Between 20 and 24 trials (each 5 s long) were conducted in each of these conditions. Trials of each force-level combination were presented in blocks, the order of which was randomised for each participant. In each trial, TMS was administered to the left cortex (see "Transcranial magnetic stimulation"). The types of trial are described below, and also shown in Table 1.

Self-triggered trials

In the self-triggered trials, participants made targeted ballistic contractions of the left APB while the right APB was either passive or maintained a tonic contraction. In active right APB conditions, the word 'push' (generated within the data collection software) was heard 1.5 s into the trial. Participants pushed on the right force platform and held the cursor within the horizontal target region for the remainder of the 5-s trial. In the passive right APB conditions, the word 'push' was replaced with 'relax'. In both passive and active right APB conditions, 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., within the next 1.5 s) produce a ballistic force pulse with their left APB. The goal was to produce a pulse 150–200-ms-wide, with the peak force between the horizontal cursors on the visual display. TMS was administered as soon as possible after the onset of the left APB pulse (see "Transcranial magnetic stimulation"). Concurrently with the left thumb ballistic force pulse, the right thumb maintained the required constant tonic contraction or, in the passive right thumb conditions, remained quiescent. Participants were instructed that following the ballistic pulse (and associated TMS pulse) they should maintain the desired level of tonic contraction with the right thumb until the end of the trial, at which point they should relax. The next trial began immediately thereafter. There were four levels of ballistic activation for the left thumb (5, 15, 30 and 45% of the left APB MVC) and three right thumb conditions (passive, 15, 30% right APB tonic activation), i.e., 12 different self-triggered conditions.

Table 1 Experimental conditions. For each left/right APB condition, the corresponding cell indicates which dependent variables were assessed: SICI = short-latency intracortical inhibition; TS = test pulse MEP size; SP = silent period duration. In the control conditions, TMS was triggered externally while the left APB remained quiescent, while for all other left APB conditions TMS to the left cortex was triggered as early as possible after the onset of the ballistic EMG burst

Left APB condition	Right APB condition		
	Passive	15% MVC tonic	30% MVC tonic
Control	SICI, TS	SICI, TS, SP	SICI, TS, SP
5% MVC ballistic	SICI, TS	SICI, TS, SP	SICI, TS, SP
15% MVC ballistic	SICI, TS	SICI, TS, SP	SICI, TS, SP
30% MVC ballistic	SICI, TS	SICI, TS, SP	SICI, TS, SP
45% MVC ballistic	SICI, TS	SICI, TS, SP	SICI, TS, SP

Control trials

To investigate how the ballistic contractions of the left APB (in the self-triggered trials) may affect excitability of the left (ipsilateral) cortex, we conducted control trials in which the left thumb (APB) remained quiescent. Control conditions were conducted for all right APB conditions, i.e., there were three blocks of control trials in which the right thumb was passive or maintained a tonic activation of 15, or 30% APB MVC, while the left thumb was always relaxed. Data from the self-triggered trials for each right APB condition could then be compared with the corresponding control trial. As in self-triggered trials, the word 'push' or 'relax' was heard at 1.5 s in the active or passive right thumb conditions, respectively. However, the word 'ready' was not heard at 3.5 s, as had been the case in self-triggered trials, as in these trials the left APB remained relaxed. Instead, TMS was generated by the computer after 3.5 s. As with self-triggered trials, participants were reminded that following TMS they should maintain the required force in the right APB until the end of the trial.

Prior to the experiment, participants practiced producing ballistic force pulses with the left APB of the desired duration, at each of the desired force magnitudes, while the right APB was quiescent or tonically active. This training lasted approximately for 10 min and trials were not recorded or analysed. The procedure, including set-up, lasted for approximately 75 min.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was delivered to the left cortex using a Magstim BiStim unit (Magstim Company, Dyfed, UK) and a standard figure of eight coil (7-cm

diameter of each wing). We used a neuronavigation system (Advanced Neuro Technologies) to provide online feedback of coil position and orientation relative to the desired stimulation location. This allowed precise reproducibility of coil location both between and within blocks of trials. All TMS pulses were delivered to the left cortex at the motor hotspot for the right APB. Motor threshold, from which the TS and CS intensities were derived, was determined as the minimum intensity required to elicit MEPs >50 μV in the right APB in three out of five consecutive trials (Garry et al. 2005; Garry and Thomson 2009). Of the 20–24 trials in each condition, half involved a single 'test' TMS pulse (TS) at 130% RMT and were designed to provide an indication of the net excitability of the corticospinal pathway. Short-interval intracortical inhibition was assessed in the other trials using a paired-pulse paradigm (Kujirai et al. 1993): a conditioning stimulus (70% RMT) was applied 3 ms prior to the 130% RMT test pulse through the same coil (Garry and Thomson 2009). Within a block, each pair of trials consisted of one TS and one SICI trial, in a random order.

In self-triggered trials, TMS was administered based on the detection of electromyographic (EMG) activity in the left APB. We used custom-written software (Signal 3.08) that allowed us to reliably detect EMG onset within ~2.5 ms of the perceptible occurrence of left APB EMG above background (noise) levels (see "Results"). In SICI (paired pulse) trials, the CS was administered at the detected EMG onset. The TS was then 3 ms later. In TS (single pulse trials), TS was administered 3 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 'control' trials, the left thumb remained quiescent and the TMS was triggered via the computer at ~3.5 s, that is, during the period when the participant was maintaining tonic force in the right thumb (in the active right thumb conditions) or when both thumbs were relaxed.

In all active right APB trials, participants were asked to maintain the tonic force within the target cursors until the end of the trial, that is, 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 stimulation. In these trials, the silent period in the right APB that followed the TMS-induced MEP was calculated in both SICI and TS conditions (see below).

Data recording and analysis

MEP responses were recorded in the right APB, abductor digiti minimi (ADM) and first dorsal interosseus (FDI) muscles at 10,000 Hz. Muscle activity in the left APB (triggering muscle) was also recorded, as was the force produced by the left and right hands. 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 left and right thumbs, the force pulse on the left hand was of the correct duration (~150–200 ms) and that the tonic force in the right hand had been maintained throughout the trial (i.e., participants had not relaxed at or close to the TMS). Furthermore, trials with EMG in the muscles which were supposedly at rest were discarded. MEP amplitudes in the right hand muscles were calculated for the remaining trials. An average MEP value was then determined for the single pulse and paired-pulse trial types within each contraction condition. Average MEP amplitude in the single pulse trials was used as an indication of net excitability. The ratio of MEP amplitude in the paired-pulse trials to MEP amplitude in the single pulse trials was calculated to give an SICI ratio for each experimental condition (SICI ratio <1 indicates inhibition, with smaller fractions indicating greater inhibition). In active right APB conditions, the silent period was determined from the TMS pulse to the time at which EMG returned to within 1 standard deviation of the pre-stimulus rms EMG.

Separate repeated measures (RM) ANOVAs were performed on the three dependent variables (MEP amplitude, SICI ratio and SP duration). For MEP amplitude and SICI ratio, we conducted a two-way [three right APB conditions (passive, 15 and 30% MVC tonic contractions) × five left APB conditions (control, 5, 15, 30 45% MVC ballistic contractions)] RM ANOVA while a three-way [two stimulation type (TS/SICI) × 2 right APB conditions (15 and 30% MVC tonic contractions) × 5 left APB conditions (control 5, 15, 30 45% MVC)] RM ANOVA was conducted for the SP duration data. Huynh–Feldt corrections were applied when the assumption of sphericity was violated ($\varepsilon < 0.7$). An a priori alpha level of 0.05 was used when determining statistical significance.

Results

All participants were able to accomplish the task by producing forces (both ballistic pulses and tonic activations) at all the required force levels. However for several participants, we found activation of the right FDI in the period when a tonic right APB contraction was being maintained. When these trials with erroneous FDI activity were removed, we were left with an incomplete data set for FDI (i.e., for some participants in some conditions there were no trials in which FDI was fully relaxed). Accordingly, we present the results for only the APB and ADM muscles. Figure 1 shows a schematic illustrating a typical self-triggered paired-pulse (SICI) trial. In this particular trial, a tonic force of 30% APB MVC was maintained by the right

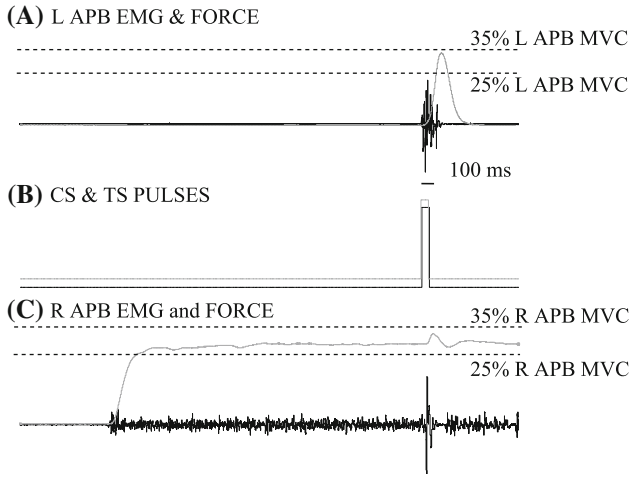

Fig. 1 Example of a self-triggered paired-pulse TMS trial in which the right thumb is active. *A* Ballistic left (*L*) APB (*black trace*) activation results in the force pulse shown in *grey*. *B* the CS and TS pulses triggered as a result of the burst of left APB activity. *C* While the left APB produced the ballistic pulse, the right (*R*) APB (*black*) maintained tonic activation resulting in the tonic force shown in *grey*. Note the MEP and subsequent silent period in the right APB EMG, together with the ensuing transient perturbation in the right APB force trace. Following the TMS, the desired tonic force is maintained. The *small bar* in the top trace indicates the horizontal time scale

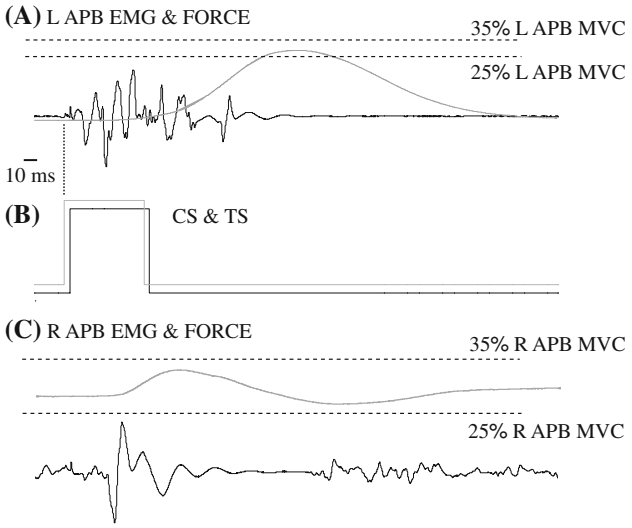

Fig. 2 Example of a self-triggered paired-pulse TMS trial in which the right thumb is active-expanded view. With a ×10 zoom in the time axis (note time bar indicates 10 ms), the very short latency between perceptible EMG onset (trace *A*) and TMS pulses (trace *B*) can be appreciated. The CS occurs within ~2.5 ms of the first perceptible (negative) deviation in the EMG trace. A clear MEP and subsequent silent period are seen in the right APB EMG activity (trace *C*). The TMS-induced perturbation in the right APB force (grey line, trace *C*) has been shown on an expanded vertical scale relative to Fig. 2. The participant re-established the desired tonic level after ~200 ms

thumb, while the left thumb produced a 200 ms (ballistic) 30% MVC force pulse. Figure 2 shows an expanded view of the same trial to show the timing of the TMS pulses with respect to the ballistic burst of left APB activity.

We wished to verify how quickly our online algorithm was able detect EMG onset during each trial. We, therefore, conducted a post-collection analysis in which we manually inspected each trial and visually determined the point at which EMG first rose above the baseline levels. We then calculated the time between this point and the TS pulse (which occurred in each trial). Overall, participants and all self-triggered conditions, the average latency between EMG onset and the TS pulse was 5.5 ± 0.7 ms. Recall, however, that we programmed a 3-ms delay between determining EMG onset and triggering the TS pulse (see "Transcranial magnetic stimulation" in "Methods"). We can, therefore, conclude that we were able detect, and trigger the first (i.e., CS) TMS stimuli, 2.5 ms after the onset (as determined in post-collection analysis) of volitional EMG activity.

Single pulse TMS trials

MEP amplitudes in single pulse TMS trials were used as a measure of net excitability of the cortex ipsilateral to the ballistic force pulses. Two-way RM ANOVA was used to determine how the task undertaken by the left thumb (control vs. ballistic contractions of various strengths) and the task undertaken by the right thumb (rest or tonic contractions) affected the MEP amplitudes of muscles of the right hand.

APB: homologous muscle

A significant right APB condition main effect ($F_{(1.1,\ 8.75)} = 32.55$, $P < 0.001$, $\eta_p^2 = 0.80$) and subsequent pairwise comparisons indicated that MEPs at 15% contraction (average MEP size across the five left APB conditions = 7.45 mV) were significantly larger than those at rest (1.91 mV), but smaller than those at 30% contraction (8.37 mV) ($Ps < 0.05$, Fig. 3a). The left APB condition main effect was also significant ($F_{(4,\ 32)} = 2.76$, $P < 0.05$, $\eta_p^2 = 0.26$). Pairwise comparisons revealed that MEP amplitudes in the self-triggered 5% MVC trials (average MEP size across the three right APB conditions = 5.71 mV) were not significantly different from MEP amplitudes when the left hand was relaxed (5.71 mV), i.e., control trials ($P = 0.99$). Self-triggered trials at 15% MVC increased MEP size 5.0% relative to control (from 5.71 to 6.00 mV), although this did not reach significance ($P = 0.14$). Self-triggered trials at 30 and 45% MVC led to significantly larger MEPs relative to control (6.08 and 6.06 mV; 6.5 and 6.1% larger than control, respectively; $Ps < 0.05$). The interaction between

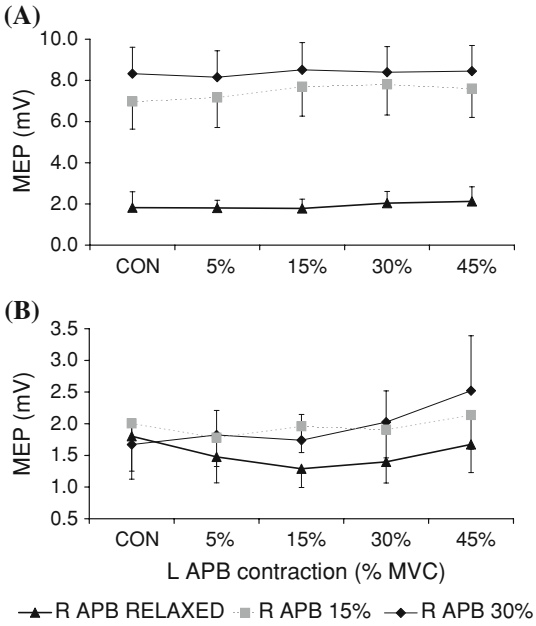

Fig. 3 MEP amplitudes in the single pulse (TS trials) for the *A* right APB and *B* right ADM muscles for each right APB condition (plotted as *separate lines*: see key) as a function of left APB condition. *Error bars* indicate SE mean

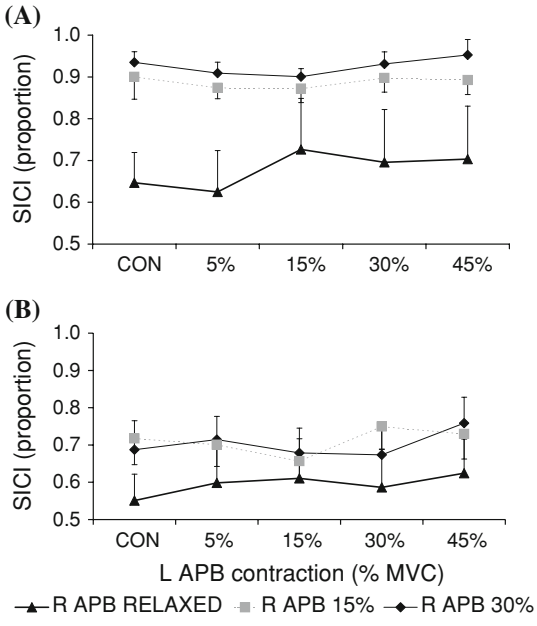

Fig. 4 SICI ratios for the *A* right APB and *B* right ADM for each right APB condition (plotted as *separate lines*: see key) as a function of left APB condition. *Errors bars* indicate SE mean

left APB and right APB conditions was not significant ($F_{(4.1,\ 32.8)} = 0.54$, $P = 0.71$, $\eta_p^2 = 0.06$).

ADM: non-homologous muscle

Two-way RM ANOVA revealed a marginal effect of right APB condition ($F_{(2,\ 16)} = 3.30$, $P = 0.06$, $\eta_p^2 = 0.29$). Figure 3b suggests this trend was due to somewhat larger right ADM MEPs when the right APB was contracted at 15 and 30% (average MEP = 1.96 mV in both conditions) compared with when the right APB was quiescent (average MEP size = 1.53 mV). Neither the left APB condition ($F_{(1.43,\ 11.45)} = 1.00$, $P = 0.37$, $\eta_p^2 = 0.11$) nor the interaction between left APB and right APB conditions ($F_{(1.80,\ 14.42)} = 0.95$, $P = 0.40$, $\eta_p^2 = 0.11$) significantly affected the right ADM MEP amplitudes.

In summary, we found that tonic contractions of the right APB lead to large increases in the MEP amplitudes measured in the right APB, and also led to marginal increases in right ADM MEP amplitude. Furthermore, the more forceful (i.e., 30 and 45% MVC) ballistic contractions of the left APB lead to a potentiation of MEPs measured in the right APB, but did not affect the amplitude of MEPs in the right ADM.

Short latency intracortical inhibition

Short latency intracortical inhibition (SICI) was quantified as the ratio of MEP amplitude in paired-pulse trials to the MEP amplitude in the single pulse trials. Inhibition, indicated by ratios of less than unity, was observed in both the right APB and right ADM muscles (Fig. 4). Furthermore, it is apparent from Fig. 4a that SICI was present, although to a lesser degree, in the tonically active right APB. Paired *t* tests revealed that for 14 out of the total of 15 (3 left APB conditions × 5 right APB) conditions SICI was significantly less than unity (Ps < 0.05). For the one condition in which the SICI was not significant (when the left hand made a ballistic contraction of 45% and the right APB maintained a tonic 30% contraction) the P value (0.12) suggested a tendency for inhibition (i.e., $0.05 < P < 0.20$). For the ADM muscle, SICI was significantly less than unity for all conditions (Ps < 0.05 for all paired *t* tests). We used two-way RM ANOVA to determine how the task undertaken by the left thumb (control vs. ballistic contractions of various strengths) and the task undertaken by the right thumb (rest or tonic contractions) affected the SICI ratio in the muscles of the right hand.

APB muscle

The extent of SICI measured in the right APB was affected by the level of activity of that muscle. This was confirmed by a significant right APB condition main effect ($F_{(1.12,8.94)} = 5.28$, $P < 0.05$, $\eta_p^2 = 0.40$). Subsequent pairwise comparisons revealed that SICI in the right APB when the right APB was activated at 15% (average SICI ratio over all left APB conditions = 0.89) was not as large (i.e., less inhibition, SICI closer to 1) compared with SICI

when the right APB was quiescent (SICI = 0.68) although this did not quite reach significance ($P = 0.07$). However, activation at 30% MVC realised significantly less SICI (0.93) relative to the resting condition ($P < 0.05$). The main effect of left APB condition ($F_{(2.16,\ 17.28)} = 0.51$, $P = 0.63$, $\eta_p^2 = 0.06$) and the interaction ($F_{(5.16,\ 41.31)} = 0.55$, $P = 0.81$, $\eta_p^2 = 0.06$) were not significant.

ADM muscle

For the ADM, two-way ANOVA indicated that the right APB condition main effect was marginal ($F_{(1.26,\ 10.06)} = 3.24$, $P = 0.10$, $\eta_p^2 = 0.29$), with a trend to suggest a reduction in the extent of SICI observed in the right ADM muscle when the right APB was activated (Fig. 3b). Averaged over the five left APB conditions, SICI ratios were 0.59, 0.71 and 0.70 for the resting, 15% MVC and 30% MVC right APB conditions, respectively. The left APB condition main effect ($F_{(1.52,\ 12.17)} = 0.24$, $P = 0.73$, $\eta_p^2 = 0.03$) and the interaction ($F_{(4.12,\ 32.99)} = 0.71$, $P = 0.68$, $\eta_p^2 = 0.08$) were not significant.

In summary, we found that the tonic activation of the right APB led to a significant reduction in the extent of SICI in that muscle, as well as a trend to suggest a reduction in SICI in the right ADM. However, ballistic contractions of the left APB did not affect the extent of SICI measured in either the homologous (i.e., right APB) or non-homologous (right ADM) muscle.

Silent period

Silent period (SP) duration (Fig. 5) was measured in the experimental conditions in which the right APB was active (maintaining a tonic contraction) and was used as an alternative measure of inhibition. Three-way RM ANOVA revealed a significant trial type (single vs. paired pulse) main effect ($F_{(1,\ 8)} = 94.75$, $P < 0.001$, $\eta_p^2 = 0.92$), with the single pulses (average SP across the 5 left × 2 right APB conditions = 157.5 ms) evoking longer SPs than the paired-pulse (SICI) trials (139.5 ms). The right APB condition main effect was not significant ($F_{(1,\ 8)} = 1.59$, $P = 0.24$, $\eta_p^2 = 0.16$) indicating that the level of tonic contraction did not affect the duration of the SP in that muscle. There was a significant effect of left APB condition ($F_{(1.87,\ 14.96)} = 5.98$, $P < 0.05$, $\eta_p^2 = 0.43$). Subsequent pairwise comparisons revealed that, averaged across the two trial types (SICI and TS) and two right APB contraction levels (15 and 30% MVC), SP duration recorded in the control trials (157.5 ms) was significantly longer than the SP duration in the left APB 5% MVC (148.9 ms) self-triggered trials ($P < 0.05$). Although the difference in SPs between the 5 and 15% MVC (147.7 ms) self-triggered conditions was not significant ($P > 0.20$), there was a small, but significant reduction in SP duration between the 15 and 30% MVC (144.4 ms) self-triggered conditions ($P < 0.05$). No significant difference was found between the SP durations in the 30 and 45% MVC (144.0 ms) self-triggered conditions ($P > 0.20$). These results indicate that the ballistic contraction of the left APB causes a reduction in the SP duration in the right APB relative to control: ballistic activation of the left APB of any force level causes significant shortening of SP; however, more forceful ballistic contractions lead to greater reductions in SP duration relative to those reductions as a result of the lighter contractions (Fig. 5). The interaction between the left APB condition and trial type was marginal ($F_{(2.77,\ 22.15)} = 2.56$, $P = 0.09$, $\eta_p^2 = 0.24$). Inspection of Fig. 5 indicates that this marginal effect is a result of a somewhat more pronounced shortening of silent periods (between the control and self-triggered conditions) in the single pulse (TS) trials (average shortening of SP = 13.7 ms) compared with the shortening of SPs in the SICI (paired pulse) trials (8.8 ms). All other two- and three-way interactions were not significant (Ps > 0.5).

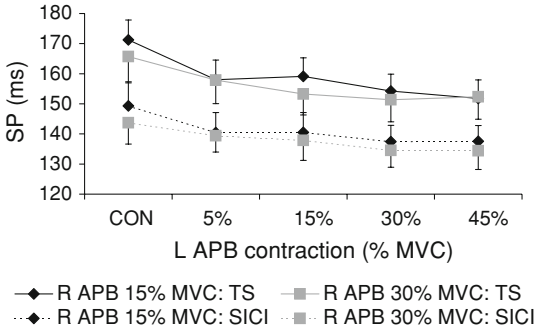

Fig. 5 Silent period duration in the right APB plotted as a function of right APB activation level and left APB contraction level for both single pulse (*TS*) and paired-pulse (*SICI*) trials. *Error bars* indicate SE mean

Discussion

This experiment investigated how ballistic contractions of various magnitudes affect excitatory and inhibitory circuits of the ipsilateral motor cortex. We were primarily interested in assessing changes that occurred in the early stages following the onset of a volitional ballistic action. To this end, we used custom-written software to reliably trigger cortical stimulation (to the left cortex) within a few milliseconds of perceptible EMG activity in the left thumb. High-force (30–45% MVC) ballistic pulses of the left APB increased MEP size in the homologous muscle in the right hand. We found that SICI and SP duration in the right hand behaved differently in response to the ballistic activations of the left APB: SICI in the passive, or tonically active,

right APB as well as in the passive right ADM was unaffected by the ballistic contraction of the left APB. In contrast, a significant reduction in SP duration was observed in the tonically active (a pre-requisite for measuring SP) right APB in conditions when the left APB made ballistic contractions compared to when the left APB was quiescent. Our results indicate that reported effects in the ipsilateral cortex as a result of ballistic activation of the hand do not only occur as a result of activation of the dominant hand (e.g. Liepert et al. 2001; Sohn et al. 2003), but rather generalise to activations of the non-dominant hand as well.

How does the excitability of the ipsilateral cortex vary as a function of time following a ballistic contraction?

Previous studies investigating the effect of voluntary contractions on the excitability of the ipsilateral cortex have reported that the largest changes in excitability occur some time after the contraction began. Specifically, Sohn et al. (2003) reported that the greatest excitability change occurred when TMS was delivered 35–70 ms after EMG onset (measured during a low-force ballistic pulse), while Liepert et al. (2001) reported that the largest changes in excitability were found when TMS was administered 100 ms after the acquisition of the desired target force. In both studies, due to differences in the length of the EMG burst, the largest ipsilateral effects were found when TMS was triggered coincident with the peak muscular activity within the EMG burst (Sohn et al. 2003). It can be assumed, therefore, that due to the conduction time from motor command to EMG onset, the greatest changes in excitability occurred $\sim$20 ms, after the peak descending motor command. Furthermore, because EMG burst durations varied across the two studies from $\sim$150 to 300 ms, the largest change in excitability occurred 95–170 ms after the initial motor command.

In contrast to the above reports, studies utilising interhemispheric inhibition (IHI) TMS protocols, in which a conditioning pulse is applied to one cortex before a test pulse to the other cortex, report inhibitory effects with interstimulus intervals of 8–50 ms (Ferbert et al. 1992; Gerloff et al. 1998; Chen et al. 2003). In Sohn et al.'s (2003) and Liepert et al.'s (2001) studies, the time delay between the motor command leaving the cortex and the subsequent change in ipsilateral excitability (measured via TMS) falls outside the time window of interstimulus intervals at which IHI is observed. To account for these timing differences, Sohn et al. (2003) suggested that ipsilateral changes in excitability due to voluntary actions and TMS-induced IHI may be mediated by different mechanisms. An alternative view was that TMS stimulates callosal fibres directly, resulting in a short interval between the conditioning stimulus and resulting inhibitory effects, while voluntary movements activate callosal fibres following the activation of the adjacent motor areas, resulting in longer delays between voluntary action and ensuing ipsilateral effects (Sohn et al. 2003).

In contrast to previous reports (Sohn et al. 2003; Liepert et al. 2001), which showed delayed excitability changes with respect to the onset of the EMG burst, we have shown changes in net excitability of the ipsilateral cortex when TMS was administered as soon as possible (within a few milliseconds) following volitional EMG onset. Furthermore, we have shown changes in the excitability of inhibitory circuits, as indicated by shortening of silent period durations in self-triggered trials can occur earlier than previously tested (Sohn et al. 2003). Our minimal ($\sim$2.5 ms) delay from EMG onset to TMS stimulation (resulting in changes in excitability) represents a delay of approximately 25 ms between the initial motor command (instructing the ballistic movement) and subsequent changes in ipsilateral excitability. Our finding is not inconsistent with Sohn et al.'s (2003) proposal that different mechanisms may mediate excitability changes as a result of IHI as compared to voluntary actions. However, we have shown that if Sohn's proposal is correct, the mechanisms responsible for ipsilateral changes in excitability as a result of voluntary movements can mediate these changes more quickly than previously shown (e.g., Sohn et al. 2003; Liepert et al. 2001). The delay between the motor command and ensuing excitability changes in our study falls within the 8–50-ms interstimulus interval that results in inhibition in IHI studies. Accordingly, excitability in our paper may have been a result of the same mechanism as that which acts in IHI protocols.

Net excitability of the homologous muscles affected by ballistic contractions

Ballistic pulses of the left APB were found to affect MEP amplitudes in the homologous muscle in the right hand (Fig. 3a). Specifically, high-force ballistic contractions (15% MVC or greater) of the APB led to an increase in MEP amplitude in the contralateral APB, consistent with the previous reports (e.g., Hess et al. 1986; Muellbacher et al. 2000; Liepert et al. 2001). We did not show a reduction in APB MEP size at our lowest force level (5% MVC). Such reductions may have been predicted based on the IHI studies using paired-pulse protocols (Kujirai et al. 1993). It is possible that the lack of net change in excitability in our lowest left APB self-triggered condition (relative to control trials) was because 5% MVC was actually too high a force. Indeed, net reduction in excitability was reported by Liepert et al. (2001) at 1–2% MVC but not at 5%. At 5% MVC, inhibition at the cortical level

due to trans-callosal effects may have been counteracted by increased excitability at the spinal level, such that the MEP size was unaltered.

The effect of ballistic contractions on the inhibitory circuits of the ipsilateral cortex

Although Sohn et al. (2003) considered changes in net excitability (measured by MEP size) at various delays (13–2,000 ms post EMG onset) they only investigated specific changes in the inhibitory circuits (assessed via SICI and silent period duration) at a fixed 50-ms delay (when the net excitability change was found to be greatest). The possibility exists that changes in inhibitory circuits may occur at shorter latencies, but reciprocal changes in excitatory circuits result in no net change in excitability. Our paradigm allowed us to assess this possibility by specifically testing both net excitability and inhibitory circuits, as soon as possible following the detection of a ballistic EMG pulse.

Consistent with the previous reports (e.g. Ridding et al. 1995; Fisher et al. 2002), we found that the tonic activation of a muscle, in this case the right APB, led to a significant reduction in the degree of SICI observed in that muscle. Nevertheless, SICI was still observed in the active muscle, with the ratio of MEP size in the paired-pulse trials relative to that in the single pulse trials always less than 1 (Fig. 4a). We found that ballistic pulses of the left APB had little effect on the degree of SICI measured in either the homologous (APB) or non-homologous (ADM) muscles of the right hand compared with SICI measured in the control trials when the left APB remained quiescent.

Silent period (SP) durations were determined in two experimental conditions in which the right APB was activated at 15 or 30% MVC, for all left APB conditions. The SP was assessed in both single- and paired-pulse (SICI) trials and was used as another measure of how the ballistic contractions of the left thumb affected the inhibitory circuits in the ipsilateral hemisphere. Our finding that SP durations were shorter in the SICI trials compared with single-pulse trials (Fig. 4) is consistent with the observation of smaller MEPs in the SICI trials (i.e., the result is consistent with smaller MEPs leading to shorter SP durations). Consistent with previous findings (e.g. Taylor et al. 1997), we observed no significant differences in silent period duration for the two right APB contraction strengths. However, we found that ballistic activation of the left APB (in self-triggered trials) resulted in a significant reduction in silent period durations (measured in the active right APB) compared with control trials. This was apparent in both SICI and TS trials (Fig. 5). Ballistic contractions of any strength resulted in a shortening of silent period durations. However, the effect was most pronounced for the stronger contractions. Specifically, ballistic contractions of 5% MVC reduced silent period duration by 5.4% (relative to control), while the reduction was 8.5% when 30% MVC ballistic contractions were performed. The magnitudes of the reductions in SP we report are comparable to those reported in a previous report (Sohn et al. 2003), where ballistic contractions resulted in a 8% shortening of SP, when TMS was applied 50 ms after the EMG onset. However, we believe that this is the first study to test, and subsequently show, systematic changes in the inhibitory circuits so close to the onset of a (ballistic) volitional action. Moreover, we have shown that this effect occurs across a wide range of contraction strengths.

How does target force affect the modulation of net excitability and inhibition?

When the left thumb made ballistic pulses to our higher force levels (30 and 45% MVC), we found an increase in net excitability of the ipsilateral cortex; we did not see a reduction in net excitability at the low-force (1–2%) levels as reported by Liepert et al. (2001). As alluded to above (see "Net excitability of the homologous muscles affected by ballistic contractions") this may have been because we did not test force levels of less than 5% MVC. In terms of inhibitory effects, we found no modulation of SICI (relative to control, i.e., when both thumbs were quiescent) when the left thumb made contractions to any of our force levels. It appears, therefore, that SICI in the ipsilateral cortex was not affected by volitional action, at least when it was assessed so close to the onset EMG associated with the volitional action. However, Sohn et al. (2003) also observed that SICI in the ipsilateral cortex was not affected when a delay was imposed between EMG onset and TMS. Our data, therefore, support the view that SICI in the ipsilateral cortex is not affected by volitional actions. In contrast to the lack of SICI effect, we found a shortening of silent periods in the right thumb when the left thumb made contractions to all of our target forces (5–45% MVC). The more forceful ballistic contractions, however, led to marginally greater shortening of silent periods compared with the lighter ballistic contractions.

Why are changes in the level of inhibition observed as changes in SP duration but not SICI ratios?

It is believed that silent periods are controlled by inhibitory circuits that are mediated by $GABA_B$ receptors (Werhahn et al. 1999), while SICI is mediated by $GABA_A$ receptors (Ziemann et al. 1996; Chen 2004). The fact that SICI ratios in the right thumb were unaffected by ballistic contractions of the left thumb, while SP durations were significantly shortened as a result of the same ballistic contractions of the left thumb suggest that, in our particular task, inhibitory

circuits that are modulated by $GABA_B$ receptors are most influenced by the ballistic activation of the contralateral limb, at least in the first few milliseconds following the ballistic action. Furthermore, the level of activation, relative to MVC, during the ballistic contractions does not appear to alter the direction of the change (i.e., a reduction) in activation of the inhibitory circuits within the ipsilateral cortex mediated by $GABA_B$ receptors. It is unclear from a behavioural or a neurophysiological level why $GABA_A$ circuitry was not modulated by this task while $GABA_B$ circuitry was. In the context of the current task, $GABA_B$ inhibitory circuitry may contribute to the coordination of separate motor actions by the two hands (i.e., tonic activation of the right hand concurrent with ballistic activation of the left hand or ballistic activation of the left hand while maintaining quiescence in the right hand) more so than $GABA_A$ inhibitory circuits. Another possibility is that the effects of ballistic action on the inhibitory circuitry of the ipsilateral cortex may sum up over time, such that their net effect is best captured by measurements of silent period, which in this case lasted between 135 and 170 ms.

Conclusion

Our study investigated the excitatory and inhibitory cortical circuits in the first few milliseconds following the ballistic activation of the ipsilateral limb. We believe it is the first of its kind to show specific changes in inhibitory circuits of the ipsilateral hemisphere so early following a volitional action. Although the ballistic contractions did not affect the extent of SICI in the contralateral limb, we found silent periods of shorter duration in the active homologous muscle. We suggest that the inhibitory circuits mediated by $GABA_B$ receptors are most crucial in mediating the net excitability of the ipsilateral cortex in the first few milliseconds following the task-related EMG onset.

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