Long-interval facilitation and inhibition are differentially affected by conditioning stimulus intensity over different time courses.

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Abstract

Intracortical facilitatory and inhibitory processes in the primary motor cortex (M1) play an important role in both the preparation and execution of motor tasks. Here we aimed to (1) confirm the existence of, and further characterise, intracortical facilitation at long conditioning-test stimulus intervals at subthreshold conditioning stimulus (CS) intensities and (2) identify the threshold for long-interval intracortical inhibition (LICI) at different inter-stimulus intervals (ISIs). To examine facilitation, stimulus-response curves at ISIs of 100 and 150 ms were obtained using a range of subthreshold CS intensities. LICI stimulus-response curves were also obtained using varying CS intensities at ISIs of 100 ($LICI_{100}$) and 150 ms ($LICI_{150}$). Facilitation of the conditioned MEP was observed at subthreshold CS intensities at an ISI of 100 ms. $LICI_{100}$ was observed at a lower CS intensity than $LICI_{150}$. First, we provide evidence of a long-interval facilitation and provide some evidence consistent with a cortical origin of this facilitation. Second, the lower threshold for evoking $LICI_{100}$ than $LICI_{150}$ suggests an intensity-duration effect whereby a more intense CS results in longer duration LICI. Investigation of the interaction between LICI and long-interval facilitation might help to elucidate the functional importance of these processes.

Highlights

- Long-interval facilitation (LIF) evident with subthreshold CS intensities.
- Different emergence of LICI at ISIs of 100 and 150 ms.
- Intensity-duration effect: a more intense CS results in longer duration LICI.
- LICI - LIF interactions might reveal the functional importance of these processes.

Keywords: long-interval intracortical inhibition; long-interval facilitation; GABAergic inhibition; primary motor cortex; transcranial magnetic stimulation.

Introduction

Intracortical inhibitory processes in the primary motor cortex (M1) play an important role in the preparation and execution of motor tasks [12, 24, 30] and have a modulatory influence on plasticity in M1 [28, 35]. Paired-pulse transcranial magnetic stimulation (TMS) can be used to investigate the excitability of (at least) two types of GABAergic intracortical inhibitory circuits, namely, short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) [17, 32].

When a suprathreshold conditioning stimulus (CS) precedes a second suprathreshold test stimulus (TS), at inter-stimulus intervals (ISIs) of ~50-200 ms, the amplitude of the motor evoked potential (MEP) elicited by the TS is suppressed [32, 33]. While the early MEP suppression (ISIs ~50 ms) is due to the action of inhibitory processes at the spinal level, the longer latency MEP suppression (80 - 200 ms) is largely due to the action of inhibitory processes within M1 [32, 33]. Pharmacological studies have shown that LICI is mediated by $GABA_B$ receptor activity [20, 21, 29]. The relationship between CS intensity and level of inhibition is 'U' shaped, with low and very high CS intensities associated with less inhibition than moderate CS intensities [13]. The descending limb of the LICI stimulus-response curve, where inhibition increases with CS intensity, indicates the progressive recruitment of inhibitory interneurons that mediate LICI.

While LICI is observed with suprathreshold CS intensities, there is one report of facilitation of the conditioned MEP with subthreshold and threshold CS intensities. Valls-Sole et al. [32] showed facilitation of the conditioned MEP when paired-stimuli of sub- or near-threshold intensities were delivered using an ISI of 100 ms. Despite this report more than 20 years ago, there has been no systematic investigation of this facilitation.

The current study had two primary aims. First, we aimed to confirm the existence of, and further characterise, facilitation of the conditioned MEP observed with subthreshold CS intensities at long ISIs. Based on Valls-Sole et al.'s [32] finding that paired-pulse TMS with long ISIs can evoke both facilitation and inhibition of the conditioned MEP, depending on CS intensity, we hypothesised that the conditioned MEP would be facilitated at subthreshold CS intensities and inhibited at suprathreshold intensities. Second, we were interested in examining whether the threshold for evoking LICI is different across the time course of LICI. We investigated the threshold for evoking LICI at ISIs of 100 ms and 150 ms by using threshold and suprathreshold CS intensities.

Materials and methods

Subjects

Twenty one right-handed subjects participated in the study. Eighteen subjects participated in Experiment 1 (10 females; 25 ± 7.6 years), three subjects participated in control Experiment 1A (1 female; 27 ± 4 years), and nine subjects participated in Experiment 2 (including 7 who participated in Experiment 1: 4 females; 26 ± 3.6). The protocol was performed in accordance with the Declaration of Helsinki and was approved by the University of Adelaide Human Research Ethics Committee. All subjects gave written informed consent prior to testing and were screened for conditions that would contraindicate TMS [26, 27].

Transcranial Magnetic Stimulation

Subjects were seated with their head and neck supported throughout the session. Electromyographic (EMG) activity was recorded from the relaxed right first dorsal interosseous (FDI) using surface electrodes placed in a belly-tendon montage. The EMG

signal was amplified (x1000; CED 1902 amplifier, CED), band pass filtered (20-1000 Hz) and digitized at a sampling rate of 2 kHz (CED 1401 interface, CED). A Magstim BiStim 200^2 stimulator (Magstim Co., Whitland) generated single- and paired-pulse stimuli, delivered through a figure-of-eight coil (90 mm diameter) placed tangentially to the scalp with the handle pointing backward and at a 45° angle away from the midline to produce a posterior-anterior current in the cortex. Suprathreshold pulses were delivered over the left M1 at numerous sites in order to identify the optimal site for consistently evoking MEPs in FDI. This site was marked on the scalp with a water-soluble pen to allow accurate placement of the coil throughout the experiment.

Resting motor threshold (rMT) was determined at baseline; minimum stimulus intensity (% of maximal stimulator output; MSO) required to elicit MEPs of at least 50 μV in at least 5/10 consecutive trials in the relaxed FDI. The TMS intensity that elicited MEPs of ~1mV (SI_{1mV}) was also determined at baseline.

Experiment 1

Stimulus-response curves were obtained by varying the CS intensity. Blocks of stimuli including a test-stimulus (TS) alone and paired-pulse stimuli were delivered, with CS intensities ranging from 50% rMT to 100% rMT (increments of 5% rMT). ISIs were 100 and 150 ms and the TS intensity was set at $SI_{1\,mV}$, which is consistent with many previous investigations of LICI [e.g. 16, 25, 31]. There were a total of 23 conditions: 11 different CS intensities for ISIs of 100 and 150 ms and the TS-alone condition. Six blocks of 46 trials were obtained, with each block containing two trials for each condition presented in a pseudo-randomised order with inter-trial intervals of 6 seconds (+/- 10%). Each block lasted ~6 minutes. Twelve trials were obtained for all conditions.

Experiment 1A

The results of Experiment 1 showed significant facilitation of the conditioned MEP at subthreshold CS intensities (ISI 100 ms). To investigate the origin of this facilitation (cortical or spinal), we used both TMS and transcranial electrical stimulation (TES). Two blocks of 30 trials each were delivered; one block consisted of 15 single-pulse TMS trials and 15 paired-pulse TMS trials, and the second block consisted of 15 single-pulse TES trials and 15 paired-pulse trials in which the CS was delivered using TMS and the TS was delivered using TES (paired TMS-TES). For each of the three subjects that participated in the TES experiment, the CS intensity was set to 75% rMT, the ISI was set to 100 ms, and the TS intensity was set to $SI_{1\ mV}$ (for both TMS and TES blocks). For two of the three subjects, the experiment was repeated using a CS intensity of 85% rMT (with ISI set to 100 ms and TS intensity set to $SI_{1\ mV}$).

Experiment 2

To examine the threshold for evoking inhibition, LICI was measured with two different CS intensities (100% and 105% rMT) at ISIs of 100 ($LICI_{100}$) and 150 ms ($LICI_{150}$). Four blocks of 30 trials were obtained; each block contained 15 single- and 15 paired-pulse trials for one of the conditions presented in a pseudo-randomised order with inter-trial intervals of 6 seconds (+/- 10%). Each of the 4 blocks lasted ~4 minutes. Fifteen trials were obtained for all conditions. The order in which conditions were tested was pseudo-randomised.

Data Analysis

Individual trials were excluded if pre-stimulus EMG activity exceeded 5 µV during the 100 ms prior to the CS or during the interval between the CS and the TS. The peak-to-peak MEP

amplitude (in mV) was obtained from the 40 ms of EMG activity beginning 15 ms after the TS. For both ISIs, inhibition and facilitation of the conditioned MEP was quantified by expressing the mean paired-pulse MEP amplitude for each CS intensity as a ratio of the mean TS-alone MEP amplitude. Data were analysed with repeated measures analysis of variance (rANOVA) with polynomial contrasts and Bonferroni correction for multiple comparisons (Expt 1: .05 / number of subthreshold CS intensities (10) = P<.005; Expt 2: .05 / number of CS intensities (2) = P<.025). Greenhouse-Geisser correction was used for analyses in which the assumption of sphericity was violated (Mauchly's test of sphericity). Statistical significance was accepted at $\alpha \leq 0.05$. To determine the CS intensity at which conditioned MEP amplitude was inhibited, one-sample *t*-tests were performed on the ratio calculated for each CS intensity. Data are presented as mean ± standard deviation, except in the figures where standard error of the mean (SEM) is presented.

Results

Experiment 1

The mean rMT was 48 ± 8.2% and the mean SI_{1mV} intensity was 58 ± 11% of MSO. SI_{1mV} was, on average, 119% RMT. The mean MEP amplitude evoked by TS-alone was 0.96 ± 0.55 mV. Figure 1A shows stimulus-response curves from FDI in Experiment 1. There was a main effect of CS intensity ($F_{[4.6,78.2]}$=5.58, P<0.001); the conditioned MEP amplitude was facilitated with moderate increases in CS intensity (to 90% rMT) and then shifted to inhibition with further increases in CS intensity (Fig 1A). There was no main effect of ISI ($F_{[1,17]}$=2.60, P=0.13), however there was an ISI*CS intensity interaction ($F_{[4.6,78.3]}$=2.8, P=0.027). Paired-samples *t*-tests showed that the conditioned MEP at an ISI of 100 ms was of larger amplitude than the conditioned MEP at an ISI of 150 ms at several CS intensities: 75% rMT, t_{17}=2.4, P=0.031; 80% rMT, t_{17}=3.8, P=0.001; 90% rMT, t_{17}=2.4, P=0.027.

Furthermore, the conditioned MEP at an ISI of 100 ms was *smaller* than the conditioned MEP at an ISI of 150 ms at 100% rMT (t_{17}=2.2, P=0.042).

To further examine the facilitation and inhibition of the conditioned MEP (at 100 and 150 ms), one-sample *t*-tests were performed. At 100 ms ISI, conditioned MEP amplitude was facilitated at a CS intensity of 75% rMT (t_{17}=3.1, P=0.007) and appeared to be facilitated at a CS intensity of 80% rMT, but this was not statistically significant when corrected for multiple comparisons (t_{17}=2.2, P=0.044). No facilitation of the MEP was seen with a 150 ms ISI.

At a CS intensity of 100% rMT, inhibition of the conditioned MEP was evident at the 100 ms ISI ($LICI_{100}$: t_{17}=3.3, P=0.004) but not the 150 ms ISI ($LICI_{150}$: t_{17}=1.3, P=0.225).

Experiment 1A

Transcranial electrical stimulation was delivered to three subjects to test for a cortical contribution to the facilitation observed in Experiment 1. Table 1 shows rMT, SI_{1mV}, and mean MEP amplitude for each of the four conditions (single-pulse TMS, paired-pulse TMS, single-pulse TES, and paired TMS-TES) for each of the three subjects. The conditioned MEP was facilitated with paired-pulse TMS (70% and 42% facilitation with CS intensities set at 75% rMT and 85% rMT respectively) but not with paired TMS-TES (i.e. TMS conditioning stimulus and TES test stimulus).

Experiment 2

The mean rMT was 46 ± 9.5% and the mean SI_{1mV} intensity was 53 ± 11.7% of MSO. SI_{1mV} was, on average, 115% RMT. The mean MEP amplitude evoked by TS-alone was 0.75 ± 0.31

mV. There was a main effect of both CS intensity ($F_{[1,8]}$=9.6, P=0.015) and ISI ($F_{[1,8]}$=6.8, P=0.031); both $LICI_{100}$ and $LICI_{150}$ increased with CS intensity, and regardless of CS intensity, $LICI_{100}$ was greater than $LICI_{150}$. There was no CS intensity*ISI interaction ($F_{[1,8]}$=1.7, P=0.23). Paired-samples t-tests showed that the conditioned MEP at an ISI of 100 ms was smaller than the conditioned MEP at an ISI of 150 ms at both 100% rMT (t_8=2.3, P=0.049) and 105% rMT (t_8=2.5, P=0.037).

One-sample t-tests were performed to further examine inhibition of the conditioned MEP (at ISIs of 100 and 150 ms). $LICI_{100}$ was evident at CS intensities of 100 and 105% rMT (100% rMT: t_8=2.8, P=0.022; 105% rMT: t_8=9.3, P<0.001). Conversely, there was no inhibition of the conditioned MEP at 150 ms ISI at either 100 or 105% rMT (100% rMT: t_8=0.4, P=0.686; 105% rMT: t_8=1.5, P=0.165) (Fig 1B).

Discussion

The current study has two novel findings: first, facilitation of the conditioned MEP at subthreshold CS intensities and an ISI of 100 ms (long-interval facilitation; LIF). This result complements and extends that of Valls-Sole et al. [32] by further characterising the emergence of LIF at subthreshold CS intensities and showing the shift to LICI with increasing CS intensity at an ISI of 100 ms. Furthermore, we provide some evidence that is consistent with a cortical contribution to LIF. The second novel finding is that the CS intensity threshold for evoking $LICI_{100}$ is lower than that for evoking $LICI_{150}$. This likely reflects a CS-intensity dependent effect, whereby a more intense CS results in longer duration LICI.

Long-Interval Facilitation (LIF)

The current results are consistent with the original finding of Valls-Sole and colleagues [32], namely facilitation of the conditioned MEP with subthreshold CS intensities (at 100 ms ISI), and extend it to characterise the shift to LICI with increasing CS intensity. We will refer to this as long-interval facilitation (LIF), but it is not possible, with the current data, to confirm whether the observed increases in MEP amplitude at subthreshold CS intensities are due to facilitation or disinhibition.

It is well established that LICI has a cortical origin. At ISIs greater than 50 ms, there is no evidence of inhibition of the conditioned MEP when the test MEP is evoked by TES [14], no change in H-reflexes [10, 36], and no suppression of late I-waves in the descending corticospinal volleys measured using epidural recordings [4, 9, 22]. Here, we showed facilitation of the conditioned MEP when the test stimulus was a TMS pulse but not when the test stimulus was a TES pulse, providing some evidence that is consistent with a cortical contribution to LIF observed at subthreshold CS intensities. It is unlikely that LIF is due to re-afferent processes as the facilitation was seen at subthreshold CS intensities which did not evoke any muscle response. However, it is difficult to speculate further on the mechanism(s) that might mediate this facilitation.

There are several reports of facilitation of the conditioned MEP at long ISIs, however, all of these used *suprathreshold* CS intensities and all reported facilitation at ISIs ≥100 ms. In the resting motor system, Cash et al. [2, 3] showed facilitation of the conditioned MEP at ISIs of 200-250 ms and suggested that this reflected a late cortical disinhibition. This late cortical disinhibition was associated with reduced SICI and increased short-interval intracortical facilitation. In the behaviourally-engaged motor system, Kouchtir-Devanne et al. [16] showed

that $LICI_{100}$ in FDI was reversed to facilitation during a precision grip but not during index finger abduction with comparable background EMG activity. While the functional role of LICI in the motor system is still unclear, this finding suggests a functional role in dextrous finger control. Finally, Wasserman et al. [33] showed LICI reverses to facilitation when evoked in the relaxed state immediately after cessation of voluntary contraction, but only with a TMS test stimulus and not a TES test stimulus, suggesting a cortical contribution to the facilitation. Here, we showed LIF at subthreshold CS intensities at an ISI of 100 ms; it remains unknown whether these are all observations of the same phenomenon.

LICI

Here, we showed the CS threshold for evoking $LICI_{100}$ was lower than that for evoking $LICI_{150}$. The most parsimonious explanation for this is that the duration of LICI is dependent on CS intensity. It is possible that lower CS intensities activate the circuits that mediate LICI for >100 but <150 ms, while higher CS intensities activate LICI circuits for at least 150 ms. Indeed, there are numerous reports of significant $LICI_{150}$ with CS intensities of ~120%RMT [e.g. 5, 13, 15, 23]. This explanation is consistent with the behaviour of the cortical silent period (cSP), an inhibitory process also thought to be mediated by $GABA_B$ receptor activity. It is well-established that the duration of the cSP increases with increasing TMS intensity [1, 12, 14, 34]. However, there is some evidence that, while both are mediated by $GABA_B$ receptor activity, the mechanisms underlying the cortical silent period and LICI are at least partially independent [e.g. 11, 12]. This, together with the results reported here, suggests that the duration of LICI and the cortical silent period is dependent on CS intensity.

An alternate explanation is that the lower threshold for evoking $LICI_{100}$ than $LICI_{150}$ might reflect the contribution of different processes to $LICI_{100}$ and $LICI_{150}$. Chu and colleagues [5,

6] have suggested that pre- and post-synaptic $GABA_B$ receptor activity might contribute differentially to $LICI_{100}$ and $LICI_{150}$. Using in vitro intracellular recording techniques and paired-pulse stimulation, peak activation of pre- and postsynaptic $GABA_B$ receptors is observed at 100 and 150 ms respectively [7, 8, 18, 19]. Using TMS in humans, Sanger et al. [29] suggested that LICI inhibits SICI via presynaptic $GABA_B$ receptor activation, and it has subsequently been shown that $LICI_{100}$ but not $LICI_{150}$ reduces SICI [5, 6]. Further evidence from plasticity-induction protocols of a double dissociation between $LICI_{100}$ and $LICI_{150}$ support the notion that they might be mediated in part by different processes. For example, theta-burst stimulation to the cerebellum bi-directionally modulate $LICI_{100}$ but do not affect $LICI_{150}$ [15], and ischemic nerve block does not affect $LICI_{80}$ but leads to an increase in $LICI_{150}$ [31]. This explanation, however, remains to be tested.

Conclusions

We have shown, for the first time, that facilitation of the conditioned MEP at an ISI of 100 ms is influenced by CS intensity and provide some evidence that is consistent with a cortical contribution to this facilitation. It is important to now determine the underlying mechanism(s) and the functional importance of this facilitation. This study also provides the first evidence that the threshold for evoking LICI, as a function of CS intensity, differs over the time course of LICI. The identification of a different threshold, possibly due to an intensity-duration effect, has important implications for the investigation of the role of long-interval inhibition in motor control. Specifically, experimental studies should measure LICI at ISIs of both 100 and 150 ms or be careful not to generalise. The investigation of the interaction between LICI and facilitation of the conditioned MEP at an ISI of 100 ms might help to elucidate the functional importance of these processes.

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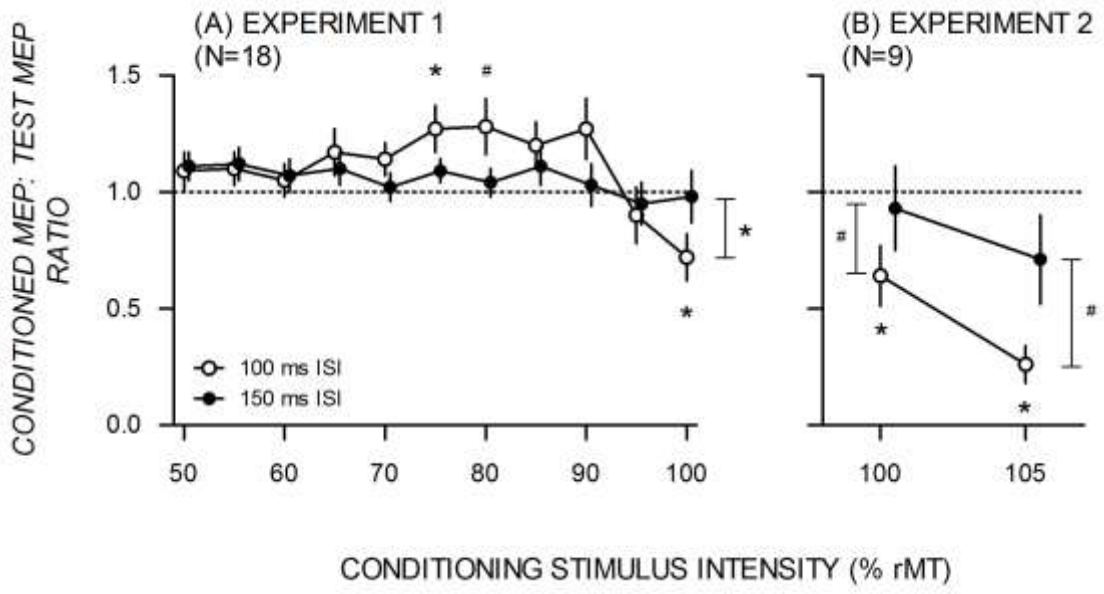

Fig. 1. Mean stimulus-response curves showing facilitation of the conditioned MEP and LICI as a function of CS intensity at ISIs of 100 ms (open symbols) and 150 ms (filled symbols). (Note: ratio of 1.0 (dashed line) indicates no difference between MEP amplitude evoked by single- and paired-pulse trials.) Facilitation of the conditioned MEP and LICI are expressed as ratios of paired-pulse to single-pulse MEP amplitude (ratios >1 facilitation, ratios <1 inhibition). In Experiment 1, the conditioned MEP was facilitated at subthreshold CS intensities at an ISI of 100 ms. In both Experiment 1 (left) and Experiment 2 (right), significant inhibition was evident at an ISI of 100 ms but not 150 ms. Error bars show +/- SEM. * indicates P < Bonferroni-corrected α value (Expt 1: P<.005; Expt 2: P<.025); # indicates P<.05.

Table 1. Each subject's rMT, SI_{1mV}, and mean peak-to-peak MEP amplitudes (mV) and standard deviation for each of the conditions in Experiment 1A. * indicates a significant difference between single-pulse MEP amplitude and paired pulse MEP amplitude (independent *t*-test, one-tailed, $P<.05$).

	Subjects	TMS intensities		TMS			TES		
		rMT	SI_{1mV}	Single	Paired (TMS-TMS)	Ratio	Single	Paired (TMS-TES)	Ratio
CS Intensity 75% rMT	S_1	53	60	1.17	* 2.35	2.01	0.73	0.38	0.52
	S_2	38	43	0.84	* 1.19	1.41	1.00	1.03	1.03
	S_3	46	54	0.31	* 0.52	1.68	0.10	0.11	1.10
	MEAN	46 (7.5)	53 (8.6)	0.77 (0.43)	1.35 (0.92)	1.70 (0.30)	0.61 (0.46)	0.51 (0.48)	0.88 (0.32)
CS Intensity 85% rMT	S_1	46	49	0.68	* 1.02	1.49	0.70	0.65	0.93
	S_2	39	41	0.71	0.97	1.36	1.32	1.04	0.79
	MEAN	43	45	0.70 (0.02)	0.99 (0.03)	1.42 (0.09)	1.01 (0.44)	0.84 (0.28)	0.86 (0.10)