Published in final edited form as:

Psychiatry Res. 2018 September ; 267: 575–581. doi:10.1016/j.psychres.2018.06.014.

Test-retest reliability of short-interval intracortical inhibition and intracortical facilitation in patients with schizophrenia

Xiaoming Du* and L. Elliot Hong

Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Impaired short-interval intracortical inhibition (SICI) elicited by paired-pulse TMS (ppTMS) has emerged as one of the most consistent TMS findings in patients with schizophrenia. Reduction of SICI has been reproducibly found, suggesting that SICI may be a new biomarker indexing the inhibitory dysfunction in schizophrenia. This study evaluated whether SICI has the test-retest reliability suitable for clinical trial and research applications. SICIs, intracortical facilitation (ICF) and other ppTMS effects were obtained using inter-stimulus intervals (ISIs) from 1 to 500 ms, on 2 occasions about 3~4 weeks apart in patients with schizophrenia and healthy individuals. Acceptable test-retest reliabilities were found for SICI (at 1 and 3 ms ISIs) in both patients and controls (all intraclass correlation coefficients $r > 0.6$). However, test-retest reliability in longer ISIs and in ICF were modest or poor. To our knowledge, this is the first study demonstrated the acceptable reliability of SICI measure in patients with schizophrenia. The data support SICI as a reliable biomarker for schizophrenia.

Keywords

schizophrenia; SICI; reliability; TMS; intersession

1. Introduction

Abnormal inhibitory functions are commonly observed in schizophrenia and many neuropsychiatric conditions (Radhu et al., 2013; Rogasch et al., 2014). Reliable biomarkers indexing inhibitory dysfunctions for schizophrenia have been sought after for decades. Reduced short-interval intracortical inhibition (SICI) is the most consistently replicated abnormality using transcranial magnetic stimulation (TMS) across studies (Bunse et al., 2014), although there is a lack of data on its test-retest reliability in schizophrenia. Establishing SICI's reliability is a prerequisite for developing this novel biomarker for inhibitory dysfunction in schizophrenia.

*Correspondence to Dr. Du, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228, Tel: 410 402 6828, Fax: 410 402 6023, xdu@mprc.umaryland.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

SICI is an intriguing TMS method to noninvasively investigate cortical inhibition *in vivo*. Specifically, when a subthreshold TMS pulse is delivered to motor cortex and followed by a suprathreshold pulse, the first pulse will have an inhibitory effect on the motor-evoked potentials (MEPs) evoked by the second pulse if the inter-pulse interval is short (e.g., 1–6 ms), which is known as SICI. On the other hand, if the interval between the 2 pulses are longer (e.g., 9–25 ms), a facilitatory effect will be observed, which is termed intracortical facilitation (ICF) (Kujirai et al., 1993; Maeda et al., 2002; McClintock et al., 2011; Rosenkranz and Rothwell, 2003; Russmann et al., 2009; Saisanen et al., 2011; Udupa et al., 2010).

Abnormal SICI has been reported in individuals at high risk for developing schizophrenia (Hasan et al., 2012), and in first-episode (Wobrock et al., 2009), recent-onset (Hasan et al., 2011), and chronic schizophrenia patients (Bunse et al., 2014; Fitzgerald et al., 2002; Hasan et al., 2011; Pascual-Leone et al., 2002; Radhu et al., 2013), and also in medicated (Pascual-Leone et al., 2002) and un-medicated patients (Daskalakis et al., 2002; Fitzgerald et al., 2004). SICI strength is correlated with positive symptoms (Daskalakis et al., 2002; Daskalakis et al., 2008; Liu et al., 2009; Wobrock et al., 2008) and cognitive impairments (Du et al., 2017; Mehta et al., 2014; Takahashi et al., 2013). A recent study of Lindberg et al. (2016) explored the task-related modulation of SICI and found patients with schizophrenia showed significantly reduced SICI when inhibiting prepared finger lift compared with siblings of patients and healthy controls (Lindberg et al., 2016). Pharmacological studies indicated that SICI is mediated by gamma-aminobutyric acid (GABA) neurotransmitter because administration of GABAA receptor agonist such as benzodiazepines increases the size of SICI (Di Lazzaro et al., 2000; Hanajima et al., 1998; Ilic et al., 2002; Ziemann, 2004; Ziemann et al., 2015). In comparison, ICF is affected by both N-methyl-D-aspartate (NMDA) (Liepert et al., 1997; Ziemann et al., 1996b) and GABA receptor agents (Ziemann et al., 1996a; Ziemann et al., 2015), suggesting a more complex neural mechanism underlying ICF. Because GABA and NMDA dysfunctions are etiologically highly relevant to schizophrenia (Cohen et al., 2015; Taylor and Tso, 2015), SICI and/or ICF may provide new biomarkers to aid the development of novel pharmaceuticals targeting these mechanisms in schizophrenia. To this end, a critical feature for biomarkers to be useful is a good test-retest reliability. The test-retest reliability of SICI is acceptable in healthy controls (Beaulieu et al., 2017; Du et al., 2014; Fleming et al., 2012) while the reliability of ICF appears more variable (Du et al., 2014; Fleming et al., 2012; Hermesen et al., 2016; Ngomo et al., 2012; O'Leary et al., 2015). Whether SICI can be reliably obtained from the same group of patients in different occasions has not been evaluated.

In the present study, we aim to evaluate the reliability of ppTMS measures (e.g., SICI and ICF) for both healthy individuals and patients with schizophrenia. For control purpose, we measured ppTMS with a wide range of inter-stimulus intervals (ISIs). The ppTMS measures were obtained in two sessions that were 3–4 weeks apart. where the reliabilities of MEP amplitudes and ppTMS effects were assessed.

2. Methods

2.1 Participants

Patients with schizophrenia ($n=25$, age 21–61 years) and healthy controls ($n=29$, age 20–57 years) were recruited (**Table 1**). The Structured Clinical Interview for DSM-IV (SCID) was used to confirm the diagnoses in patients and no current DSM-IV Axis I diagnoses in controls. Major medical and neurological illnesses, history of head injury with loss of consciousness, substance dependence within the past 6 months, or substance abuse within 1 month (except nicotine or marijuana) were grounds for exclusion. Except for five medication-free participants, all schizophrenia patients were on antipsychotic medications, including 1 taking typical antipsychotics, 18 taking atypical antipsychotics, and 1 taking a combination of antipsychotic types. Seven patients and none healthy controls were on anti-depression medication. There was no change in medication or dose of medication between the two testing sessions. Brief Psychiatric Rating Scale (BPRS) was administered to patients for assessing their overall clinical symptoms (BPRS total score) (Hedlund and Vieweg, 1980). All subjects gave their written informed consent. The test-retest reliability data from 20 of the 29 healthy controls have been reported in another study (Du et al., 2014).

2.2 TMS and electromyography procedure

TMS pulses were delivered through a figure-of-eight coil (70 mm diameter) using Magstim 200 BiStim stimulators (Magstim Co., Whitland, UK). Participants were scanned using a Siemens 3T MRI (Erlangen, Germany) system equipped with a 32-channel phase array head coil prior to TMS assessment. A high resolution T1-weighted image (0.8 mm isotropic) was obtained (TE/TR/TI=3.04/2100/785 ms, flip angle=11 degrees) for TMS localization. The structural image of each subject was imported into Brainsight™ Navigation system (Rogue Research Inc, Montreal, Canada) to allow individualized anatomic positioning of the coil. The coil was held pointing backward with a 45° angle from the midline over left motor cortex where TMS induced the maximum response from right first dorsal interosseous (FDI) muscle (Brasil-Neto et al., 1992; Kammer et al., 2001; Werhahn et al., 1994). The TMS site used for the first session was marked in the Brainsight system. In the second session, we used the TMS site from the first session as the starting point for search until the maximum response was identified, which was on or slightly different from the location of the first session (Du et al., 2014). The M1 coordinates (MNI; mean $\pm$ SD) from the two sessions were (-37.5 ± 4.4 , -10.8 ± 7.6 , 60.6 ± 6.0) and (-38.0 ± 5.0 , -11.4 ± 7.8 , 60.5 ± 6.1), respectively, in healthy controls. The M1 coordinates from the two sessions in patients with schizophrenia were (-39.4 ± 4.0 , -13.5 ± 5.1 , 57.3 ± 5.5) and (-39.4 ± 4.2 , -13.3 ± 5.7 , 57.6 ± 5.7), respectively. The Euclidean distances between the M1 sites in the two sessions were 1.9 ± 2.0 mm (mean $\pm$ SD) in healthy controls and 1.6 ± 1.7 mm in patients with schizophrenia. Within each session, the misalignment from coil to TMS site was kept less than 1–2 mm. Surface electromyography (EMG) was recorded from right FDI. EMG was recorded with NeuroScan Synamp² amplifier (Charlotte, NC) amplified (gain of 10) and sampled at 1000 Hz (Du et al., 2015; Sommer et al., 2001). Peak-to-peak amplitude of the motor-evoked potentials (MEP) was measured. Subjects were instructed to remain relaxed throughout the application of TMS, while the muscle was monitored for relaxation through

visual inspection of the EMG. The EMG root mean squared (RMS) value from 5 to 50 ms prior to TMS pulse was verified to ensure appropriate resting levels for each trial.

2.3 Motor threshold and paired pulse paradigm

Resting motor threshold (RMT) was defined according to conventional criteria as the minimum intensity needed to elicit a MEP of $> 50 \mu\text{V}$ in at least 5 out of 10 consecutive stimuli (Rossini et al., 1994). RMT is reported as a percentage of the maximum stimulator output. The first subthreshold conditioning stimulus (CS) was at the intensity of 80% RMT and the intensity of the second, testing stimulus (TS) was suprathreshold (120% RMT), which have been reported for SICI and/or ICF (Garry and Thomson, 2009; Kujirai et al., 1993; Maeda et al., 2002; Orth et al., 2003). Many other studies set the intensity of TS to 1 mV (e.g., Fitzgerald et al., 2002; Mehta et al., 2014; Eichhammer et al., 2004) and our TS evoked MEP did not differ from 1 mV in both schizophrenia patients (all $p>0.05$) and healthy individuals (all $p>0.05$). Typically, SICI protocols include 1 and 3 ms ISIs to induce inhibition (Fisher et al., 2002; Roshan et al., 2003; Vucic et al., 2009), while ICF protocols are more variable although 9 to 15 ms ISIs can typically elicit facilitation (e.g., Saisanen et al., 2011; Wobrock et al., 2008). In order to cover variable range of potential inhibitory and facilitatory ISIs, 14 ISIs were tested: 1, 3, 6, 9, 12, 15, 18, 21, 30, 40, 80, 120, 200 and 500 ms. ISIs from 30 to 500 ms were rarely used (Nakamura et al., 1997) but were included to evaluate inhibition and facilitation over a wider range of ISIs as well as to identify potential patterns of inter-session variations across different ISIs. Single 120% RMT stimuli were delivered as a control condition (TS). A session included 6 trials for each ISI and 12 trials of TS. They were randomized and delivered in one session, with intertrial intervals that were also randomly assigned and jittered between 4 and 10 seconds. The two sessions were separated by about 3~4 weeks.

2.4 Data analysis

The modulation of the CS on the following TS was expressed as paired-pulse TMS (ppTMS) ratio ($\text{MEP}_{\text{ISI}} / \text{MEP}_{\text{TS}}$), such that values less than 1 reflect inhibitory responses and values more than 1 reflect facilitatory responses. A mixed-design analysis of variance (ANOVA) was conducted to examine effects of ISI variation across the 2 sessions, where ppTMS ratio of each ISI was the dependent variable, Session (2 sessions) and ISI (14 ISIs) were within-subject factors and Group (SZ and HC) as between-subject factor. Greenhouse-Geisser corrections were applied for ANOVA when the assumption of sphericity was not met. Post-hoc analysis for group differences on SICI (1 and 3 ms) and ICF (9, 12 and 15 ms) were evaluated using t-tests, two-tailed. The inter-session reliability was first assessed for raw MEP amplitudes and ppTMS ratio, respectively, using intraclass correlation coefficient (ICC) with a two way mixed effects model, based on the Shrout and Fleiss model (Shrout and Fleiss, 1979). The reliabilities of SICI, ICF and effects from other control ISIs were then evaluated by the same ICC procedure. By convention, ICC above 0.6 was considered acceptable: between 0.6 – 0.8 moderate and above 0.8 good reliability (Du et al., 2014; Portney and Watkins, 2000). Besides reliability measurements, we utilized Bland-Altman method to show the limits of agreement between the two sessions at each ISI (Bland and Altman, 1999). Because the differences between sessions largely depend on the level of averages, which is common in data from biomedical research (Ludbrook 2010), for each ISI,

we plotted difference/mean ratio against the mean of two sessions. The mean and 95% limits (i.e., 1.96 SD) were shown in the Bland-Altman plots.

3. Results

The demographic information was shown in **Table 1**. RMT was similar across sessions in healthy controls [$t(28)=1.61$, $p=0.12$] and schizophrenia patients [$t(24)=-0.69$, $p=0.50$], MEP amplitudes of TS (at 120% of the RMT stimulator strength) did not show significant difference between sessions in healthy controls [$t(28)=0.20$, $p=0.85$] and patients with schizophrenia [$t(24)=1.10$, $p=0.29$], suggesting a stable and comparable cortical excitability at motor cortex between sessions.

For ppTMS response ratios, the main effect of Session was not significant [$F(1, 274.9)=0.1$, $p=0.92$] and Session related interactions were not significant either [session $\times$ diagnosis ($p=0.96$), session $\times$ ISI ($p=0.70$), and session $\times$ ISI $\times$ diagnosis ($p=0.36$)] (**Figure 1**). At the pre-defined ISI for SICI (1 and 3 ms) and ICF (9, 12 and 15 ms), schizophrenia patients showed significantly reduced SICI at 1 [$t(33.73)=-2.77$, $p=0.009$] and 3 ms [$t(35.34)=-2.76$, $p=0.009$] ISIs, but not at 9 [$t(52)=0.40$, $p=0.69$] or 12 ms [$t(52)=0.43$, $p=0.67$], or 15 ms [$t(52)=-0.27$, $p=0.79$] ISIs compared with controls after merging the 2 sessions. None of the other ISI showed significant group differences (all $p>0.05$).

Raw MEP amplitudes showed satisfactory reliability across conditions with ICC at all ISIs to be above 0.6 (except for 80 ms ISI in the healthy control group with where the reliability was 0.59). Importantly, moderate or good test-retest reliabilities were obtained for the raw MEP amplitudes of TS in controls [ICC = 0.77, 95% confidence interval (CI): 0.51–0.89] and patients [ICC = 0.91, 95% CI: 0.79–0.96], This is important as TS MEP provides the denominator for all ppTMS ratio calculation (**Figure 2**).

The ICCs for 1 and 3 ms ISIs in the controls were 0.68 (95% CI: 0.33–0.85) and (95% CI: 0.36–0.86), respectively. In the patients, the ICCs were 0.64 (95% CI: 0.19–0.84) for 1 ms ISI and 0.69 (95% CI: 0.29–0.86) for 3 ms ISI (**Figure 3**). ICCs for the other ISI were also explored (Figure 3). Briefly, schizophrenia patients showed acceptable reliability at ICF at 9 ms (ICC = 0.63, 95% CI: 0.16–0.84) and 15 ms ISIs (ICC = 0.78, 95% CI: 0.50–0.90). However, ICF in healthy subjects showed poor reliability (all ICCs<0.6). Poor ICCs were also observed in other ISI from 30 to 500 ms.

The Bland-Altman plots for MEP amplitudes at typical SICI-ISIs (i.e., 1 and 3 ms ISIs), ICF-ISIs (9, 12, 15 ms ISIs) and TS were shown in Figure 4. Further, the plots for ppTMS ratio at SICI-ISIs and ICF-ISIs were shown in Figure 5. The Bland-Altman plots for all ISIs can be found in the supplementary materials (Figure S4 and Fig S5).

4. Discussion

In the current study, acceptable moderate test-retest reliabilities were observed at ISIs that evokes inhibition (i.e., SICI at 1 and 3 ms ISIs) in both groups, whereas poor reliabilities

were observed at ICF-related ISIs and other ISIs except for acceptable ICC at 9 and 15 ms ISIs in patient group.

Impaired SICI impairment was found in this group of schizophrenia patients, which is a replication of the majority of the data in the literature. However, to our knowledge, this is the first study addressing the reliability of SICI in schizophrenia. The ICC values on 1 and 3 ms ISIs SICI were above 0.6 for both healthy and patient groups, suggesting acceptable, but not great, test-retest reliabilities, which are consistent with the observation in healthy individuals (Boroojerdi et al., 2000; Corp et al., 2015; Du et al., 2014; Fleming et al., 2012; O'Leary et al., 2015; Matamala et al., 2018). An acceptable test-retest reliability 3~4 weeks apart is helpful also because many clinical trials exploring novel pharmaceutical mechanisms typically use 2 to 8 weeks of dosing to evaluate initial efficacy. Other ISIs under the current TMS protocol appeared poorly suited for research that relies on biomarkers with good test-retest reliability.

Schizophrenia patients also showed acceptable ICC based reliability of ICF at 9 and 15 ms ISIs but the reliability was poor in the controls. The reason for the poor ICCs in healthy individuals is unclear but is in line with some previous studies showing poor reliability for ICF in healthy adults (Fleming et al., 2012; Hermesen et al., 2016). One potential explanation is that the ppTMS output is determined by the dynamic balance between inhibition and excitation at motor cortex (Ni and Chen, 2008). The number of underlying neural sources of a measurement may largely affect its reliability. SICI is mainly mediated by GABAA receptor, while ICF is affected by both NMDA and GABA receptors (Ziemann, 2004; Ziemann et al., 2015). Therefore, SICI with less underlying neural sources may be more likely staying stable across sessions as compared with ICF which is affected by multiple underlying neural sources in healthy controls. It is well demonstrated that patients with schizophrenia have GABA abnormality, therefore, the ICF in schizophrenia patients might mainly affected by NMDA receptors as the contribution from GABA was reduced, which may lead to a higher reliability in patients as compared with healthy controls. However, further psychopharmacological studies are needed to test this hypothesis.

The intensity of TS can be determined by RMT (e.g., 120% RMT), by a threshold-tracking method (Vucic et al., 2006), or more commonly by the MEP amplitude induced by TS (e.g., 1 mV). The SICI deficit in schizophrenia has been observed with both the RMT-method (Du et al., 2017) and 1-mV MEP method (e.g., Fitzgerald et al., 2002; Mehta et al., 2014; Eichhammer et al., 2004). The TS intensity of 120% RMT was used here mainly because the studies evaluating the effects of TS intensity on ppTMS output often used RMT as a reference and showed that TS intensity of 120% RMT can induce robust SICI (e.g., Ilic et al., 2002; Garry and Thomson, 2009). Further, our present study is highly comparable to previous research on SICI reliability which used RMT-based TS intensity (e.g., Corp et al., 2015; O'Leary et al., 2015; Ngomo et al., 2012). Despite the fact that the MEP amplitudes induced by TS here in both groups did not significantly differ from 1 mV and using 120%RMT or 1-mV did not lead to significantly different reliability (Hashemirad et al., 2017), it should still be cautious to generalize the satisfactory reliability of SICI in schizophrenia patients observed here to studies using 1-mV TS or other TS intensity in SICI.

There are several factors that may potentially impact on the test-retest reliability, such as number of repetitions for each condition and whether neuronavigation was used for coil positioning. Although neuronavigation system was used to minimize the stimulation difference within and between sessions, one limitation of the present study was that the number of repetitions for each ppTMS condition was relatively small. Twenty trials have been suggested to get reliable SICI in healthy controls (Chang et al., 2016). It is possible that the low reliability observed at ICF and some other ISIs may be due to the small number of repetitions here, although all of them showed acceptable reliability of MEP amplitudes. In fact, the direct TMS outputs (raw MEP amplitude) showed good reliabilities across most ISIs in the current study. We used 6 trials for each ISI and 12 trials for TS, leaving open the question on whether the ICC for SICI and other ISIs may be further improved if more trials were used for each ISI, as others have suggested that increasing the number of trials may further help (Bastani and Jaberzadeh, 2012; Cavaleri et al., 2017; Goldsworthy et al., 2016; Ngomo et al., 2012). Neuronavigation system for coil positioning was used here to minimize potential differences between sessions (Bastani and Jaberzadeh, 2012; Cavaleri et al., 2017; Goldsworthy et al., 2016). By using the neuronavigation system, the coil orientation and position both within the sessions and between the sessions were monitored and kept constant, which should minimize potential variances induced by misplacement and movement of the coil. The impacts of medications on SICI reliability were not assessed, although by keeping each patient on their own medication and dose during the study, we should have minimized effects due to change of medication between sessions.

There are several limitations of the present study. Although 1 ms and 3 ms ISIs were commonly used to represent SICI in many studies (e.g., Fitzgerald et al., 2002; Hasan et al., 2011; Wobrock et al., 2010; Wobrock et al., 2008), the test-retest reliability at other ISIs (e.g., 2 ms and 4 ms, or more intervals between 1 and 3 ms) were not evaluated here. This need to be tested in the future research. No subject reported changes in medication or substance use between the two sessions. Cortical excitability at motor cortex can be represented by RMT and MEP evoked by TS. For both groups, there was no significant difference in RMT or TS evoked MEP between sessions, suggesting a comparable inter-session cortical excitability at motor cortex. However, possible changes in symptoms, life events and physical morbidities between sessions were not measured. Nonetheless, we argue that those potential changes, if exist, may not be able to explain the observed satisfactory reliability of SICI as they would more likely worsen the reliability. The sample sizes for patients with schizophrenia and healthy controls were relatively small. Future large sample studies are needed to confirm the findings of the present study.

In summary, we replicated the SICI impairment and found acceptable test-retest reliability of SICI in patients with schizophrenia, supporting SICI as a potential biomarker for indexing an inhibitory dysfunction in schizophrenia. The results addressed an important aspect of the research application of SICI as a biomarker for schizophrenia diagnostic, prognostic and clinical trial research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

LEH has received or plans to receive research funding or consulting fee on research projects from Mitsubishi, Your Energy Systems LLC, Neuralstem, EyeDirect, Taisho, Heptares, Pfizer, Sound Pharma, and Regeneron. All other authors declare no conflict of interest.

Funding

Support was received from NIH grants MH085646, MH103222, MH108148, MH067533, a NARSAD award, State of Maryland contract (M00B6400091), and a generous private philanthropic donation from the Clare E. Forbes Trust.

References

- Bastani A, Jaberzadeh S, 2012 A higher number of TMS-elicited MEP from a combined hotspot improves intra- and inter-session reliability of the upper limb muscles in healthy individuals. *PLoS One* 7 (10), e47582. [PubMed: 23077645]
- Beaulieu LD, Flamand VH, Masse-Alarie H, Schneider C, 2017 Reliability and minimal detectable change of transcranial magnetic stimulation outcomes in healthy adults: A systematic review. *Brain Stimul.* 10 (2), 196–213. [PubMed: 28031148]
- Bland JM, Altman DG, 1999 Measuring agreement in method comparison studies. *Stat. Methods Med. Res* 8 (2), 135–160. [PubMed: 10501650]
- Borojerdi B, Kopylev L, Battaglia F, Facchini S, Ziemann U, Muellbacher W, et al., 2000 Reproducibility of intracortical inhibition and facilitation using the paired-pulse paradigm. *Muscle Nerve* 23 (10), 1594–1597. [PubMed: 11003798]
- Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG, 1992 Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. *Electroencephalogr. Clin. Neurophysiol* 85 (1), 9–16. [PubMed: 1371748]
- Bunse T, Wobrock T, Strube W, Padberg F, Palm U, Falkai P, et al., 2014 Motor cortical excitability assessed by transcranial magnetic stimulation in psychiatric disorders: a systematic review. *Brain Stimul.* 7 (2), 158–169. [PubMed: 24472621]
- Cavaleri R, Schabrun SM, Chipchase LS, 2017 The number of stimuli required to reliably assess corticomotor excitability and primary motor cortical representations using transcranial magnetic stimulation (TMS): a systematic review and meta-analysis. *Systematic reviews* 6 (1), 48. [PubMed: 28264713]
- Chang WH, Fried PJ, Saxena S, Jannati A, Gomes-Osman J, Kim Y-H, et al., 2016 Optimal number of pulses as outcome measures of neuronavigated transcranial magnetic stimulation. *Clin. Neurophysiol* 127 (8), 2892–2897. [PubMed: 27156431]
- Cohen SM, Tsien RW, Goff DC, Halassa MM, 2015 The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. *Schizophr. Res* 167 (1–3), 98–107. [PubMed: 25583246]
- Corp DT, Rogers MA, Di Lazzaro V, Pearce AJ, 2015 Intrasession Reliability of Single and Paired Pulse TMS Evoked From the Biceps Brachii Representation of the Human Motor Cortex. *Brain Stimul.* 8 (3), 660–661. [PubMed: 25697589]
- Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S, 2002 Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Arch. Gen. Psychiatry* 59 (4), 347–354. [PubMed: 11926935]
- Daskalakis ZJ, Christensen BK, Fitzgerald PB, Moller B, Fountain SI, Chen R, 2008 Increased cortical inhibition in persons with schizophrenia treated with clozapine. *J. Psychopharmacol* 22 (2), 203–209. [PubMed: 18308816]
- Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, et al., 2000 Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clin. Neurophysiol* 111 (5), 794–799. [PubMed: 10802448]

- Du X, Choa FS, Summerfelt A, Tagamets MA, Rowland LM, Kochunov P, et al., 2015 Neural summation in human motor cortex by subthreshold transcranial magnetic stimulations. *Exp. Brain Res* 233 (2), 671–677. [PubMed: 25399245]
- Du X, Kochunov P, Summerfelt A, Chiappelli J, Choa FS, Hong LE, 2017 The role of white matter microstructure in inhibitory deficits in patients with schizophrenia. *Brain Stimul.* 10 (2), 283–290. [PubMed: 27867023]
- Du X, Summerfelt A, Chiappelli J, Holcomb HH, Hong LE, 2014 Individualized brain inhibition and excitation profile in response to paired-pulse TMS. *J. Mot. Behav* 46 (1), 39–48. [PubMed: 24246068]
- Fisher RJ, Nakamura Y, Bestmann S, Rothwell JC, Bostock H, 2002 Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. *Exp. Brain Res* 143 (2), 240–248. [PubMed: 11880900]
- Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J, 2002 A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. *Psychiatry Res.* 114 (1), 11–22. [PubMed: 11864806]
- Fitzgerald PB, Brown TL, Marston NA, Oxley T, De Castella A, Daskalakis ZJ, et al., 2004 Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. *Schizophr. Res* 71 (1), 17–26. [PubMed: 15374568]
- Fleming MK, Sorinola IO, Newham DJ, Roberts-Lewis SF, Bergmann JHM, 2012 The Effect of Coil Type and Navigation on the Reliability of Transcranial Magnetic Stimulation. *IEEE Trans. Neural Syst. Rehab. Eng* 20 (5), 617–625.
- Garry MI, Thomson RH, 2009 The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states. *Exp. Brain Res* 193 (2), 267–274. [PubMed: 18974984]
- Goldsworthy MR, Hordacre B, Ridding MC, 2016 Minimum number of trials required for within- and between-session reliability of TMS measures of corticospinal excitability. *Neuroscience* 320, 205–209. [PubMed: 26872998]
- Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, et al., 1998 Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. *J. Physiol. (London)* 509 (2), 607–618. [PubMed: 9575308]
- Hasan A, Nitsche MA, Rein B, Schneider-Axmann T, Guse B, Gruber O, et al., 2011 Dysfunctional long-term potentiation-like plasticity in schizophrenia revealed by transcranial direct current stimulation. *Behav. Brain Res* 224 (1), 15–2 [PubMed: 21645555]
- Hasan A, Wobrock T, Grefkes C, Labusga M, Levold K, Schneider-Axmann T, et al., 2012 Deficient inhibitory cortical networks in antipsychotic-naïve subjects at risk of developing first-episode psychosis and first-episode schizophrenia patients: a cross-sectional study. *Biol. Psychiatry* 72 (9), 744–751. [PubMed: 22502988]
- Hashemirad F, Zoghi M, Fitzgerald PB, Jaberzadeh S, 2017 Reliability of Motor Evoked Potentials Induced by Transcranial Magnetic Stimulation: The Effects of Initial Motor Evoked Potentials Removal. *Basic Clin. Neurosci* 8 (1), 43–50. [PubMed: 28446949]
- Hedlund Vieweg, 1980 The brief psychiatric rating scale (BPRS): a comprehensive review. *Journal of operational psychiatry* 11, 48–65.
- Hermesen AM, Haag A, Duddek C, Balkenhol K, Bugiel H, Bauer S, et al., 2016 Test-retest reliability of single and paired pulse transcranial magnetic stimulation parameters in healthy subjects. *J. Neurol. Sci* 362, 209–216. [PubMed: 26944150]
- Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U, 2002 Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. *J. Physiol* 545 (Pt 1), 153–167. [PubMed: 12433957]
- Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, Topka H, 2001 Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin. Neurophysiol* 112 (2), 250–258. [PubMed: 11165526]
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al., 1993 Corticocortical inhibition in human motor cortex. *J. Physiol* 471, 501–519. [PubMed: 8120818]
- Liepert J, Schwenkreis P, Tegenthoff M, Malin JP, 1997 The glutamate antagonist riluzole suppresses intracortical facilitation. *J. Neural Transm* 104 (11–12), 1207–1214. [PubMed: 9503266]

- Lindberg PG, Teremetz M, Charron S, Kebir O, Saby A, Bendjemaa N, et al., 2016 Altered cortical processing of motor inhibition in schizophrenia. *Cortex* 85, 1–12. [PubMed: 27770667]
- Liu SK, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ, 2009 The relationship between cortical inhibition, antipsychotic treatment, and the symptoms of schizophrenia. *Biol. Psychiatry* 65 (6), 503–509. [PubMed: 18950746]
- Ludbrook J, 2010 Confidence in Altman-Bland plots: a critical review of the method of differences. *Clin. Exp. Pharmacol. Physiol* 37 (2), 143–149. [PubMed: 19719745]
- Maeda F, Gangitano M, Thall M, Pascual-Leone A, 2002 Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS). *Clin. Neurophysiol* 113 (3), 376–382. [PubMed: 11897538]
- Matamala JM, Howells J, Dharmadasa T, Trinh T, Ma Y, Lera L, et al., 2018 Inter-session reliability of short-interval intracortical inhibition measured by threshold tracking TMS. *Neurosci Lett*.
- McClintock SM, Freitas C, Oberman L, Lisanby SH, Pascual-Leone A, 2011 Transcranial magnetic stimulation: a neuroscientific probe of cortical function in schizophrenia. *Biol. Psychiatry* 70 (1), 19–27. [PubMed: 21571254]
- Mehta UM, Thirthalli J, Basavaraju R, Gangadhar BN, 2014 Association of intracortical inhibition with social cognition deficits in schizophrenia: Findings from a transcranial magnetic stimulation study. *Schizophr. Res* 158 (1–3), 146–150. [PubMed: 25048423]
- Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H, 1997 Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. *J. Physiol* 498 (Pt 3), 817–823. [PubMed: 9051592]
- Ngomo S, Leonard G, Moffet H, Mercier C, 2012 Comparison of transcranial magnetic stimulation measures obtained at rest and under active conditions and their reliability. *J. Neurosci. Methods* 205 (1), 65–71. [PubMed: 22227444]
- Ni Z, Chen R, 2008 Short-interval intracortical inhibition: a complex measure. *Clin. Neurophysiol* 119 (10), 2175–2176. [PubMed: 18752992]
- O'Leary TJ, Morris MG, Collett J, Howells K, 2015 Reliability of single and paired-pulse transcranial magnetic stimulation in the vastus lateralis muscle. *Muscle Nerve* 52 (4), 605–615. [PubMed: 25620286]
- Orth M, Snijders AH, Rothwell JC, 2003 The variability of intracortical inhibition and facilitation. *Clin. Neurophysiol* 114 (12), 2362–2369. [PubMed: 14652096]
- Pascual-Leone A, Manoach DS, Birnbaum R, Goff DC, 2002 Motor cortical excitability in schizophrenia. *Biol. Psychiatry* 52 (1), 24–31. [PubMed: 12079727]
- Portney LG, Watkins MP, 2000 Foundations of clinical research: applications to practice. Prentice Hall.
- Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ, 2013 A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. *Clin. Neurophysiol* 124 (7), 1309–1320. [PubMed: 23485366]
- Rogasch NC, Daskalakis ZJ, Fitzgerald PB, 2014 Cortical inhibition, excitation, and connectivity in schizophrenia: a review of insights from transcranial magnetic stimulation. *Schizophr. Bull* 40 (3), 685–696. [PubMed: 23722199]
- Rosenkranz K, Rothwell JC, 2003 Differential effect of muscle vibration on intracortical inhibitory circuits in humans. *J. Physiol* 551 (Pt 2), 649–660. [PubMed: 12821723]
- Roshan L, Paradiso GO, Chen R, 2003 Two phases of short-interval intracortical inhibition. *Exp. Brain Res* 151 (3), 330–337. [PubMed: 12802553]
- Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al., 1994 Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr. Clin. Neurophysiol* 91 (2), 79–92. [PubMed: 7519144]
- Russmann H, Lamy JC, Shamim EA, Meunier S, Hallett M, 2009 Associative plasticity in intracortical inhibitory circuits in human motor cortex. *Clin. Neurophysiol* 120 (6), 1204–1212. [PubMed: 19435676]

- Saisanen L, Julkunen P, Niskanen E, Hukkanen T, Mervaala E, Karhu J, et al., 2011 Short- and intermediate-interval cortical inhibition and facilitation assessed by navigated transcranial magnetic stimulation. *J. Neurosci. Methods* 195 (2), 241–248. [PubMed: 21144864]
- Shrout PE, Fleiss JL, 1979 Intraclass correlations: uses in assessing rater reliability. *Psychol. Bull* 86 (2), 420–428. [PubMed: 18839484]
- Sommer M, Classen J, Cohen LG, Hallett M, 2001 Time course of determination of movement direction in the reaction time task in humans. *J. Neurophysiol* 86 (3), 1195–1201. [PubMed: 11535669]
- Takahashi S, Ukai S, Kose A, Hashimoto T, Iwatani J, Okumura M, et al., 2013 Reduction of cortical GABAergic inhibition correlates with working memory impairment in recent onset schizophrenia. *Schizophr. Res* 146 (1–3), 238–243. [PubMed: 23523695]
- Taylor SF, Tso IF, 2015 GABA abnormalities in schizophrenia: a methodological review of in vivo studies. *Schizophr. Res* 167 (1–3), 84–90. [PubMed: 25458856]
- Udupa K, Ni Z, Gunraj C, Chen R, 2010 Effect of long interval interhemispheric inhibition on intracortical inhibitory and facilitatory circuits. *J. Physiol* 588 (Pt 14), 2633–2641. [PubMed: 20519316]
- Vucic S, Cheah BC, Krishnan AV, Burke D, Kiernan MC, 2009 The effects of alterations in conditioning stimulus intensity on short interval intracortical inhibition. *Brain Res.* 1273, 39–47. [PubMed: 19332031]
- Vucic S, Howells J, Trevillion L, Kiernan MC, 2006 Assessment of cortical excitability using threshold tracking techniques. *Muscle Nerve* 33 (4), 477–486. [PubMed: 16315324]
- Werhahn KJ, Fong JK, Meyer BU, Priori A, Rothwell JC, Day BL, et al., 1994 The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. *Electroencephalogr. Clin. Neurophysiol* 93 (2), 138–146. [PubMed: 7512920]
- Wobrock T, Hasan A, Malchow B, Wolff-Menzler C, Guse B, Lang N, et al., 2010 Increased cortical inhibition deficits in first-episode schizophrenia with comorbid cannabis abuse. *Psychopharmacology (Berl.)* 208 (3), 353–363. [PubMed: 19997844]
- Wobrock T, Schneider M, Kadovic D, Schneider-Axmann T, Ecker UK, Retz W, et al., 2008 Reduced cortical inhibition in first-episode schizophrenia. *Schizophr. Res* 105 (1–3), 252–261. [PubMed: 18625547]
- Wobrock T, Schneider-Axmann T, Retz W, Rosier M, Kadovic D, Falkai P, et al., 2009 Motor circuit abnormalities in first-episode schizophrenia assessed with transcranial magnetic stimulation. *Pharmacopsychiatry* 42 (5), 194–201. [PubMed: 19724982]
- Ziemann U, 2004 TMS and drugs. *Clin. Neurophysiol* 115 (8), 1717–1729. [PubMed: 15261850]
- Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W, 1996a The effect of lorazepam on the motor cortical excitability in man. *Exp. Brain Res* 109 (1), 127–135. [PubMed: 8740215]
- Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al., 2015 TMS and drugs revisited 2014. *Clin. Neurophysiol* 126 (10), 1847–1868. [PubMed: 25534482]
- Ziemann U, Rothwell JC, Ridding MC, 1996b Interaction between intracortical inhibition and facilitation in human motor cortex. *J. Physiol. (London)* 496 (3), 873–881. [PubMed: 8930851]

Highlights

- The test-retest reliability of reduced SICI in patients with schizophrenia is unknown.
- We found acceptable reliability of SICI in both patients with schizophrenia and healthy controls.
- Test-retest reliability in ICF and longer ISIs were modest or poor.

Figure 1.

The ppTMS ratios of two separate sessions at each ISI. There was no significant inter-session difference of ppTMS ratio in healthy controls (A) and patients with schizophrenia (B). Values below 1 is inhibition and above 1 is facilitation. ISI, inter-stimulus interval; HC, healthy controls; SCZ, patients with schizophrenia. Error bar indicates standard error.

Figure 2. Intraclass correlations (ICC) of raw amplitudes of motor-evoked potentials. Moderate to good test-retest reliabilities were observed at most ISI, suggesting acceptable reliability for the raw motor-evoked potential values across conditions. HC, healthy controls; SCZ, patients with schizophrenia.

Figure 3.

Intraclass correlations (ICC) of ppTMS ratio at each inter-stimulus interval (ISI). Moderate test-retest reliabilities were observed for SICI (ppTMS ratios at 1 and 3 ms ISIs) in both groups. For ICF, patients with schizophrenia showed acceptable ICCs at 9 and 15 ms ISIs. Poor reliabilities were observed at other ISIs for both groups. All negative ICCs were set to zero for presentation purpose. HC, healthy controls; SCZ, patients with schizophrenia.

Figure 4.

The Bland-Altman plots of MEP amplitudes at TS (A), SICI- and ICF-related ISIs. SICI-related ISIs were 1 and 3 ms ISIs (B - C) and ICF-related ISIs were 9, 12 and 15 ms ISIs (D - F). The difference of MEP amplitudes between session 1 and session 2 was normalized by the mean of the two sessions, then plotted against the mean. The dotted lines show the upper and lower limits of agreement and the solid line shows the mean ratio of $\Delta \text{MEP} / \text{mean}$. Red thicker line indicates patient group, while black line indicates healthy group.

Figure 5.

The Bland-Altman plots of ppTMS ratio at amplitudes at SICI- and ICF-related ISIs. SICI-related ISIs were 1 and 3 ms ISIs (A - B) and ICF-related ISIs were 9, 12 and 15 ms ISIs (C - E). The difference of ppTMS ratio between session 1 and session 2 was normalized by the mean of the two sessions, then plotted against the mean. The dotted lines show the upper and lower limits of agreement and the solid line shows the mean ratio of Ratio/mean. Red thicker line indicates patient group, while black line indicates healthy group.

Table 1.

Demographic and clinical characteristics and their group difference.

	Healthy control <i>n</i> =29	Schizophrenia <i>n</i> =25	Statistics <i>F</i> or χ^2	<i>p</i> value
Age (years) ($\pm$ SD)	41.07 $\pm$ 14.15	36.86 $\pm$ 13.65	1.23	0.27
Male/Female	16/13	18/7	1.63	0.20
Illness duration (years)	--	16.40 $\pm$ 15.2	--	--
Education (years)	13.41 $\pm$ 2.03	12.16 $\pm$ 1.77	5.76	0.02
BPRS total score	--	41.80 $\pm$ 11.87	--	--
RMT (%)	46.19 $\pm$ 7.41	47.78 $\pm$ 9.32	0.47	0.50
Smoker/non-smoker	6/23	8/17	0.89	0.34
Intersession interval (days)	29.41 $\pm$ 23.88	24.60 $\pm$ 19.25	0.67	0.42
TS (mV)	1.32 $\pm$ 0.78	1.08 $\pm$ 0.99	0.95	0.33
SICI (1 ms)	0.22 $\pm$ 0.15	0.40 $\pm$ 0.31	7.67	0.009
SICI (3 ms)	0.28 $\pm$ 0.19	0.49 $\pm$ 0.35	7.62	0.009
ICF (9 ms)	1.61 $\pm$ 0.71	1.53 $\pm$ 0.66	0.16	0.69
ICF (12 ms)	1.43 $\pm$ 0.54	1.37 $\pm$ 0.38	0.18	0.67
ICF (15 ms)	1.38 $\pm$ 1.23	1.32 $\pm$ 0.80	0.07	0.79

Note: resting motor threshold (RMT) was reported as a percentage of the maximum stimulator output. For short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) here, the ppTMS ratios were merged from the 2 sessions. BPRS, Brief Psychiatric Rating Scale. SD, standard deviation.