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Short-interval intracortical inhibition: Comparison between conventional and threshold-tracking techniques

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ABSTRACT

Background: Short-interval intracortical inhibition (SICI) is conventionally measured as the *relative amplitude reduction* of motor evoked potentials (MEPs) by subthreshold conditioning stimuli. In threshold-tracking SICI (T-SICI), stimulus intensity is instead adjusted repeatedly to maintain a constant MEP and inhibition is measured as the *relative threshold increase*. T-SICI is emerging as a useful diagnostic test, but its relationship to conventional amplitude SICI (A-SICI) is unclear.
Objective: To compare T-SICI and its reliability with conventional A-SICI measurements.
Methods: In twelve healthy volunteers (6 men, median age 30 years), conventional and T-SICI were recorded at conditioning stimuli (CS) of 50–80% resting motor threshold (RMT) and interstimulus interval of 2.5 ms. Measurements were repeated on the same day and at least a week later by a single operator.
Results: Across the CS range, mean group T-SICI showed a strong linear relationship to the mean group values measured by conventional technique ($y = 29.7–0.3x$, $R^2 = 0.99$), but there was considerable interindividual variability. At CS 60–80% RMT, T-SICI had excellent intraday (intraclass correlation coefficient, ICC, 0.81–0.92) and adequate-to-excellent interday (ICC 0.61–0.88) reproducibility. Conventional SICI took longer to complete (median of 5.8 vs 3.8 min, $p < 0.001$) and tended to have poorer reproducibility (ICC 0.17–0.42 intraday, 0.37–0.51 interday). With T-SICI, smaller sample sizes were calculated for equally powered interventional studies.
Conclusion: The close relationship between conventional and T-SICI suggests that both techniques reflect similar cortical inhibitory mechanisms. Threshold-tracking measurements of SICI may be able to improve reproducibility, to shorten acquisition time and to reduce sample sizes for interventional studies compared with the conventional technique.
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Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method that can be employed to study inhibitory and excitatory microcircuits of the brain [1]. Short-interval intracortical inhibition (SICI) is one of the most widely studied inhibitory phenomena. When subthreshold conditioning and subsequent suprathreshold test stimuli are delivered through the same coil at interstimulus intervals (ISIs) of 1–6 ms, their interaction results in suppression of the motor evoked potential (MEP) amplitude [2]. Two distinct phases of SICI have been observed at 1 ms and 2.5 ms ISIs [3,4]. While the mechanism of the first phase is not fully understood, SICI

Abbreviations: A-SICI, short-interval intracortical inhibition obtained by conventional paradigm; CR, coefficient of repeatability; EMG, electromyography; ICC, intraclass correlation coefficient; IQR, interquartile range; MEP, motor evoked potential; rmANOVA, repeated measures analysis of variance; T-SICI, short-interval intracortical inhibition obtained by threshold-tracking; AT, A-SICI - T-SICI recording protocol sequence; TA, T-SICI - A-SICI recording protocol sequence; TS_{1mV}, test stimulus intensity to evoke a peak-to-peak MEP of 1 mV.

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at an ISI of 2.5 ms is thought to reflect gamma-aminobutyric acid (GABA) mediated inhibition in the motor cortex [5].

Conventional TMS paradigms for SICI use a *constant stimulus* approach in which fixed intensity stimuli are applied and multiple responses are averaged to obtain a reliable estimate [2]. SICI is then expressed as the reduction of the average conditioned MEP amplitude in comparison to the average control MEP size. Due to high trial-to-trial variability of MEPs, it is recommended to obtain at least 8–10 responses for each condition [5]. If multiple conditions are investigated, recordings may become time-consuming. Another potential disadvantage of this approach is that it assumes that the resting motor threshold (RMT) remains constant throughout the lengthy recording. However, it may change considerably due to biological or technical factors [5,6]. Thus, the pre-defined conditioning stimulus (CS) intensity, commonly set as a percentage of RMT, may become suboptimal for eliciting SICI.

By contrast, a *constant response* approach is used in threshold-tracking. This method was pioneered by Bostock and colleagues [3,7]. Its main principle is that the stimulation intensity is dynamically adjusted to maintain the response at a predetermined target level. Therefore, if the CS suppresses the response, the test stimulus intensity will increase to counteract this effect. In this technique, RMT is the control condition and SICI is reflected by the relative increase in test stimulus intensity over RMT (the bigger the increase, the stronger the inhibition). The main advantage of this paradigm is that any drifts in motor threshold are continuously monitored and adjusted for.

Impairment of SICI has been reported across a wide range of neurological disorders [8–18], but due to its large variability between patients and overlap with normal subjects, conventional SICI has limited clinical diagnostic use [19,20]. However, T-SICI is emerging as a potentially useful diagnostic test [21–24]. Recent data shows its diagnostic utility in distinguishing amyotrophic lateral sclerosis from mimic disorders [21] and as a possible biomarker for the effect of therapeutic interventions [25].

While reliability of conventional SICI measurements has been previously studied [8,26–29], little is known about reliability of threshold-tracking TMS and its comparability with conventional technique. Therefore, the aim of this study was a head-to-head comparison of the two techniques for SICI measurement. We tested the hypothesis that threshold-tracking paradigms which allow monitoring of the naturally occurring fluctuations in RMT can improve the reliability of SICI making it a preferred tool for both clinical practice and research.

Methods

The study was carried out in accordance with the Declaration of Helsinki, approved by local ethics committee, and a written informed consent was obtained from participants prior to investigations.

Subjects

16 healthy volunteers with no known neurological disorder or contraindications for TMS and not on any regular medication were recruited for the study. Twelve subjects (6 men; median age 30 years, age range 23–52 years) completed the full set of experiments. Four subjects were excluded due to inability to maintain relaxation of the hand ($n = 1$) or incomplete stimulation sessions due to coil overheating ($n = 3$).

Experimental setup

During the experiment participants were comfortably seated in an armchair and instructed to stay relaxed but alert. Surface electromyography (EMG) was recorded from the relaxed right first dorsal interosseous muscle with Ag/AgCl electrodes (Kendall 5500 Diagnostic Tab Electrodes, Covidien, Dublin, Ireland) placed in a belly-tendon montage. The EMG signal was amplified (×600 gain), filtered (10–3000 Hz), and sampled at 10 kHz using the EA-2 amplifier of a Viking Select EMG Unit (Nicolet Biomedical Inc, Madison, WI, USA). EMG of the target muscle was displayed on a screen in front of the subjects as a visual feedback to aid maintaining relaxation of the hand.

TMS was carried out using two Magstim 200^2 stimulators connected in BiStim mode and a figure-of-eight $D70^2$ coil (Magstim, Whitland, UK). Stimulus delivery and data acquisition were controlled by QTRACW software (©Institute of Neurology, University College London, London, UK, distributed by Digitimer Ltd. at www.digitimer.com) using bespoke recording protocols.

The coil was hand-held over the left hemisphere with the handle pointing postero-laterally at a 45° angle to the mid-sagittal line to induce posterior-to-anterior flow of the current in the motor cortex. Magnetic stimuli were delivered at 4.1 s intervals.

Once the hotspot was identified, an automated stimulation protocol was started, allowing a single operator to carry out the whole recording without the need to reposition the coil or manually control the stimulator.

Resting motor threshold

In conventional protocols, RMT is usually defined as the minimal stimulus intensity required to obtain a peak-to-peak MEP amplitude of >0.05 mV in 50% of consecutive trials and 10 out of 20 trials are recommended for obtaining reliable results [5]. In threshold-tracking paradigms, RMT is defined as the stimulation intensity required to maintain the target MEP which is usually set as peak-to-peak amplitude of 0.2 mV (further referred to as $RMT_{0.2mV}$) [3,30]. We used threshold-tracking to obtain $RMT_{0.2mV}$ estimates employing a proportional tracking mode in which stimulus intensity is adjusted proportionally to the percentage error in the logarithm of the previous response [3] with the maximum stimulus step limited to 2% MSO. Tracking was deemed stable when the MEP hit or oscillated around the target amplitude six times. $RMT_{0.2mV}$ was then used to set CS intensities for both conventional and T-SICI measurements to allow direct comparison between the techniques.

Short-interval intracortical inhibition

SICI measurements at an ISI of 2.5 ms and CS intensities of 50%, 60%, 70%, and 80% $RMT_{0.2mV}$ were obtained using both conventional ('amplitude', A-SICI) and threshold-tracking (T-SICI) techniques. ISI of 2.5 ms was chosen as SICI at this interval is thought to reflect GABA Aα2,3 receptor mediated inhibition [31] and can potentially serve as a biomarker of the effect of GABA A receptor modulating drugs. As the relationship between SICI and CS intensity is non-linear and varies between individuals [5,32], a range of CS intensities was used to explore whether SICI recruitment curve may provide a more reliable measure than SICI estimates at a single CS intensity.

For A-SICI, test stimulus intensity required to evoke MEPs of peak-to-peak amplitude of approximately 1 mV (TS_{1mV}) was determined by threshold tracking (target set at 1 mV). Test and conditioning stimuli of fixed intensity were then used to record fifteen MEPs for control and each SICI condition in a pseudorandom order.

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