available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Modulation of long-interval intracortical inhibition and the silent period by voluntary contraction

*Geoffrey Hammond**, *Ann-Maree Vallence*

School of Psychology, The University of Western Australia, Crawley, WA 6009, Australia

ARTICLE INFO

Article history:
Accepted 10 May 2007
Available online 18 May 2007

Keywords:
Motor cortex
Transcranial magnetic stimulation
Intracortical inhibition
LICI
Silent period
Voluntary movement

ABSTRACT

Transcranial magnetic stimulation was used to examine the effect of voluntary contraction on the magnitude of long-interval intracortical inhibition (LICI) and the duration of the silent period in intrinsic hand muscles. The magnitude of LICI acting on the first dorsal interosseus (FDI) measured with a paired-pulse protocol with an inter-pulse interval of 100 ms decreased with increasing tonic level of voluntary abduction force generated by the index finger. LICI in abductor pollicis brevis (APB) decreased from the condition in which the index finger was at rest to the conditions in which it was abducted, whereas LICI in abductor digiti minimi (ADM) was unaffected by the level of index finger abduction. During voluntary abduction of the index finger, the magnitude of LICI was least in FDI, intermediate in ADM, and greatest in APB, suggesting that it may be a mechanism by which tonic activation of hand muscles is fractionated. The magnitude of LICI increased with conditioning stimulus intensity, but intensity did not interact with abduction force. The duration of the silent period (SP) in FDI decreased with the level of voluntary index finger abduction and increased with eliciting stimulus intensity. Within-subject correlations showed that the effects of voluntary drive on SP duration and motor-evoked potential amplitude did not covary, implying an indirect effect of voluntary drive on SP duration. It is proposed that whereas voluntary drive directly reduces the magnitude of slow-acting inhibition acting on the active movement representations and near neighbors, sensory feedback from the contracting muscle acts to limit its time course.

1. Introduction

Transcranial magnetic stimulation (TMS) studies have revealed the presence of two potent inhibitory processes in primary motor cortex (M1). The first, short-interval intracortical inhibition (SICI), is shown by suppression of the motor-evoked potential (MEP) to a test stimulus when it is preceded by about 1–6 ms by a conditioning stimulus that is below motor threshold (Kujirai et al., 1993). The second, long-interval intracortical inhibition (LICI), is shown by suppression of the MEP to a test stimulus when it is preceded by about 50–200 ms by a conditioning stimulus that is above motor threshold (Valls-Solé et al., 1992; Wassermann et al., 1996). SICI is mediated by $GABA_A$ receptors (Hanajima et al., 1998; Ilic et al., 2002; Ziemann et al., 1996a), whereas LICI is mediated by $GABA_B$ receptors (McDonnell et al., 2006; Pierantozzi et al., 2004; Werhahn et al., 1999). Both inhibitory processes modulate the outflow of M1 and are likely to be important in the control of voluntary movement. Later I-waves are suppressed at inter-pulse intervals from 100 to 200 ms, indicating that LICI

* *Corresponding author*. Fax: +61 08 6488 1006.
E-mail address: geoff@psy.uwa.edu.au (G. Hammond).

0006-8993/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2007.05.014

at these intervals is at least partly due to the inhibition of M1 excitability following the conditioning stimulus (Di Lazzaro et al., 2002; Nakamura et al., 1997). A slow-acting and prolonged inhibitory process is also evident in the silent period (SP) evoked in the electromyogram (EMG) from an active muscle by a single TMS pulse (Fuhr et al., 1991; Inghilleri et al., 1993; Roick et al., 1993). There is a strong evidence that the first part of the SP (about 50 ms) is due mainly to spinal inhibitory mechanisms and the later part to cortical inhibitory mechanisms (Chen et al., 1999; Inghilleri et al., 1993).

The magnitude of SICI acting on the cortical representation of an intrinsic hand muscle is reduced just before its voluntary contraction (Reynolds and Ashby, 1999) and increased just before the voluntary termination of contraction (Buccolieri et al., 2004), suggesting that its release and reinstatement are mechanisms by which voluntary movement is gated on and off. The magnitude of SICI is simultaneously maintained in a nearby hand muscle when it is kept quiescent, suggesting that differential distribution of SICI to neighboring muscles has a selective function in voluntary movement (Stinear and Byblow, 2003). SICI has also been implicated in 'volitional inhibition', the ability to suppress unwanted voluntary movement. The magnitude of SICI acting on the agonist muscle was increased from rest during the No-Go phase of a Go/No Go reaction time task (Sohn et al., 2002), and when a prepared movement was successfully withheld in a countermanded reaction time task (Coxon et al., 2006). This increase in SICI was not selective and was present in other muscles that were not engaged in the movement. The distribution of SICI to the cortical representations of neighboring muscles may therefore be controlled depending on whether fractionated movement or a widespread suppression of movement is required.

While the available evidence gives some understanding of the function of SICI in voluntary motor control the functional significance of the slow intracortical inhibitory processes is less clear. There is less evidence on their relationship to aspects of movement, and no consensus view of their function. The magnitude of LICI increases with conditioning stimulus intensity (Hammond and Garvey, 2006) and the duration of the TMS-evoked SP increases with stimulus intensity (Cantello et al., 1992; Wilson et al., 1993), showing more pronounced and more prolonged activation of the inhibitory circuits with increasing intensity. Surprisingly, the effect of such a basic process as the level of voluntary contraction of a muscle on slow intracortical inhibition remains unclear. If the intracortical inhibitory processes that underlie LICI and the SP are important in regulating motor behavior, then the magnitude of LICI and the duration of the SP should vary systematically with the level of voluntary contraction. In particular, if LICI regulates voluntary contraction its magnitude would be expected to decrease with increasing contraction levels. There has been only one relevant study reported, which showed no apparent effect of a relatively small increase in voluntary contraction, from rest to 10% of maximum voluntary contraction, on the magnitude of LICI in wrist extensors assessed with a paired-pulse protocol (Wassermann et al., 1996).

Similarly, if the inhibitory process active in M1 during the SP regulates voluntary contraction, its duration would be expected to shorten with increasing contraction levels. The evidence reported to date is mixed. There are two reports that SP duration in a hand muscle decreased with increasing tonic contraction (Cantello et al., 1992; Wilson et al., 1993), but three reports that SP duration in hand and forearm muscles did not change with tonic contraction level (Haug et al., 1992; Taylor et al., 1997; Wu et al., 2002). This empirical conflict cannot be explained by the type of coil used to deliver the stimulus (all used a circular coil) or by the muscle tested: although the SP is longer in distal hand muscles than in more proximal arm muscles (Cantello et al., 1992; Wu et al., 2002), both decreases in SP duration with contraction level and no change in SP duration with contraction level have been reported for intrinsic hand muscles. The failure to find an effect of the level of voluntary contraction on SP duration cannot be attributed to the levels of contraction examined (the three studies that failed to find an effect tested a wide range of contraction levels) or to the range of stimulus intensities used (although Wu et al. (2002) used only a single stimulus intensity, both Haug et al. (1992) and Taylor et al. (1997) used a wide range of intensities). The contradictory findings might result from procedural variations. All the studies cited relied on a subjective evaluation of the specified contraction level to be met before TMS delivery and none used an objective measure. The aims of the experiments reported here were to establish the effect of tonic contraction level on LICI and the SP using an objective procedure in which TMS was delivered only after the specified contraction level was maintained continuously for 500 ms.

From the hypothesis that the underlying inhibitory processes in M1 act to regulate motor output, we predicted that the magnitude of LICI and the duration of the SP would both decrease with increasing contraction level. We measured the magnitude of LICI with a paired-pulse protocol in three intrinsic hand muscles (first dorsal interosseus, FDI; abductor pollicis brevis, APB; and abductor digiti minimi, ADM) as a function of abduction force generated by the index finger and conditioning stimulus intensity, and SP duration in FDI as a function of abduction force and eliciting stimulus intensity. Force level was varied from rest in the LICI protocol and from 10% of maximum voluntary contraction (MVC) in the SP protocol to 40% of MVC. Stimulus intensity was varied in both protocols to determine the generality of the results obtained across different levels of this variable.

2. Results

2.1. *Paired-pulse protocol*

The background EMG levels in each muscle in the 50 ms immediately before the first TMS pulse was scheduled are shown in Fig. 1. In contrast to the large increase in FDI activity with contraction of this muscle (an 11.5-fold increase in mean activation level from rest to 40% MVC), only small concomitant increases were present in APB (a 1.9-fold increase from rest to 40% MVC) and ADM (a 1.3-fold increase from rest to 40% MVC), indicating some co-contraction of these muscles. Although muscle activation was not completely fractionated at the highest force level, subjects were nevertheless able to confine voluntary activation largely to the target muscle. Uncondi-

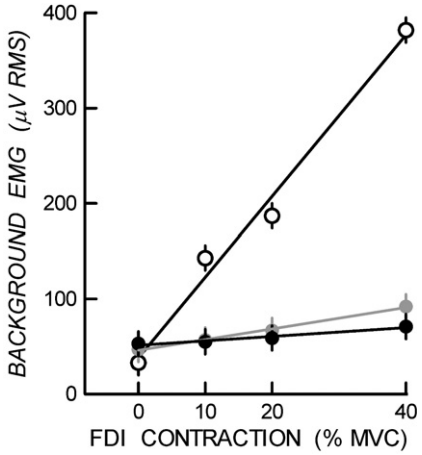

Fig. 1 – Background EMG levels (in μV RMS) in the 50-ms period immediately before TMS in FDI (open circles), APB (grey circles), and ADM (closed circles) as a function of abduction force by the index finger. The best fitting straight lines to the data points for each muscle are shown. Error bars show ± 1 standard error of the mean.

tioned MEP amplitudes were largest in FDI (mean across the four force levels = 5.2 mV, SE = 0.9) and smaller in APB (mean = 3.3 mV, SE = 1.0) and ADM (mean = 2.7 mV, SE = 1.2). The three upper panels in Fig. 2 show the mean conditioned:test amplitude ratios from the paired-pulse protocol with a 100-ms inter-pulse interval from FDI (left panel), APB (middle panel), and ADM (right panel). In FDI, the ratios decreased with increasing intensity of the conditioning stimulus (linear component: $F_{1,5}=8.27$, $P=0.035$, $\eta_p^2=0.62$), showing greater LICI with increasing stimulus intensity. The ratios ranged from 0.78 (95% confidence interval: 0.59–1.03) with the conditioning stimulus at 1.0 rMT to 0.38 (95% confidence interval: 0.29–0.50) with the conditioning stimulus at 1.1 rMT, showing increasing activation of the circuits responsible for LICI over the range of intensities used. The ratios increased with increasing abduction force (linear component: $F_{1,5}=11.44$, $P=0.02$, $\eta_p^2=0.70$; quadratic component: $F_{1,5}=4.38$, $P=0.09$, $\eta_p^2=0.47$), showing a diminution of LICI acting on the cortical representation of FDI with increasing contraction of the muscle. All components of the interaction of Intensity and Force were small and none approached statistical significance. In APB, the ratios decreased with conditioning stimulus intensity (linear component: $F_{1,5}=15.26$, $P=0.011$, $\eta_p^2=0.75$) and increased with abduction force of the index finger. The latter effect was a complex function, with moderate-sized

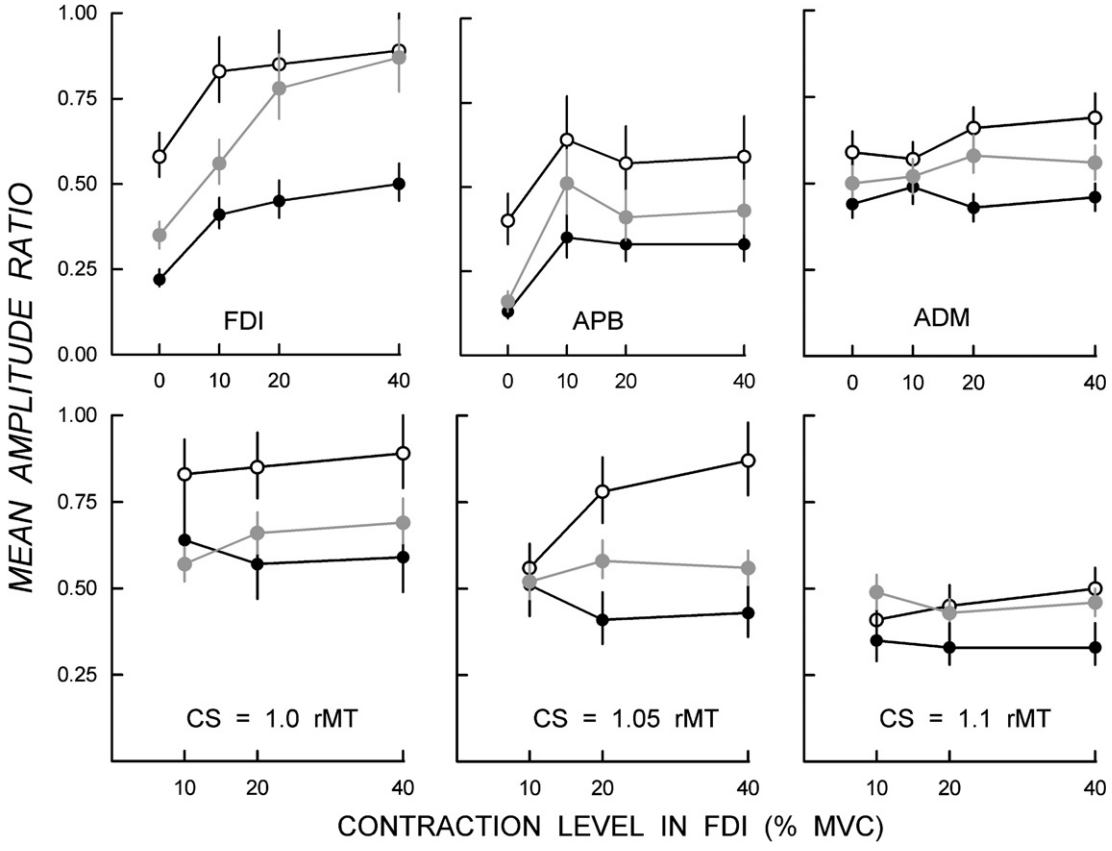

Fig. 2 – Upper panels show mean MEP amplitude ratios in FDI (left panel), APB (middle panel), and ADM (right panel) as a function of abduction force and intensity of the conditioning TMS stimulus (open circles: 1.0 rMT; grey circles: 1.05 rMT; closed circles: 1.1 rMT). Lower panels show mean MEP amplitude ratios in FDI (open circles), ADM (grey circles), and APB (closed circles) as a function of abduction force with a conditioning stimulus intensity of 1.0 rMT (left panel), 1.05 rMT (middle panel), and 1.1 rMT (right panel). Error bars show ± 1 standard error of the mean.

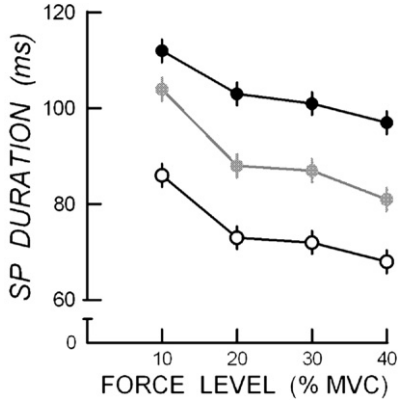

Fig. 3 – Mean SP duration (in ms) in FDI as a function of abduction force and TMS intensity (open circles: 1.05 rMT; grey circles: 1.10 rMT; closed circles: 1.15 rMT). Error bars show ± 1 standard error of the mean.

linear, quadratic, and cubic functions that each approached statistical significance ($Fs_{1,5}$=4.13, 5.09, and 4.20, Ps=0.098, 0.074, and 0.096, η_p^2s=0.45, 0.50, and 0.46 respectively). Inspection of the means from the four force levels generated by the index finger showed that the ratio scores for APB increased from the condition in which FDI was at rest (mean ratio with 95% confidence interval: 0.20, 0.14–0.30) to the conditions in which FDI was active, with only minor changes between the different levels of FDI (mean ratios with 95% confidence intervals for 10%, 20%, and 40% MVC: 0.49, 0.33–0.72; 0.42, 0.29–0.63; and 0.44, 0.30–0.64 respectively). In ADM, the ratios decreased with stimulus intensity but with a linear effect that did not approach statistical significance ($F_{1,5}$=3.18, P=0.135, η_p^2=0.40). MEP amplitudes in ADM were smaller than those in FDI and APB, and the attenuated effect of conditioning stimulus intensity in this muscle may be attributable to an attenuation of effective stimulus intensities at its cortical representation, which was distant from that of FDI. The ratio scores for ADM were not affected by the level of abduction force generated by the index finger (all Fs<1.0, all η_p^2s<0.03).

The three lower panels in Fig. 2 show the subset of the data from the conditions in which FDI was active redrawn to facilitate comparison of LICI acting on each of the three muscles. At the two lowest conditioning stimulus intensities (1.0 and 1.05 rMT), the ratio scores were graded when FDI was contracted at 20% and 40% of MVC and were largest in FDI, intermediate in ADM, and smallest in APB. This differentiation was lost at the highest conditioning stimulus intensity, where the ratio scores were smallest. These results show a topographic grading of LICI across the three intrinsic hand muscles during contraction of FDI, with the least LICI acting on the active FDI, the greatest LICI acting on APB, a frequent synergist of FDI, and an intermediate degree of LICI acting on ADM.

2.2. *Silent period protocol*

Fig. 3 shows SP duration in FDI as a function of stimulus intensity and abduction force by the index finger. SP duration increased with stimulus intensity, with a large linear component ($F_{1,8}$=40.40, P<0.001, η_p^2=0.84), and decreased with force level, with linear and cubic components ($Fs_{1,8}$=5.78, P=0.043, η_p^2=0.42 and 13.61, P=0.006, η_p^2=0.63 for the two components respectively). All components of the interaction of Intensity and Force on each hand were small and none approached statistical significance.

We examined the covariation of excitatory processes evoked by TMS (measured by MEP amplitude) and the duration of the inhibitory process (measured by SP duration) by calculating Pearson correlation coefficients between these variables for each subject. Table 1 shows the mean within-subject correlation coefficients between MEP amplitude and SP duration for each force level (where variation in the two measures was due primarily to variation in an exogenous factor, stimulus intensity) and for each stimulus intensity (where variation in the two measures was due primarily to variation in an endogenous factor, the level of voluntary drive). Positive correlations were found between the two variables when force level was held within limits and stimulus intensity was allowed to vary. In contrast, when stimulus intensity was held constant and force level was allowed to vary, the correlations were near zero with one exception, where there was a small positive correlation. Fig. 4 shows example scatterplots from one subject for each force level (top panels) and each stimulus intensity (bottom panels). The figure shows that although the range of each of the variables (SP duration and MEP amplitude) varied somewhat in the different conditions, the positive correlations present when force level was fixed were not artifacts of outlying data points and the absence of correlations when intensity was fixed was not an artifact of a restricted range of either of the two variables.

3. Discussion

The present results show for the first time that LICI, measured with an inter-pulse interval of 100 ms, decreases systematically with the level of voluntary contraction and so indicate

Table 1 – Mean within-subject correlations of MEP amplitude and silent period duration with force level held constant (and stimulus intensity allowed to vary) and with stimulus intensity held constant (and force level allowed to vary)

Force level (%MVC)				Stimulus intensity (re threshold)		
10	20	30	40	1.05	1.10	1.15
0.49 (0.29, 0.64)	0.61 (0.45, 0.74)	0.42 (0.22, 0.59)	0.32 (0.10, 0.51)	0.08 (−0.07, 0.23)	−0.01 (−0.16, 0.14)	0.07 (−0.08, 0.22)

The 95% confidence limits of the correlation coefficients are in parentheses.

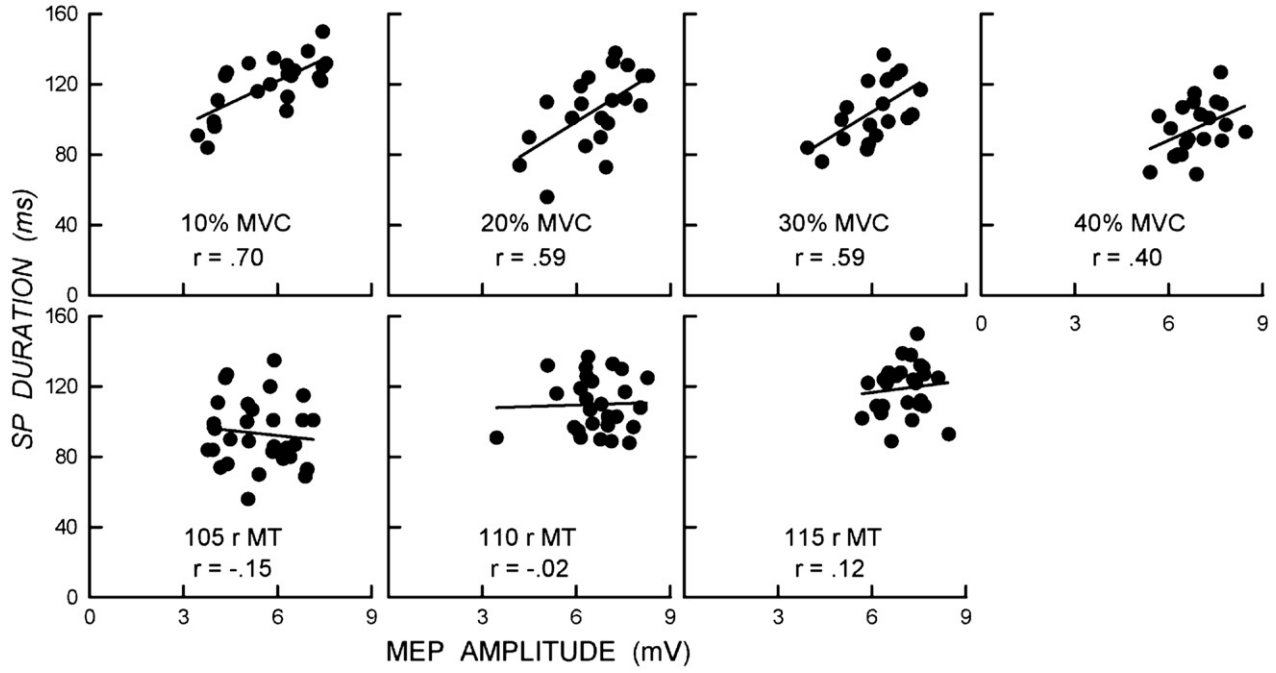

Fig. 4 – Scatterplots of the relationship between SP duration and MEP amplitude in one subject in conditions where force level was held constant (at 10%, 20%, 30%, and 40% of MVC) and stimulus intensity allowed to vary (top four panels) and in conditions where stimulus intensity was held constant (at 1.05, 1.1, and 1.15 times resting motor threshold) and force level allowed to vary (bottom three panels).

a functional role of LICI in tonic contraction. The decrease in LICI in the active muscle would release tonic inhibition of M1 output and hence facilitate the tonic contraction. Release of LICI might in this way act in parallel with the release in SICI before and during voluntary contraction (Reynolds and Ashby, 1999). Although SICI and LICI have been reported to interact, with SICI reduced when LICI is active (Sanger et al., 2001), the present finding and the results of studies of SICI during voluntary contraction (Buccolieri et al., 2004, Ridding et al., 1995) show that both intracortical inhibitory processes are reduced in concert during tonic contraction. The effect of force level on LICI did not interact with conditioning stimulus intensity, showing that the effects of these two variables were independent. A previous report that muscle vibration increased the magnitude of LICI in the vibrated muscle implies that sensory feedback from contracting muscle would normally act to increase the effect of this inhibitory process (Rosenkranz and Rothwell, 2003). The current finding that LICI is progressively reduced with contraction level indicates that any increase of LICI caused by increasing sensory feedback from the contracting muscle is overridden by a reduction in LICI caused by increasing voluntary drive.

The reduction of the magnitude of LICI by voluntary drive was not limited to the cortical representation of the active muscle (FDI) but was also seen in a neighboring muscle (APB) which is a common synergist. While the absolute level of LICI was greater in APB than FDI (including the condition when FDI was at rest), it was reduced when the index finger was in tonic abduction, although the degree of reduction was not graded with the level of force generated by the index finger. This release of LICI did not depend on concurrent activation of the synergist and might act normally to facilitate synergistic action. LICI in a more distant intrinsic hand muscle (ADM), which is not a common synergist of FDI, was unaffected by the level of force generated by the index finger. Taken together, these results suggest that the distribution of LICI to different intrinsic hand muscles during sustained contraction of one might be a cortical mechanism that facilitates synergistic action while at the same time fostering fractionated activation.

The present results also show that SP duration decreased systematically with level of voluntary contraction at each eliciting stimulus intensity. The decrease in SP duration with force was relatively small (about 20 ms from 10% to 40% MVC) but was consistent at each of the three TMS intensities. This finding is consistent with some previous reports (Cantello et al., 1992; Wilson et al., 1993) but not others (Haug et al., 1992; Taylor et al., 1997; Wu et al., 2002). The present experiment, with objective control of the level of contraction at the time TMS was delivered, would have been more sensitive to relatively small changes in SP duration than the previous experiments without objective control of contraction level. The systematic increase in SP duration with eliciting stimulus intensity is consistent with previous reports (Cantello et al., 1992; Wilson et al., 1993).

Although the results are straightforward, the functional significance of a progressive shortening of SP duration with increasing contraction is unclear. The correlational data (Table 1) show that, when the level of voluntary drive was held within limits, variations in stimulus intensity drove correlated changes in MEP amplitude and SP duration; both an excitatory effect of stimulation (indicated by MEP amplitude)

and an inhibitory effect of stimulation (indicated by SP duration) covaried. This covariation of excitatory and inhibitory effects can be explained by assuming that the TMS pulses excited both excitatory and inhibitory intracortical elements that converge on the output elements of M1. When stimulus intensity was held constant, and variation in both MEP amplitude and SP duration was driven by changes in the level of voluntary drive, there was little or no covariation of the two measures. The excitatory effect of voluntary drive on M1 output was independent of its inhibitory effect, a dissociation which suggests that the latter is an indirect effect of voluntary drive on M1 excitability. Like stimulus intensity, voluntary drive appears to activate excitatory intracortical elements that act on the output cells of M1, but unlike stimulus intensity, not to directly affect the duration of activity of the inhibitory elements responsible for the SP.

This dissociation raises the question on how the force generated by the muscle had a level-dependent effect on SP duration (Fig. 3). One possibility is that the SP is controlled by feedback from the contracting muscle and is progressively shortened by feedback from more intense contraction. This possibility is supported by previous work which has shown that sensory stimulation modulates slow intracortical inhibitory processes in M1 (Hess et al., 1999). In these experiments, electrical stimulation of the median nerve while subjects maintained a tonic pinch grip at 20% of maximum force shortened SP duration in FDI and in APB without affecting MEP amplitude. The shortening of SP duration was greatest when the nerve was stimulated 20 ms before TMS and increased with intensity of nerve stimulation. These experiments also showed that during a tonic pinch the SP in FDI was shortened by electrical stimulation of cutaneous afferents supplying the fingers and by electrical stimulation of muscle afferents supplying APB. These observations are consistent with the proposal that the effect of force level on SP duration is indirect and mediated by sensory feedback from the contracting muscle. This proposal also accounts for the finding that SP duration did not vary with contraction level when subjects stopped the voluntary contraction as quickly as possible after TMS delivery (Taylor et al., 1997). Stopping the contraction, which was intended to create comparable levels of voluntary drive in the different experimental conditions after the delivery of the TMS pulse, would have reduced or abolished feedback from the contracting muscle and so removed the factor postulated to limit SP duration. Hess et al. also found that peripheral electrical stimulation reduced the magnitude of LICI measured with a paired-pulse protocol, raising the possibility that the effect of voluntary contraction on the magnitude of LICI shown in the present study might also be an indirect effect mediated by feedback from the muscle. This possibility, however, is refuted by the finding that sustained sensory input from muscle vibration increased the magnitude of LICI (Rosenkranz and Rothwell, 2003).

More generally, the prolonged time course of the inhibitory processes responsible for LICI and the SP would allow sensory feedback from contracting muscles to modulate the excitability of their circuits, a process which would make them functionally more suited for the control of sustained than ballistic movements. It is also likely that, in addition to any modulation by sensory feedback, the slow inhibitory processes in M1 will be affected by input from other brain regions. Functional brain imaging during production of a controlled static hand-grip force has shown force-related activation increases in non-primary cortical motor regions and in the cerebellum as well as in M1 (Dai et al., 2001). The recruitment of widespread brain activity during tonic voluntary contraction, and the increase in the level of activation with contraction, shows that processes in M1 during tonic contraction will be subject to a variety of cortico-cortical influences in addition to any effect of sensory feedback.

Finally, it is worth considering whether LICI and the SP are two manifestations of a common long-lasting cortical inhibitory process, with LICI indicating its magnitude and the SP its duration (Chen, 2004). The duration of the SP corresponds with the inter-pulse intervals at which LICI is present with a paired-pulse protocol (Wassermann et al., 1996), and electrical stimulation of a peripheral nerve simultaneously with TMS both shortens the duration of the SP and restricts the range of inter-pulse intervals over which LICI is present (Hess et al., 1999). Furthermore, both processes might reflect $GABA_B$-mediated postsynaptic inhibition of the output cells of M1: there is good evidence that implicates $GABA_B$ in LICI (McDonnell et al., 2006; Pierantozzi et al., 2004; Werhahn et al., 1999) and some evidence that implicates $GABA_B$ in the SP (Siebner et al., 1998; Werhahn et al., 1999), although negative findings have also been reported (Berardelli et al., 1996; McDonnell et al., 2006; Ziemann et al., 1996b). In any case, the magnitude and duration of the inhibition obtained even with relatively low intensity stimuli show that slow intracortical inhibitory processes exert powerful control over the output of M1 during sustained contraction.

4. Experimental procedures

4.1. *Subjects*

A total of 11 unique neurologically normal volunteers (six females) aged from 21 to 61 years were tested in two experiments. Six subjects (three females) participated in the paired-pulse measurements and nine subjects (five females) participated in the silent period measurements. Four subjects participated in both procedures. The protocol was in accord with the Declaration of Helsinki and had been approved by the Human Research Ethics Committee of the University of Western Australia. All subjects gave informed written consent before participating.

4.2. *Stimulation and recording*

Magnetic stimuli were generated by two Magstim 200 stimulators connected through a BiStim unit and delivered through a figure-of-eight coil (90-mm diameter) aligned in the parasagittal plane (handle posterior) with the coil tangential to the scalp. The stimulators were controlled programmatically (Sinclair et al., 2006). Scalp sites were identified on a snugly fitting cap with a pre-marked grid with 1-cm spacing referenced to C3 and C4 from the International 10–20 system for EEG recording. In both experiments the optimal site for eliciting an MEP in the relaxed FDI and the resting motor

threshold (rMT) at the optimal site were determined. The rMT was taken as the minimum TMS intensity required to elicit an MEP of at least 75 μV in three of five successive stimulus presentations. EMG activity was recorded with surface electrodes in a belly-tendon configuration. The EMG signal was amplified (200–1000×), bandpass filtered (10–1000 Hz), digitized at 2 kHz, and saved for later analysis.

4.3. *Experimental protocols*

In both protocols subjects sat comfortably with the forearm and hand pronated and the index finger fitted snugly in a plastic cup fixed to a metal rod fitted with a strain gauge to transduce the force produced by finger abduction. Before the test trials began, the maximum voluntary contraction (MVC) was taken as the maximum force produced in three index finger abductions. On each test trial, the target force and a tolerance band (±5% of the target) appeared as horizontal markers on a graduated vertical indicator on a computer screen. The indicator also showed the instantaneous readout of the applied force as feedback. The subjects were instructed to match the target force with tonic index finger abduction while keeping other hand and arm muscles at rest. TMS pulses were given after the force (which was also sampled at 2 kHz) was within the tolerance band for a continuous 500-ms period. Subjects maintained the target force level until a tone which sounded after the TMS was delivered. The inter-trial interval was 6 s in both protocols.

The paired-pulse protocol determined the magnitude of LICI in FDI, APB, and ADM of the dominant hand as a function of conditioning pulse intensity (1.0, 1.05, and 1.1 times rMT) and index finger abduction force (rest, and 10%, 20%, and 40% of MVC). The intensity of the test pulse was 1.1 times rMT in all conditions and the inter-pulse interval was 100 ms on paired-pulse trials. The 16 experimental conditions (formed by the factorial combination of four conditioning stimulus intensities (including a conditioning stimulus intensity of zero, which specified a test trial) and the four contraction levels) were presented in eight randomized blocks for a total of 128 trials.

The duration of the SP evoked by a single TMS pulse in FDI of the dominant hand was determined as a function of pulse intensity (1.05, 1.10, and 1.15 times rMT) and index finger abduction force (10%, 20%, 30%, and 40% of MVC). The 12 experimental conditions formed by the factorial combination of the three pulse intensities and the four contraction levels were presented in eight randomized blocks for a total of 96 trials.

4.4. *Data analysis*

In the paired-pulse protocol, each subject's median conditioned MEP amplitude in each paired-pulse condition was expressed as a ratio of that subject's median single-pulse test MEP amplitude. Because the distribution of ratios is skewed (they cannot be less than zero but their maximum value is not limited) and because ratios are not symmetrical they were log-transformed before analysis with analyses of variance with two repeated-measures factors (Conditioning Stimulus Intensity and Force). The transformed ratios were back-transformed after analysis and the arithmetic means of the back-transformed ratios (the geometric means of the untransformed ratios) are reported. As a result of the transformation, standard errors are not symmetrical around the mean and are reported as separate negative and positive values relative to the mean in graphs and in the text. In the silent period protocol, SP duration was measured for each trial with screen cursors from the onset of the MEP to the return of continuous EMG activity and the mean SP duration calculated for each experimental condition. In both protocols, within-subject standard errors are presented because the interest is in comparison of experimental conditions and not estimation of population values (Loftus and Masson, 1994). Partial eta-squared values (η_p^2) are reported as measures of effect size; medium and large effect sizes ($\eta_p^2 \geq 0.40$) are reported. Where Pearson product–moment correlation coefficients were analyzed they were first transformed using Fisher's *r*-to-*z* transformation, and the results back-transformed for presentation.

REFERENCES

Berardelli, A., Rona, S., Inghilleri, M., Manfredi, M., 1996. Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. Brain 119, 71–77.

Buccolieri, A., Abbruzzese, G., Rothwell, J.C., 2004. Relaxation from a voluntary contraction is preceded by increased excitability of motor cortical inhibitory circuits. J. Physiol. 558, 685–695.

Cantello, R., Gianelli, M., Civardi, C., Mutani, R., 1992. Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42, 1951–1959.

Chen, R., 2004. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp. Brain Res. 154, 1–10.

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

Coxon, J.P., Stinear, C.M., Byblow, W.D., 2006. Intracortical inhibition during volitional inhibition of prepared action. J. Neurophysiol. 95, 3371–3383.

Dai, T.H., Liu, J.Z., Sahgal, V., Brown, R.W., Yue, G.H., 2001. Relationship between muscle output and functional MRI-measured brain activation. Exp. Brain Res. 140, 290–300.

Di Lazzaro, V., Oliviero, A., Mazzone, P., Pilato, F., Saturno, E., Insola, A., Visocchi, M., Colosimo, C., Tonali, P.A., Rothwell, J.C., 2002. Direct demonstration of long latency cortico-cortical inhibition in normal subjects and in a patient with vascular parkinsonism. Clin. Neurophysiol. 113, 1673–1679.

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

Hammond, G.R., Garvey, C.-A., 2006. Asymmetries of long-latency intracortical inhibition in motor cortex and handedness. Exp. Brain Res. 172, 449–453.

Hanajima, R., Ugawa, Y., Terao, Y., Sakai, K., Furubayashi, T., Machii, K., Kanazawa, I., 1998. Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J. Physiol. 509, 607–618.

Haug, B.A., Schonle, P.W., Knobloch, C., Kohne, M., 1992. Silent period measurement revives as a valuable diagnostic tool with transcranial magnetic stimulation. Electroencephalogr. Clin. Neurophysiol. 85, 158–160.

Hess, A., Kunesch, E., Classen, J., Hoeppner, J., Stefan, K., Benecke, R., 1999. Task-dependent modulation of inhibitory actions within the primary motor cortex. Exp. Brain Res. 124, 321–330.

Ilic, T.V., Meintzschel, F., Cleff, U., Ruge, D., Kessler, K.R., Ziemann,

U., 2002. Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J. Physiol. 545, 153–167.
Inghilleri, M., Berardelli, A., Cruccu, G., Manfredi, M., 1993. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. J. Physiol. 466, 521–534.
Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P., Marsden, C.D., 1993. Corticocortical inhibition in human motor cortex. J. Physiol. 471, 501–519.
Loftus, G.R., Masson, M.E.J., 1994. Using confidence intervals in within-subject designs. Psychon. Bull. Rev. 1, 476–490.
McDonnell, M.N., Hillier, S.L., Ridding, M.C., Miles, T.S., 2006. Impairments in precision grip correlate with functional measures in adult hemiplegia. Clin. Neurophysiol. 117, 1474–1480.
Nakamura, H., Kitagawa, H., Kawaguchi, Y., Tsuji, H., 1997. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J. Physiol. 498, 817–823.
Pierantozzi, M., Marciani, M.G., Palmieri, M.G., Brusa, L., Galati, S., Caramia, M.D., Bernardi, G., Stanzione, P., 2004. Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. Brain Res. 1028, 1–8.
Reynolds, C., Ashby, P., 1999. Inhibition in the human motor cortex is reduced just before a voluntary contraction. Neurology 53, 730–735.
Ridding, M.C., Taylor, J.L., Rothwell, J.C., 1995. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J. Physiol. 487, 541–548.
Roick, H., von Giesen, H.J., Benecke, R., 1993. On the origin of the postexcitatory inhibition seen after transcranial magnetic brain stimulation in awake human subjects. Exp. Brain Res. 94, 489–498.
Rosenkranz, K., Rothwell, J.C., 2003. Differential effect of muscle vibration on intracortical inhibitory circuits in humans. J. Physiol. 551, 649–660.
Sanger, T.D., Garg, R.R., Chen, R., 2001. Interactions between two different inhibitory systems in the human motor cortex. J. Physiol. 530, 307–317.
Siebner, H.R., Dressnandt, J., Auer, C., Conrad, B., 1998. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 21, 1209–1212.
Sinclair, C., Faulkner, D., Hammond, G., 2006. Flexible real-time control of MagStim 2002 units for use in transcranial magnetic stimulation studies. J. Neurosci. Methods 158, 133–136.
Sohn, Y.H., Wiltz, K., Hallett, M., 2002. Effect of volitional inhibition on cortical inhibitory mechanisms. J. Neurophysiol. 88, 333–338.
Stinear, C.M., Byblow, W.D., 2003. Role of intracortical inhibition in selective hand muscle activation. J. Neurophysiol. 89, 2014–2020.
Taylor, J.L., Allen, G.M., Butler, J.B., 1997. Effect of contraction strength on responses in biceps brachii and adductor pollicis to transcranial magnetic stimulation. Exp. Brain Res. 117, 472–478.
Valls-Solé, J., Pascual-Leone, A., Wassermann, E.M., Hallett, M., 1992. Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr. Clin. Neurophysiol. 85, 355–364.
Wassermann, E.M., Samii, A., Mercuri, B., Ikoma, K., Oddo, D., Grill, S.E., Hallett, M., 1996. Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscles. Exp. Brain Res. 109, 158–163.
Werhahn, K.J., Kunesch, E., Noachtar, S., Benecke, R., Classen, J., 1999. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J. Physiol. 517, 591–597.
Wilson, S.A., Lockwood, R.J., Thickbroom, G.W., Mastaglia, F.L., 1993. The muscle silent period following transcranial magnetic cortical stimulation. J. Neurol. Sci. 114, 216–222.
Wu, L., Goto, Y., Taniwaki, T., Kinukawa, N., Tobimatsu, S., 2002. Different patterns of excitation and inhibition of the small hand and forearm muscles from magnetic brain stimulation in humans. Clin. Neurophysiol. 113, 1286–1294.
Ziemann, U., Lonnecker, S., Steinhoff, B.J., Paulus, W., 1996a. The effect of lorazepam on the motor cortical excitability in man. Exp. Brain Res. 109, 127–135.
Ziemann, U., Lonnecker, S., Steinhoff, B.J., Paulus, W., 1996b. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann. Neurol. 40, 367–378.