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Research article

Inter-session reliability of short-interval intracortical inhibition measured by threshold tracking TMS

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ABSTRACT

Paired-pulse transcranial magnetic stimulation (TMS) using fixed test stimuli suffers from marked variability of the motor evoked potential (MEP) amplitude. Threshold tracking TMS (TT-TMS) was introduced to overcome this problem. The aim of this work was to describe the absolute and relative reliability of short-interval intracortical inhibition (SICI) using TT-TMS. Cortical excitability studies were performed on twenty-six healthy subjects over three sessions (two recordings on the same day and one seven days apart), with MEPs recorded over abductor pollicis brevis. Reliability was established by calculating the standard error of the measurements (SEm), minimal detectable change (MDC) and intraclass correlation coefficient (ICC). Resting motor threshold and averaged SICI presented the lowest SEm and highest ICCs. SICI at 1 ms showed a higher SEm than SICI at 3 ms, suggesting different physiological processes, but averaging SICI over a number of intervals greatly increases the reproducibility. The variability was lower for tests undertaken at the same time of day seven days apart compared to tests performed on the same day, and in both instances the ICC for averaged SICI was ≥0.81. The MDC in averaged SICI was reduced from 6.7% to 2% if the number of subjects was increased from one to eleven. In conclusion, averaged SICI is the most reproducible variable across paired-pulse TT-TMS measures, showing an excellent ICC. It is recommended that, in longitudinal studies, testing be performed at the same time of day and that changes in cortical excitability should be measured and averaged over a number of interstimulus intervals to minimise variability.

1. Introduction

Transcranial magnetic stimulation (TMS) has been used to assess cortical excitability using a paired-pulse paradigm, in which short-interval intracortical inhibition (SICI) has been defined as the standard method to estimate excitability in the $GABA_A$-ergic circuits in the human cortex [1,2]. The assessment of SICI, using the traditional 'constant stimulus' paired-pulse technique is affected by the variability in motor evoked potential (MEP) amplitude from stimulus to stimulus, which has been shown to be up to 200% for single-pulse stimuli [3]. To overcome this limitation, the threshold tracking TMS (TT-TMS) technique was developed, in which the threshold needed to produce a constant target MEP (0.2 mV) is tracked [4,5]. In recent years, TT-TMS has been used to explore several neurological disorders, particularly in amyotrophic lateral sclerosis (ALS) [6]. In addition, TT-TMS has been utilized to interrogate brain physiology, such as cortical modifications following exercise and the mechanisms of activity-dependent fatigue [7] and fine motor control [8].

In recent years the effects of age and gender [9] and hand dominance [10] have been explored using TT-TMS but the variability and reliability of SICI using this particular paradigm have not been assessed in a systematic fashion. TMS measures have shown significant within- and between-subject variability in 'constant stimulus' paired-pulse paradigms, limiting clinical utility. This variability can in part be attributed to known intrinsic fluctuations in neuronal excitability and subject-related factors, including medication [11,12]. Moreover, comparisons between these studies have been challenging due to a number of methodological differences in the muscles tested, stimulation

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protocols (e.g. number of ISI), type of coil and statistical analysis [13].

Reliability is defined as the ability of an instrument to give accurate and consistent measures ("free of error") in stable subjects [14], and includes the degree to which the measurements remain the same over time (e.g. test-retest), as assessed by the same rater at different times (e.g. intra-rater) or by different raters at the same time (e.g. inter-rater) [15]. Exploring reliability is a crucial step in the validation of any new technique, as an unreliable measure may generate large systematic and random errors, with resultant invalid measurements [16]. The concept of reliability can be divided into two subtypes: absolute reliability and relative reliability. Absolute reliability refers to the degree to which repeated measurements vary within stable subjects, and is therefore useful for establishing how suitable a measure is to track longitudinally [17]. Absolute reliability is measured using the standard error of the measurement (SEm), from which the minimal detectable change (MDC) can be estimated. The MDC reflects the minimal change (i.e the smallest increase or decrease) required in a subject between measurements to be confident at the 95% level that a change is truly significant [18]. That is, when the MDC remains undefined, it is unclear if a detected change represents a 'real' change or is just due to 'noise'. On the other hand, relative reliability is usually expressed using the intra-class correlation coefficient (ICC), which relates how well subjects maintain their position relative to each other over repeat measurements [16]. This reliability subtype is most useful for diagnostic and prognostic purposes, as it evaluates how well a measure can distinguish subjects from each other [13,17]. To our knowledge, the reliability of SICI using TT-TMS has not previously been evaluated. Therefore, the present study aimed to determine the absolute and relative test-retest reliability (within-day and between-day) of SICI as a measure of cortical function.

2. Materials and methods

2.1. Subjects and study design

Twenty-six healthy subjects (15 males and 11 females) were recruited from staff and relatives of patients attending the ForeFront Clinic at the Brain and Mind Centre, The University of Sydney, Australia. All participants provided written informed consent in accordance with the Declaration of Helsinki. The research was approved by the Human Research Ethics Committee of the University of Sydney.

The inclusion criteria were: age over 18 years; absence of neurological disorders; and absence of medication known to affect nerve function. Exclusion criteria included history of seizures, intracranial metallic implants or a pacemaker [19]. The protocol recommendation for each TMS session specified cessation of caffeine for 12 h, cessation of alcohol for 24 h and avoidance of exhaustive exercise for 48 h. All subjects completed a TMS safety questionnaire before enrolling in the study.

Protocol design followed recommendations of the International Federation of Clinical Neurophysiology (IFCN) [20] and a recently published systematic review of TMS reliability [13]. Three identical testing sessions were used to assess the test-retest reliability (within-day and between-day) of TT-TMS. Subjects were studied over two days, 7 days apart. On the first day, two consecutive studies were performed: the first session in the morning (session A, between 9:00 and 10:00 a.m.) and the second session 3 h later (session B). On the second day (7 days later) the TMS session was repeated once in the morning (session C, between 9:00 and 10:00 am). Each TMS session lasted 20 min. No experimental interventions were given between sessions. All TMS studies were performed on the dominant side, which was determined using the revised Edinburgh Handedness Inventory [21]. All TMS measurements and analyses were undertaken by the same rater (JMM), a clinical neurophysiologist with more than 5 years of experience in TMS.

2.2. Threshold tracking TMS

Cortical function was assessed using TT-TMS as previously described [4]. The following TMS parameters were recorded in each session: resting motor threshold (RMT), SICI at 1 ms, SICI at 3 ms, peak SICI and averaged SICI (between 1–7 ms).

Subjects were comfortably seated with their hands pronated in a relaxed position. Surface EMG was recorded over the abductor pollicis brevis (APB) using 5-mm Ag/AgCl surface electrodes, following standard recommendations [22]. The motor evoked potentials (MEP) were amplified (1 mV/V) and band-pass filtered (2 Hz–2 kHz) using a purpose-built amplifier. The amplified signals had mains frequency contamination removed on-line using a HumBug 50/60 Hz Noise Eliminator (Quest Scientific; North Vancouver, BC, Canada) and were then digitised with a 16-bit data acquisition system (NI-USB6251; National Instruments; Austin, TX, USA). All the MEPs were recorded at rest and EMG activity was monitored online to ensure maximal muscle relaxation.

Cortical function was evaluated using a 90-mm circular coil oriented to induce current flow in the posterior-anterior direction over the motor cortex (M1), with currents generated by two magnetic stimulators connected via a BiStim system (Magstim Co., Whitland, South West Wales, UK). The coil was initially centred over the vertex and then moved in anterior-posterior and medial-lateral directions in order to find the optimal position for evoking a MEP from the thenar muscles using minimal stimulus intensity. The TT-TMS technique automatically adjusts (or tracks) the stimulator output to elicit a target MEP of 0.2 mV [23]. RMT was defined as the stimulus intensity required to elicit the target MEP, and recorded as a percentage of the maximum stimulator output. Using a paired-pulse paradigm, a subthreshold conditioning stimulus set to 70% of RMT preceded the test stimulus at increasing interstimulus intervals (ISIs) as follows: 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 7 ms [4,9]. SICI was determined as the increase in the test stimulus intensity required to evoke the target MEP and was calculated off-line using the following formula:

$$\text{SICI}(\%) = (\text{Conditioned test stimulus intensity} - \text{RMT})/\text{RMT} \times 100$$

Data acquisition and stimulus delivery were performed using QTRACS software and the off-line analysis of the TMS variables was done using QTRACP software (© Professor Hugh Bostock, Institute of Neurology, University College London, UK).

2.3. Data analysis

Data distribution was assessed using the Shapiro-Wilk test and heteroscedasticity (when the variability of a dependent variable is unequal across the range of values of an independent variable that predicts it) was analysed with Levene's test.

To evaluate the absolute reliability, the SEm and the MDC were determined. The SEm was calculated using the following formula: $SEm = \sqrt{MSE}$, which uses the mean squared error (MSE) defined from an ANOVA test performed on test and re-test measurements. The SEm was also expressed as a percentage of the pooled mean from both testing sessions (SEm%) according to published recommendations [17,24]. We used a cut-off value of 10% to define a low SEm% [17]. The MDC was calculated from SEm using the following formula: $MDC = SEm * 1.96 * \sqrt{2}$ [25]. Moreover, MDC was used to determine a real change for a group mean (MDC_{group}), using the following formula: $MDC\ group = MDC/\sqrt{n}$, where n represents the sample size [30,31]. ICC was used to evaluate the relative reliability. Our study considered ICC scores to be poor if ≤ 0.20; fair from 0.21 to 0.40; moderate from 0.41 to 0.60; good from 0.61 to 0.80 and excellent if ≥ 0.81 [26]. The ICC was determined using the ICC (2,k) model: Two-way random average measure, absolute agreement.

For comparison of continuous variables with normal distribution we used unpaired and paired Student's *t*-tests. Multiple comparisons were established using repeated measures analysis of variance (ANOVA). Net and absolute differences in TMS parameters were determined between TMS sessions. Pearson's correlation coefficient was used to assess the association between variables collected in each TMS session using the net difference between sessions A and B for within-day comparisons (Δ_{B-A}) and sessions A and C for between-days comparisons (Δ_{C-A}). These analyses explored: (i) the relationship between the net difference in RMT and the net difference in SICI at 1 ms, SICI at 3 ms, and averaged SICI and (ii) the relationship between the net difference in SICI at 1 ms and the net difference in SICI at 3 ms. Finally, correlation analyses were performed on the absolute value of the inter-session difference ($|\Delta_{B-A}|$ and $|\Delta_{C-A}|$), as a measurement of the variability between TT-TMS sessions. This analysis explored the relationship between the absolute difference in TT-TMS measures with age, gender and revised Edinburgh Handedness Inventory score. Differences were considered statistically significant at a value of $p < 0.05$. All statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software Inc., CA, USA) and SPSS Statistics version 22 (IBM Corp., Armonk, New York).

3. Results

3.1. Sample characteristics and TMS raw data

All twenty-six subjects completed the three TMS sessions. The mean age of the group was 31.3 ± 6.8 years (range 19–50). In the two subjects who were left-handed the TT-TMS study was performed on their left APB (dominant side). All participants tolerated the TT-TMS sessions with no adverse effects recorded.

RMT and SICI variables had normal distribution and heteroscedasticity was not detected across the data. Results of cortical function established that all indices (RMT, SICI at 1 ms, SICI at 3 ms, peak SICI and averaged SICI) were similar for within-day and between-day sessions (Supplementary Table 1) and after compared all sessions (repeated measures ANOVA, minimum p-value = 0.344). All resultant values were consistent with normative TT-TMS data values [9].

3.2. Absolute reliability

From the cortical measures, only RMT showed a low level (< 10%) of SEm%, which was 5.8% for the within-day and 5.5% for between-days comparisons (Table 1). For paired-pulse TT-TMS parameters, larger SEm% levels were obtained for SICI at 1 ms, SICI at 3 ms, peak SICI and averaged SICI. Specifically, SICI at 1 ms presented the highest and averaged SICI the lowest SEm% across paired-pulse TMS variables.

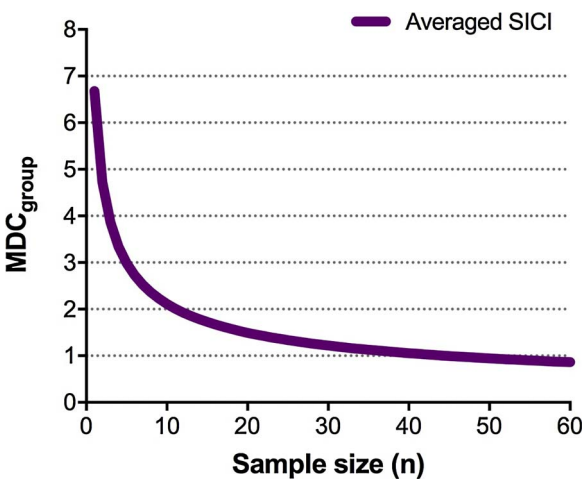

Fig. 1. Minimal detectable changes of averaged SICI and sample size effect. The MDC for between-day comparisons of averaged SICI was 6.7% for a single subject, but was dramatically reduced when estimated using the MDC_{group}, even for small sample sizes.

The SEm% for averaged SICI was 28.3% for the within-day comparison and 19.4% for the between-days comparison, which suggests a lower relative error for tests done seven days apart than tests performed on the same day. For all other paired-pulse TT-TMS variables, between-days comparisons also displayed lower relative error than within-day comparisons. MDC results also followed this pattern with lowest results seen for RMT and averaged SICI in comparison with the other variables. Regarding the application of MDC scores obtained from this study, we found that averaged SICI should change by more than 6.7% to be considered a true difference and not due to random variation. Importantly, the MDC allows sample size calculations for a given MDC_{group}. Specifically, in the case of averaged SICI, an increase of the sample size from one to eleven would decrease the MDC_{group} from 6.7% to 2%, and an MDC_{group} of 1% would require 44 subjects (Fig. 1).

3.3. Relative reliability

Excellent relative reliability (defined as an ICC ≥ 0.81) was observed for RMT and averaged SICI for both within-day and between-days comparisons (Table 1). SICI at 3 ms also displayed excellent reliability but only for between-days comparisons. The highest ICC was observed for averaged SICI obtained with between-days comparison (ICC = 0.95), representing the most reliable paired-pulse TT-TMS variable (Fig. 2). All other variables presented good relative reliability, with an exception of SICI at 1 ms (within-days comparison), which showed only moderate reliability (ICC = 0.39). In addition, all paired-

Table 1
Within-day and between-day reliability of paired-pulse TT-TMS.

Cortical variables	Standard error for the measurement (percentage of SEm,%)		Minimal detectable change		Intraclass correlation coefficient (95% CI)	
	Within-day	Between-days	Within-day	Between-days	Within-day	Between-days
RMT (MSO, %)	3.21 (5.76)	3.00 (5.45)	8.80	8.32	0.91 (0.79–0.95)	0.91 (0.79–0.96)
SICI at 1 ms (%)	5.58 (71.15)	3.60 (40.29)	15.47	9.98	0.39 (−0.35–0.73)	0.79 (0.52–0.91)
SICI at 3 ms (%)	7.56 (37.68)	5.07 (25.99)	20.96	14.07	0.72 (0.44–0.89)	0.91 (0.79–0.96)
Peak SICI (%)	7.55 (33.54)	6.89 (30.04)	20.9	19.11	0.72 (0.37–0.88)	0.79 (0.53–0.91)
Averaged SICI (ISI 1–7 ms, %)	3.51 (28.29)	2.41 (19.39)	9.75	6.68	0.88 (0.74–0.95)	0.95 (0.89–0.98)

TT-TMS, threshold tracking transcranial magnetic stimulation; 95% CI, 95% confidence intervals; SEm, standard error for the measurement; RMT, resting motor threshold; MSO, maximum stimulator output; SICI, short-interval intracortical inhibition; ISI, interstimulus interval.

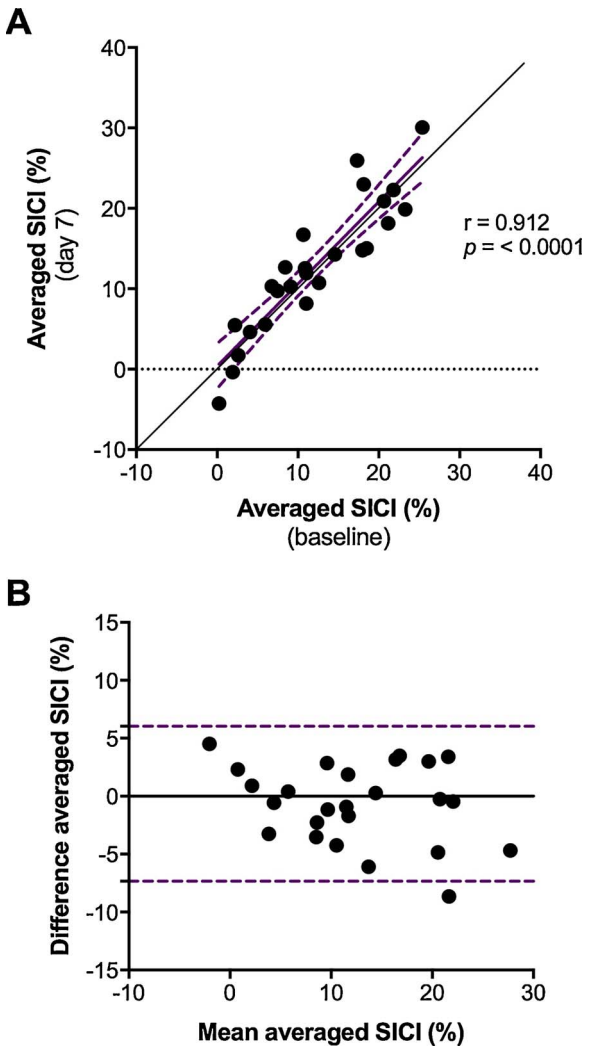

Fig. 2. Test-retest reliability of averaged SICI measured by TT-TMS. (A) Correlation scatter plot of averaged SICI values between baseline and day 7 sessions, with the regression line and confidence intervals (95% CI). The uninterrupted black line represents the line of equality if all values at test 1 were equal to all values at test 2; r, Pearsońs correlation coefficient. Note that the regression line corresponds closely to the line of equality. (B) Distribution plots from Bland–Altman test showing mean averaged SICI (%) against differences between measurements for baseline and day 7 sessions (between-day comparison), showing the agreement between the two different measurements; dotted lines represent ± 1.96 standard deviations of the difference.

pulse TT-TMS variables presented higher ICC for tests done seven days apart than tests performed on the same day.

3.4. Analysis of net and absolute difference between TMS sessions

Results of net difference between TMS sessions were similar for within-day and between-day sessions (Supplementary Table 2). Regarding the relationship between changes in RMT and paired-pulse TT-TMS variables, we found that the net difference in RMT was significantly correlated with the net difference in SICI at 3 ms, both for within-days ($r = 0.415$, $p = 0.044$) and between-days comparisons ($r = 0.446$, $p = 0.028$). The net difference in RMT was not correlated with changes in SICI at 1 ms or averaged SICI. In addition, the net difference in SICI at 1 ms did not correlate significantly with the net difference in SICI at 3 ms.

Regarding the analysis of the absolute difference between TMS session, we found a significantly higher absolute difference in SICI at 3 ms for the within-day comparison (within-day 8.4 ± 6.5%; between-day 5.7 ± 4.2%, $p = 0.033$). Also, there was a trend for a higher absolute difference in averaged SICI for the within-day comparison (within-day 3.7 ± 3.1%; between-day 2.7 ± 2.1%, $p = 0.073$). Moreover, there were no significant differences between males and females in the absolute difference of paired-pulse TT-TMS variables (Fig. S1). Finally, regarding the correlation analysis, no significant correlations were observed between the absolute difference in any of the paired-pulse TT-TMS variables with age, gender or revised Edinburgh Handedness Inventory score.

4. Discussion

The present study determined the reliability of measures of cortical excitability obtained with TT-TMS in healthy controls, using variance calculated from within-day and between-days test-retest comparisons. In general, measurement error was low for RMT, but all paired-pulse TT-TMS variables had a measurement error over 10%. However, most TT-TMS variables presented good to excellent ICCs, with the highest ICC obtained for averaged SICI in the between-days test-retest comparison. Importantly, these results quantify the overall reliability of TT-TMS measurements, crucial to assess the ability of this technique to discriminate between individual subjects or patients within a sample.

This is the first study to explore the reliability of SICI measured using TT-TMS, and our results can only be compared with the reliability data obtained using the “constant stimulus” TMS method [27–29]. However, a recent systematic review published by Beaulieu and colleagues underlined the weakness of previous studies, which were affected by several methodological and statistical difficulties [13]. Given the heterogeneity across studies there is still limited evidence on the reliability of TMS variables. Recently however, Shambra and colleagues described the reliability of single-rater test-retest design in older healthy controls and patients with subacute and chronic stroke, recording the MEP from the first dorsal interosseous, applying a rigorous methodology [17]. In the healthy control group they found a low SEm% for RMT (< 10%), but a higher SICI SEm%, ranging from 24.28 to 40.83%, together with excellent ICCs for RMT, but moderate and good ICCs for SICI ranging from 0.44 to 0.78. In another recent study, Hermsen and colleagues (2016) explored TMS reliability in 93 healthy subjects finding an excellent ICC for RMT (ICC = 0.82), but a moderate ICC for SICI (ICC = 0.38) [30]. However, ICC results can only be generalized between studies if they have the same sample characteristics and variance [17]. Furthermore, most of these “constant stimulus” studies have determined SICI using just one ISI to quantity SICI, commonly 3 ms, which significantly differs from the paired-pulse threshold-tracking protocols which use 9 ISIs (from 1 to 7 ms). These differences in methodology make it challenging to compare reliability studies between TMS paradigms accurately. Nevertheless, in the present study, the TT-TMS protocol has lower measurement error and higher ICCs for SICI (particularly for averaged SICI), than published studies using the “constant stimulus” method.

The relatively large measurement error for paired-pulse TT-TMS variables limits their ability to identify small changes in longitudinal studies of individual subjects with confidence. Specifically, SEm% was higher for SICI at 1 ms, SICI at 3 ms and peak SICI than averaged SICI. SICI at 1 ms was the least reproducible parameter, showing SEm% up to 71.2%. This inhibitory period has been associated with two possible phenomena: relative refractoriness of cortical axons with secondary resynchronisation of cortico-cortical and corticomotoneuronal volleys [23,31], and/or synaptic processes driven by activation of cortical inhibitory circuits different to the circuits involved in the generation of SICI at 3 ms [7,32]. The difference in measurement error and ICCs between SICI at 1 ms and SICI at 3 ms are consistent with the view that two distinct physiological mechanisms are involved in these two SICI phases. In the correlation analysis we found a positive correlation amongst the net difference in RMT and SICI at 3 ms between sessions, which suggests that the variability of RMT and SICI at 3 ms are related. Specifically, the increase in RMT between sessions is associated with an

increase in SICI at 3 ms. This finding may support that these two parameters could be affected similarly by extrinsic and intrinsic factors able to modulate central excitatory and inhibitory circuits [11,12].

Interestingly, absolute and relative reliability were better for test-retest comparisons performed at the same time of day on different days than within the same day. Similarly there was a significantly higher absolute difference in SICI at 3 ms for the within-day comparison. These findings could be due to modulation of intracortical circuits by circadian rhythms [33,34]. Specifically, Lang and colleagues have shown that GABA-mediated intracortical inhibition, particularly LICI and cortical silent period, progressively decreased during the day [33]. The findings from the present study suggest that testing would be more reproducible if performed at the same time of day for repeat studies.

Variables such as age, gender, handedness, hormonal changes, and glucose levels could all impact on cortical excitability, and contribute to the variability of SICI [35–39]. Interestingly, it has been demonstrated that cortical inhibition is lower in males than females, given that progesterone may increase cortical inhibition through enhancing GABAergic function [38]. However, in this study, the variability of SICI did not correlate with age, gender and handedness. Further studies may shed light on the effect of hormonal status on the reproducibility of cortical excitability parameters.

The MDC score is a useful parameter to determine the measurement changes needed to exceed the measurement "noise" of a single subject. On the other hand, by increasing the sample size, the MDC_{group} becomes smaller, allowing detection of smaller average measurement changes. For the averaged SICI estimated in the current study (between-day comparison), an increase in the sample size from one to eleven decreases the MDC_{group} from 6.7% to 2%. Therefore, TT-TMS measures could be used to detect a difference induced by an intervention in a group, even if the same test may be less useful to evaluate changes in a single subject.

From a clinical point of view TT-TMS has largely been used to date to study ALS patients. Using this technique, several studies have described the significance of SICI across ALS phenotypes, and this has been described as an early feature in sporadic and familial ALS [6,40,41,42]. Moreover, a recent study established that a SICI lower than 5.5% differentiated ALS from ALS mimics disorders with a sensitivity of 73.2% and specificity of 80.8% at an early disease stage [42]. It is relevant to point out that the reliability of a tool is unique to each population, given that pathological conditions can impact on the variability due to changes in the underlying physiological processes. Therefore, further studies would need to address the reliability of TT-TMS in their respective disease cohorts, such as stroke or ALS, to establish the utility of this tool in the specific clinical context.

In summary, our findings suggest that averaged SICI is the most reproducible paired-pulse TT-TMS variable, showing the highest ICC, and that variability can be minimised by testing subjects at the same time of day. These reliability characteristics suggest that averaged SICI is the most appropriate variable to distinguish individuals for diagnostic and/or prognostic purposes. In addition, the present results suggest that changes in cortical excitability should be measured and averaged over a number of interstimulus intervals to reduce variability of single measurements. It is likely that, but remains to be established whether these same insights are applicable to conventional constant-stimulus paired-pulse protocols and within specific patient populations. Finally, this study provides insight into the ability of TT-TMS to be used for diagnosis, prognosis and for longitudinal studies.

Conflict of interest

Drs Matamala, Howells, Dharmadasa, Trinh, Ma and Vucic report no disclosures. Drs Kiernan and Burke serve as Editors-in-Chief of *Journal of Neurology, Neurosurgery and Psychiatry* and *Clinical Neurophysiology Practice*, respectively.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neulet.2018.02.065.

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