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Modulation of short- and long-interval intracortical inhibition with increasing motor evoked potential amplitude in a human hand muscle

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HIGHLIGHTS

- Intracortical inhibition assessed with paired-pulse transcranial magnetic stimulation (TMS) is influenced by test TMS intensity.
- Using two different experimental approaches, we also show that intracortical inhibition can vary with the amplitude of the test motor evoked potential (MEP) when expressed relative to the maximal compound muscle action potential (%M_{max}).
- We suggest that the test MEP should be normalised to the maximal muscle response when assessing intracortical inhibition.

ABSTRACT

Objective: The aim of the current study was to investigate the effect of increasing test motor evoked potential (MEP) amplitude on short- (SICI) and long-interval intracortical inhibition (LICI) at rest and during activation of the first dorsal interosseous (FDI) muscle.
Methods: In 22 young subjects, a conditioning-test transcranial magnetic stimulation (TMS) paradigm was used to assess SICI and LICI at 5 different test TMS intensities (110–150% motor threshold) in resting and active FDI. In 9 additional subjects, SICI and LICI data were quantified when the test MEP amplitude represented specific proportions of the maximal compound muscle action potential (M_{max}) in each subject.
Results: Test TMS intensity influenced SICI and LICI in rest and active FDI muscle. The normalised test MEP amplitude (%M_{max}) did not influence SICI at rest, whereas there was a decrease in LICI at rest and an increase in SICI in active FDI with an increased normalised test MEP amplitude (%M_{max}).
Conclusions: Our results demonstrate differential effects of normalised test MEP amplitude (%M_{max}) on SICI and LICI in resting and active FDI muscle.
Significance: Estimation of SICI and LICI under some circumstances may be influenced by the normalised test MEP amplitude in subject populations with different M_{max} characteristics.

1. Introduction

Paired-pulse transcranial magnetic stimulation (TMS) is a commonly utilised method of non-invasive brain stimulation that allows a functional assessment of intracortical inhibition within primary motor cortex (M1). Short-interval intracortical inhibition (SICI) consists of a subthreshold conditioning pulse followed 2–5 ms later by a suprathreshold test pulse (Kujirai et al., 1993). In this paradigm, a reduction in the amplitude of a test motor evoked potential (MEP) occurs due to the activation of gamma-amino butyric acid $(GABA)_A$-mediated inhibitory interneurons in primary motor cortex (M1) by the subthreshold conditioning TMS pulse (Ziemann et al., 1996a,b). Another paired-pulse paradigm, known as long-interval intracortical inhibition (LICI), uses a suprathreshold conditioning pulse that reduces the size of a suprathreshold test pulse when delivered 100–150 ms later (Valls-Sole et al., 1992), which is thought to be due to the activation of $GABA_B$-related inhibitory interneurons (Werhahn et al., 1999). Several lines of evidence suggest that SICI is functionally important, as it is reduced with muscle activation (Ridding et al., 1995; Zoghi et al., 2003), is abnormal in some movement disorders (Berardelli et al.,

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2008) and is altered after interventions that change motor performance (e.g., fatigue; see Vucic et al., 2011). Although the functional relevance of LICI is less well established, changes in this paradigm have also been observed during muscle activation (Hammond and Vallence, 2007; McNeil et al., 2009) and in motor control pathologies (Berardelli et al., 2008).

Along with these functional effects, methodological factors are known to influence estimates of intracortical inhibition with paired-pulse TMS. For example, several studies have shown that increasing the size of the test MEP can influence the magnitude of SICI and LICI (Daskalakis et al., 2002, 2004; Sanger et al., 2001). This effect is thought to be due predominantly to an increase in test TMS intensity to generate a larger test MEP, which alters the relative contribution of indirect (I) waves in the corticospinal descending volley (Di Lazzaro et al., 1998a; Garry and Thomson, 2009; McNeil et al., 2011). However, a recent study has suggested that the amplitude of the test MEP when normalised to the maximum muscle response (maximal compound muscle action potential; M_{max}) may also influence the estimate of SICI in resting first dorsal interosseous muscle (FDI) (Lackmy and Marchand-Pauvert, 2010). In this previous study, they found that the relationship between the estimate of SICI and the normalised test MEP (%M_{max}) was non-linear, and suggested that this effect was partly due to properties of the motor neuron pool where small and large motor units have unequal contributions to the MEP (Lackmy and Marchand-Pauvert, 2010). These findings suggest that the more than twofold difference in M_{max} that is commonly observed between young healthy subjects (Lee and Carroll, 2005) could confound comparisons of SICI when a similar absolute test MEP amplitude is used between subjects. However, it is not currently known whether the normalised test MEP amplitude (%M_{max}) influences the assessment of LICI, or whether SICI and LICI are influenced by normalised test MEP amplitude (%M_{max}) when the muscle is voluntarily activated.

The aim of the current study was to investigate the effect of increasing test MEP amplitude on SICI and LICI at rest and during activation of the FDI muscle. Our approach was to quantify the effect of increasing test TMS intensity on SICI and LICI to produce a range of test MEP amplitudes in each subject, and to compare this with SICI and LICI responses when the test MEP was expressed relative to M_{max} obtained in each subject. Based on the previous results for SICI in resting FDI (Lackmy and Marchand-Pauvert, 2010), and the sensitivity of both paradigms to changes in test TMS intensity, we expected that the estimation of LICI at rest would also be influenced by the normalised test MEP amplitude (%M_{max}). Furthermore, as muscle activation changes the magnitude of both SICI (Ridding et al., 1995; Zoghi et al., 2003) and LICI (Hammond and Vallence, 2007; McNeil et al., 2009), we expected that the effect of normalised test MEP amplitude (%M_{max}) on SICI and LICI would be reduced when the muscle was voluntarily activated. The findings from this study will determine whether normalising the test MEP amplitude to the maximum motor response of the muscle (M_{max}) is an important consideration in the estimation of SICI or LICI in resting and active FDI muscle.

2. Methods

Thirty-one young (mean ± SD; 21.8 ± 2.8 years), healthy subjects were recruited from the university and wider community to participate in the current study. Twenty-two (mean ± SD; 22.3 ± 3.1 years) subjects participated in the main experiment (Experimental Series 1), and an additional 9 subjects (mean ± SD; 20.7 ± 1.1 years) were recruited for a second series of experiments (Experimental Series 2). Exclusion criteria included a history of stroke or epilepsy, history of neurological or psychiatric disease, or currently taking psychoactive medication (antidepressants, antipsychotics, anxiolytics, etc.). Hand preference and laterality was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Each subject provided written, informed consent prior to participation. All experimentation was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the declaration of Helsinki.

2.1. Experimental arrangement

For all experiments, subjects were seated in a comfortable chair with their right arm abducted approximately 45° at the shoulder. This allowed the forearm and hand to sit comfortably on an arm support placed next to them. Surface electromyography (EMG) was used to record responses from the first dorsal interosseous (FDI) muscle of the right hand. Two Ag–AgCl electrodes (3.2 cm diameter) were attached to the skin over the muscle in a belly-tendon montage, with a grounding strap around the wrist acting as a reference. EMG recordings were conditioned using a CED1902 (Cambridge Electronic Design, Cambridge, UK) and sampled using a CED1401 interface (Cambridge Electronic Design). EMG was amplified (×300), band-pass filtered (20 Hz high pass, 1 kHz low pass) and digitized at 2 kHz before being recorded and stored offline for analysis. To facilitate muscle relaxation, real-time EMG signals were displayed under high gain on an oscilloscope placed in front of the subject. During the active trials, force was measured with a load cell (model MLP-100; Transducer Techniques, Temecula, CA, USA) that was mounted between two polished brass disks that were 30 mm apart. When activating the target muscle (FDI), subjects grasped the brass discs between the index finger and thumb using a precision grip. Force was amplified (×1000) and sampled at 400 Hz with the CED data acquisition system.

2.2. Experimental procedures

2.2.1. Maximum voluntary contraction

For the assessment of maximum muscle strength, subjects produced a maximal contraction that was held for 3 s. This procedure was repeated several times, separated by a 60 s break, until the three largest contractions were within a 10% margin. The largest of these contractions was designated the maximum voluntary contraction (MVC). To optimise force production, feedback was displayed on a computer monitor placed at eye level in front of the subject and verbal encouragement was provided by the experimenter.

2.2.2. Transcranial magnetic stimulation

TMS was applied to the left primary motor cortex using a figure-of-eight coil (external wing diameter 9 cms) with two Magstim 200 magnetic stimulators connected through a Bistim unit (Magstim, Dyfed, UK). The coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, with the handle pointed backwards and laterally, producing a current flow in the brain with a posterior to anterior direction. The coil was positioned on the scalp over the location producing an optimum response in the relaxed FDI muscle. This location was marked on the scalp for reference and continually checked throughout the experiment.

Resting and Active motor thresholds (RMT and AMT, respectively) were obtained in FDI while the TMS coil was placed at the optimal location over primary motor cortex. RMT was defined as the minimum TMS intensity, relative to the maximum stimulator output (%MSO), producing a response amplitude $\geqslant$50 μV in three out of five trials in resting FDI muscle (Carroll et al., 2001). Active motor threshold (AMT) was defined as the minimum TMS intensity producing a response amplitude $\geqslant$ 300 μV in three out of five trials while FDI was active in performing a precision grip held at 5% of