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TECHNICAL NOTE

Short interval intracortical inhibition: Variability of amplitude and threshold-tracking measurements with 6 or 10 stimuli per point

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Abstract Reduced short-interval intracortical inhibition (SICI) in motor neuron disease has been demonstrated by amplitude changes (A-SICI) and threshold-tracking (T-SICI) using 10 stimuli per inter-stimulus interval (ISI). To test whether fewer stimuli would suffice, A-SICI and T-SICI were recorded twice from 30 healthy subjects using 6 and 10 stimuli per ISI. Using fewer stimuli increased mean A-SICI variances by 23.8% but the 7.3% increase in T-SICI variance was not significant. We conclude that our new parallel threshold-tracking SICI protocol, with 6 stimuli per ISI, can reduce time and stimulus numbers by 40% without appreciable loss of accuracy.

List of abbreviations: A-SICI, short-interval intracortical inhibition obtained by amplitude measurements; A-SICI$_{(n)}$, A-SICI recorded with n stimuli per ISI; A-SICI-T, A-SICI transformed into equivalent threshold changes; ISI, inter-stimulus interval; MEP, motor evoked potential; MND, motor neuron disease; MSO, maximum stimulator output; RMT200, stimulus required to evoke 200 μV MEP; SD, standard deviation; SEMeas, standard error of measurement; SICI, short-interval intracortical inhibition; T-SICI, short-interval intracortical inhibition obtained by threshold tracking different ISIs in parallel; T-SICI$_{(n)}$, T-SICI recorded with n stimuli per ISI; TMS, transcranial magnetic stimulation; TS1mV, stimulus required to evoke 1 mV MEP.

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Introduction

The transcranial magnetic stimulation (TMS) technique of short-interval intracortical inhibition (SICI) can be recorded by using constant stimuli, and measuring the effect of the conditioning stimulus on the amplitude of the response to the test stimulus (i.e. amplitude SICI: A-SICI), or by tracking the effect of the conditioning stimulus on the threshold stimulus required to elicit a constant target response (i.e. threshold-tracking SICI: T-SICI). Both methods showed reduced inhibition in patients with motor neuron disease (MND), with high specificity and sensitivity, using 10 stimuli at each of nine inter-stimulus intervals (ISI) from 1 to 7 ms [9]. This study was undertaken to determine how much loss in accuracy would result from using only 6 stimuli per ISI.

Methods

The study was carried out in accordance with the Declaration of Helsinki and approved by The Central Denmark Region Committees on Health Research Ethics and the local ethics committee in Ankara. All participants gave their written informed consent before the investigations.

Subjects

Thirty healthy volunteers (9 men, 21 women) were recruited who had no known neurological disorder or contraindications for TMS, and were not on any regular medication. They were aged 37.6 ± 11.7 years (mean ± S.D., range 24−63).

TMS and SICI

The methods were described previously [8,9]. Briefly, a Magstim® D70 figure-of-8 coil was positioned on the contralateral hemisphere, to excite motor evoked potentials (MEPs) of the right first dorsal interosseus (FDI) muscle. The coil current was generated by two Magstim® 200^2 stimulators in BiStim configuration. After identifying the hotspot, all the stimulation sequences were controlled automatically by QtracW software (© UCL, London, UK), using QTMSG-12 protocols (© QTMS Science Ltd.).

For A-SICI, resting motor thresholds were first determined for 200μV (RMT200) and 1 mV (TS1mV) peak-to-peak MEPs, using a '4→2→1' tracking rule [8]. The TS1mV test stimulus was then preceded by conditioning stimuli at 70% RMT200, at the nine ISIs (1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7 ms) presented in pseudo-random order, while every fourth test stimulus was delivered alone. Ten stimuli were delivered at each ISI, then A-SICI$_{(10)}$ data was generated from the geometric means of all 10 conditioned and all 30 unconditioned MEPs, while A-SICI$_{(6)}$ data was generated from the first 6 conditioned and first 18 unconditioned MEPs.

For T-SICI, RMT200 was estimated as above, then tracked continuously with 1% of maximum stimulator output (MSO) steps as every fourth stimulus, and the conditioning stimuli were set to 70% of the updated RMT200. The conditioned test stimuli were delivered at the same pseudo-randomised 9 ISIs after the conditioning stimuli as for A-SICI, and initially set to 106% RMT200. Thresholds for the 9 ISIs were estimated independently in parallel by proportional tracking, with the maximum permitted change in stimulus diminishing from 6 to 2%MSO (6→5.5→5→4.5→4→3.5→3→2.5→2%MSO for T-SICI$_{(10)}$ and 6→5→4→3→2%MSO for T-SICI$_{(6)}$). The T-SICI$_{(10)}$ protocol was previously designated T-SICIp2 [8] and distinct from the earlier serial threshold-tracking protocol T-SICIs [4,5,8,10].

All 120 A-SICI and T-SICI$_{(10)}$ stimuli (each comprising 90 paired and 30 single pulses) and 72 T-SICI$_{(6)}$ stimuli were applied to each of the 30 subjects twice. The coil was removed from the hotspot after each protocol, and other protocols interposed before a repetition.

Data analysis

A-SICI amplitudes were averaged as geometric means, and T-SICI thresholds were estimated by log regression [4,8]. For comparison with T-SICI thresholds, A-SICI amplitudes were normalized by log conversion and scaled, using the relationship found previously [8]:

$$\text{A-SICI-}T = 100 - 17.85 \times \text{Log10(A-SICI/100)}.$$

For statistical tests, $P<0.05$ was considered significant.

Results

Variability of A-SICI, A-SICI-T and T-SICI estimates

For each type of recording, there were 2 measurements from each of 30 subjects, so Fig. 1A shows the geometric means and geometric means × /÷ geometric SD for all 60 recordings with n = 10 stimuli per ISI, and 60 recordings with n = 6. Similarly, Fig. 1C shows means ± SDs for the 60 T-SICI recordings with n = 6 and n = 10 stimuli per ISI. To enable the variability of the A-SICI recordings to be compared more readily with the T-SICI ones, the transformed A-SICI-T values are shown in Fig. 1B. Although the A-SICI-T means closely resemble the T-SICI ones, the SDs are smaller, and this is shown more clearly in Fig. 2, where SDs of the 1st and 2nd measurements are shown separately.

The variances averaged over the two measurements at 9 ISIs were 24.37 for A-SICI-T$_{(10)}$, 30.18 for A-SICI-T$_{(6)}$, 64.58 for T-SICI$_{(10)}$ and 69.28 for T-SICI$_{(6)}$ (all in [%RMT200]^2). The T-SICI/A-SICI-T differences were highly significant: $P = 9.32 \times 10^{-8}$ for n = 10 and $P = 5.27 \times 10^{-9}$ for n = 6 by paired t-tests). The n = 6/n = 10 differences (calculated by comparing 1st measurement at n = 10 with 2nd measurement at n = 6, and vice versa, to avoid comparing overlapping observations) were much smaller. The null hypothesis that n = 6 observations were no more variable than n = 10 ones could be rejected for A-SICI-T (P = 0.0248) but not for T-SICI

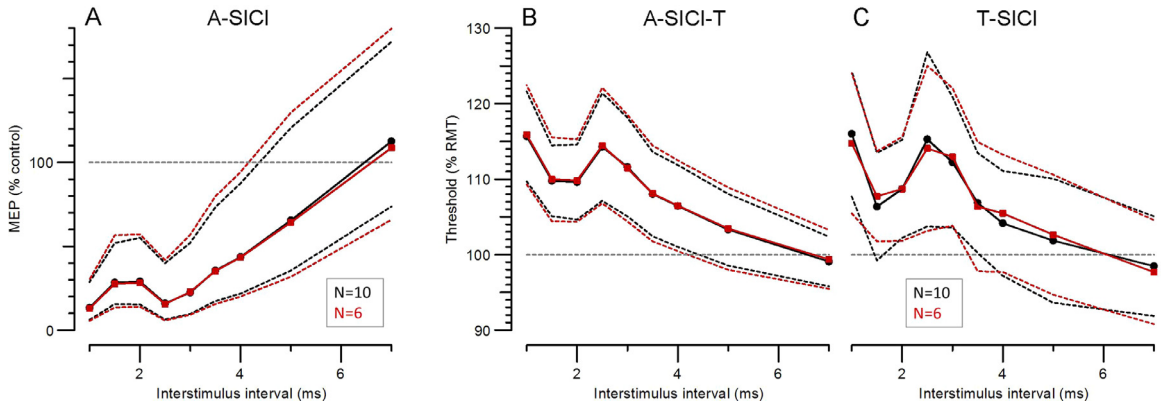

Figure 1 Means and variabilities for 60 SICI recordings made with 10 or 6 stimuli per ISI. A: Conventional amplitude SICI, with geometric means × /÷ geometric SDs. B: Amplitude SICI normalized by log conversion to resemble threshold tracking SICI (mean ± SD). C: Threshold-tracking SICI (mean ± SD).

(P = 0.187). Although the percentage differences in the above variances were much greater for A-SICI-T (23.8%) than T-SICI (7.3%), the absolute differences were similar (5.81 for A-SICI and 4.71 for T-SICI).

Within-subject and between-subject variability

Since each recording was repeated, the sources of variation can be separated into within-subject and between-subject components. Whereas between-subject variability can help determine whether a patient's SICI is abnormal or not, within-subject variability determines how many subjects are needed to demonstrate differences over time due to disease progression or treatment interventions. The within-subject SD or standard error of measurement (SEMeas), is simply related to the Minimal Detectable Change (MDC):

$$MDC = SEMeas \times \sqrt{2} \times 1.96$$ [7]

MDC is the minimal change that can be detected in an individual with 95% probability, and is a measure of absolute reliability for TMS outcomes [1]. For a group of size n, the minimal detectable change reduces to:

$$MDC_n = MDC/\sqrt{n}$$ [7]

From which it follows that:

$$n = (MDC/MDC_n)^2 = 2 \times (SEMeas \times 1.96/MDC_n)^2$$

This enables us to compare the 4 SICI methods used in this study and estimate how many more subjects will be needed to compensate for the shorter A-SICI$_{(6)}$ and T-SICI$_{(6)}$ protocols.

All 4 methods give a mean threshold increase from 1 to 3.5 ms (a useful SICI measure for MND studies) of 10.5% RMT200. The within-subject SDs or SEMeas values for A-SICI-T$_{(10)}$, A-SICI-T$_{(6)}$, T-SICI$_{(10)}$ and T-SICI$_{(6)}$ from 1 to 3.5 ms were

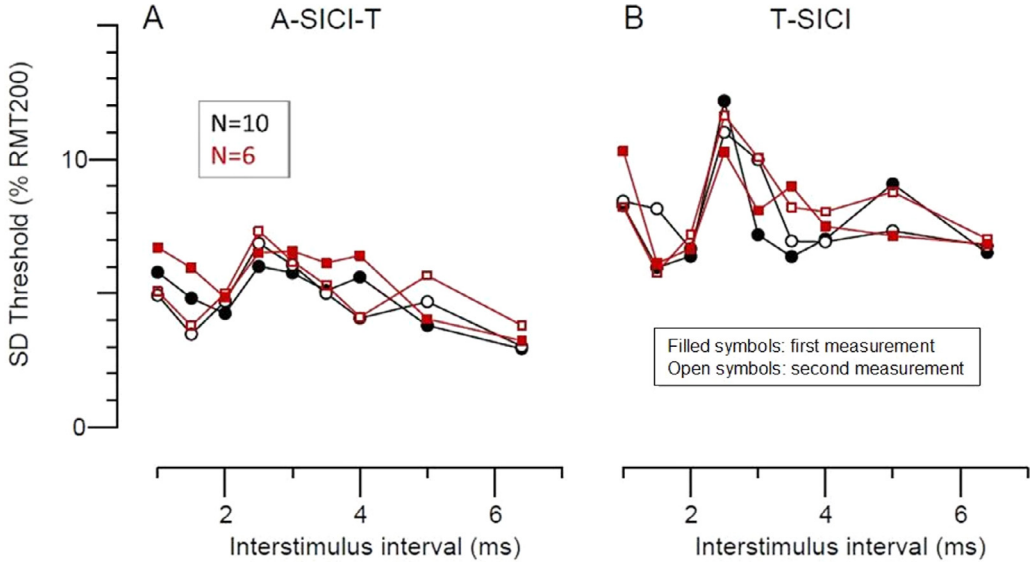

Figure 2 Variability of two sets of SICI estimates made with 10 and 6 stimuli per ISI. A: Normalized amplitude SICI. B: Threshold tracking SICI. Filled symbols: first measurement. Open symbols: second measurement. Black circles: n = 10. Red squares: n = 6.

2.18, 2.49, 3.33 and 3.15% RMT200 respectively. From the formulae above, we can estimate the numbers of subjects required to detect a change in SICI over time of 20% or 2.1% RMT200 as 9, 11, 20 and 18 (rounded to the next highest integer).

Discussion

The main aim of this study was to determine whether fewer stimuli could be used in clinical tests of SICI without seriously impairing their reliability. This would save time (especially when using TMS equipment limited to one stimulus every 4 or 5 s), improve patient tolerance, and reduce coil heating. One way to reduce stimulus numbers is to limit the ISI range, and for MND, ISIs 4—7 ms can be omitted without impairing discrimination [9]. Here we tested reducing the number of stimuli per ISI, both for conventional A-SICI measurements and the new parallel method of T-SICI [8,9] which requires similar stimulus numbers. Previous A-SICI versus ISI studies have used between 6 [3] and 20 [2] paired stimuli per ISI, with 10, as used in our previous studies [8,9] the most popular number [6,11]. Boroojerdi and colleagues [2] showed that the coefficient of variation of their responses increased, as expected, when calculations were based on 20, 15, 10 or 5 trials. As in that study, our estimates of A-SICI variability with different numbers of stimuli were not independent, since A-SICI$_{(6)}$ variability was estimated from a subset of A-SICI$_{(10)}$ measurements, invalidating direct A-SICI$_{(6)}$/A-SICI$_{(10)}$ comparisons. By comparing non-overlapping recordings, however, we could demonstrate that averaging only 6 stimuli increased the variance of the observations. On the other hand, despite making 30 recordings at each ISI, we were unable to demonstrate any disadvantage in using 6 rather than 10 stimuli per ISI for the T-SICI measurements. Analysis of variances indicated that this was mainly due to the higher variability of the T-SICI measurements.

As previously reported [8], the A-SICI-T measurements were consistently less variable than the T-SICI ones using the same number of stimuli, indicating that conventional amplitude measurements provide a more efficient means of measuring intra-cortical inhibition than these threshold-tracking methods, so that approximately twice the number of subjects are expected to be needed to demonstrate a comparable change in SICI due, for example to a drug. This does not, however, mean that threshold-tracking SICI is less efficient as a clinical biomarker. Our recent comparison of these two methods in MND patients found that T-SICI was much better than A-SICI at detecting abnormal corticospinal excitability in patients with few upper motor neuron signs, since threshold-tracking is sensitive to changes in fewer neurons [9]. Consequently, the two techniques had comparable overall sensitivity and specificity as biomarkers [9].

In conclusion, whereas reducing stimulus numbers by 40% incurs a small loss in A-SICI accuracy, our new 6-stimulus T-SICI protocol carries no appreciable penalty, and can be recommended for future MND studies.

Declaration Competing of Interest

HB and JH receive from UCL shares of the royalties for sales of the Qtrac software used in this study. HB, HT, BC, and MK are shareholders of QTMS Science Ltd., which licences the QTMSG-12 recording protocols used. GS has no potential conflict of interest to declare.

Acknowledgements

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