Behavioural Brain Research 407 (2021) 113266

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short intracortical facilitation associates with motor-inhibitory control

Qian Ding [a,1], Huiting Cai [b,1], Manfeng Wu [a], Guiyuan Cai [a], Hongying Chen [a], Wanqi Li [a], Tuo Lin [a], Yinghua Jing [a], Tifei Yuan [b,c,***], Guangqing Xu [d,**], Yue Lan [a,*]

[a] Department of Rehabilitation Medicine, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou, Guangdong, China
[b] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China
[c] Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China
[d] Department of Rehabilitation Medicine, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China

ARTICLE INFO

Keywords:
Transcranial magnetic stimulation
Intracortical facilitation
Intracortical inhibition
Inhibitory control
Impulsivity

ABSTRACT

The ability of motor-inhibitory control is important in daily life. Inhibitory control deficits are commonly observed in psychiatric conditions with enhanced impulsivity. The physiological mechanisms underlying the inhibitory control deficits are not well elucidated. We systematically investigated the relationship between resting-state intracortical inhibition or facilitation and inhibitory control (indicated by stop signal reaction time, SSRT) to determine whether reduced intracortical inhibition or increased intracortical facilitation was related to the poorer inhibitory control. Thirty-three healthy subjects (age: 21.46 ± 1.40 years) participated in this study. We used paired-pulse transcranial magnetic stimulation to induce short intracortical inhibition, intracortical facilitation, long intracortical inhibition, and short intracortical facilitation at rest. SSRT was derived from stop signal task. We performed all measurements in two repeat sessions conducted two weeks apart. A negative correlation between short intracortical inhibition and SSRT was only observed in session 1; however, the correlation did not persist after controlling for short intracortical facilitation. Positive correlation between short intracortical facilitation and SSRT was observed in both sessions, indicating that individuals with greater resting-state short intracortical facilitation tend to have less efficient stopping performance. Our results help explain the inconsistency with respect to the relationship between short intracortical inhibition and SSRT in the existing literature. Short intracortical facilitation may be used as a potential physiological biomarker for motor-inhibitory control, which may have clinical implications for disorders associated with inhibitory control deficits.

1. Introduction

The ability of motor-inhibitory control is important in daily life, which allows individual to inhibit inappropriate responses and express more appropriate responses [1]. The ability of motor-inhibitory control is commonly measured by stop signal task (SST) [2–4]. In SST, participants are instructed to inhibit an already initiated action, and the latency to inhibit a prepotent response (*i.e.* stopping efficiency) can be estimated, which is known as stop-signal reaction time (SSRT). Prolonged SSRT indicates poor ability of motor-inhibitory control [1]. Prolonged SSRT has been observed in many psychiatric conditions characterized by impaired urge control (*i.e.*, impulsivity), such as attention deficit/hyperactivity disorder [5] and schizophrenia [6], suggesting a theoretical link between motor-inhibitory control deficits and impulsivity [2,7]. The physiological mechanisms underlying inhibitory control deficits are yet to be fully elucidated [2].

Single and paired-pulse transcranial magnetic stimulation (TMS) provides a safe, non-invasive approach for stimulating both corticospinal neurons and intracortical interneurons within the primary motor cortex (M1) [8]. When a suprathreshold stimulus is preceded by a subthreshold conditioning stimulus, the resulting motor evoked potential (MEP) is either inhibited or facilitated depending on the interstimulus interval (ISI) [9]. Generally, short ISIs (1–5 ms) produce inhibition of the MEP, which is believed to be a $GABA_A$-mediated phenomenon and is known as short intracortical inhibition (SICI) [9,10]. Longer ISIs (10−15 ms) produce facilitation of the MEP [9,10], which is believed to be

* Corresponding author at: 1st Panfu Rd., Guangzhou, Guangdong, China.
** Corresponding author at: 106 Zhongshan 2nd Rd., Guangzhou, Guangdong, China.
*** Corresponding author at: 3210 Humin Rd., Shanghai, China.
E-mail addresses: ytf0707@126.com (T. Yuan), guangchingx@163.com (G. Xu), bluemooning@163.com (Y. Lan).
[1] These authors contributed equally.

https://doi.org/10.1016/j.bbr.2021.113266
Received 18 January 2021; Received in revised form 17 February 2021; Accepted 24 March 2021
Available online 29 March 2021

mediated by glutamatergic interneurons and is known as intracortical facilitation (ICF) [11,12]. A subthreshold stimulus applied after a suprathreshold stimulus at short ISIs (1–5 ms) produces facilitation of the MEP, which is known as short intracortical facilitation (SICF) [13,14]. SICF has been suggested to be related to the activity of both $GABA_A$-ergic and dopaminergic neurons [15]. $GABA_B$-ergic intracortical inhibition can be assessed by two suprathreshold stimuli with ISIs of 50−200 ms, which is known as long intracortical inhibition (LICI) [16–18]. Resting-state paired-pulse TMS has been suggested to reveal trait-like information about individual differences in neuronal activities within the motor cortex and may serve as a useful approach to investigate the physiological mechanisms for inhibitory control deficits [19].

Altered intracortical inhibition and facilitation has been reported in conditions with inhibitory control deficits [20–23]. For example, reduced SICI and increased ICF were observed in individuals with attention deficit/hyperactivity disorder [20,21] and individuals with obsessive compulsive disorder [22,23]. However, those studies did not investigate the relationship of the magnitude of intracortical inhibition and facilitation with inhibitory control deficits (*i.e.*, prolonged SSRT) at the individual level. Till date, there are no effective physiological biomarkers for indicating the ability of motor-inhibitory control. Although a few studies have investigated the relationship of SSRT with intracortical inhibition and facilitation at the individual level, the results have been largely inconsistent [19,24–26]. For example, some studies found a negative correlation between resting-state SICI and SSRT [19,24,26]; however, this result was not replicated in another study [25].

Several possible reasons may explain these conflicting results. One reason could be that different approaches were used to estimate SSRT among studies. Some studies [19,25] used the mean method to estimate SSRT, while others used the integration method [24,26]. The interactions between intracortical inhibitory and facilitatory circuits could be another possible reason for the inconsistency. Due to the interaction between SICI and ICF, the correlation between ICF and SSRT disappeared after statistically controlling for SICI [19]. Similarly, the reported interaction between SICI and SICF [14,27,28] may influence their relationship with SSRT. However, to the best of our knowledge, SICI and SICF have never been measured at the same time in previous SSRT studies [19,24–26]. In addition, neuronavigation system was not used for TMS testing in any of the previous SSRT literature [19,24–26]. The use of neuronavigation system ensures reliable and consistent coil positioning over the hotspot throughout the experiment; the absence of neuronavigation system may introduce noise in the TMS data and render the results less convincing [29].

The present study sought to systematically investigate the relationship between resting-state intracortical inhibition (*i.e.*, SICI and LICI) or facilitation (*i.e.*, ICF and SICF) and the ability of inhibitory control. We used neuronavigation system throughout the TMS testing and performed all measurements in two repeated sessions to assess the test-retest reliability of the relationship. We estimated SSRT using both the mean and integration approach. We hypothesized that participants with reduced resting-state intracortical inhibition or increased intracortical facilitation would have less efficient stop performance (*i.e.*, poor ability of inhibitory control).

2. Materials and methods

2.1. Participants

A total of 33 healthy individuals [9 males; mean age: 21.46 ± 1.40 years] participated in this study. Subjects were included if they were right-handed healthy adults without neurological diseases. Subjects were excluded if they were pregnant; using medications that reduce seizure threshold; had any disease, injury, or prior surgery that could affect upper limb motor function. Written informed consent was obtained prior to enrollment. All procedures were approved by the Guangzhou First People's Hospital Human Research Ethics Committee. The study was performed in accordance with the Declaration of Helsinki.

2.2. Self-report measure of general impulsivity

The Barratt Impulsiveness Scale (BIS) was used to measure self-report impulsivity in this study [30,31]. This is a 30-item questionnaire consisting of three subscales of impulsivity: motor, attentional and non-planning impulsiveness subscales [30]. The total score of impulsiveness was measured along with the scores of each subscale.

2.3. Stop signal task

SST was used to measure the ability of motor-inhibitory control [32]. A 13.5-inch Dell laptop running E-Prime v.3.0 (Psychological Software Tools Inc.) was used to present stimuli and record keypresses. At the beginning, participants were asked to read onscreen instructions. On 'Go' trials, a black arrow was presented on the screen, and participants were instructed to press the left-arrow key for a leftward pointing arrow with their left index finger, and to press the right-arrow key for a rightward pointing arrow with their right index finger. On 'Nogo' trials, a red arrow was presented on the screen, and participants were instructed not to press any key. On 'Stop' trials, a 'Stop' signal (red arrow) would occur after the 'Go' signal (*i.e.*, the black arrow turned red after a delay). Participants were asked to stop their initial response when the 'Stop' signal occurred. Participants were instructed to respond as quickly and accurately as possible to black arrows, and not to delay their response to wait in case the 'Stop' signal occurred.

On each trial, a fixation cross was presented for 300 ms, followed by the 'Go' or 'Nogo' signal (*i.e.*, a black or red arrow, respectively). The maximum response time was 1000 ms, and the intertrial interval was 500 ms. On 'Stop' trials, the 'Stop' signal was delivered after the onset of the 'Go' signal. At the start of the session, the 'Stop' signal occurred 250 ms after the 'Go' signal. In the trials where response inhibition was successful, the stop signal delay (SSD) was increased by 50 ms on the subsequent 'Stop' trial. In the trials where inhibition failed, SSD was decreased by 50 ms on the subsequent 'Stop' trial. This ensured an overall successful rate of inhibition (*i.e.*, P (respond|signal)) close to 50 %. There were 24 practice trials and 400 experimental trials, including 70 % 'Go' trials, 10 % 'Nogo' trials and 20 % 'Stop' trials, administered in a completely random sequence. The illustration of SST is presented in Fig. 1.

2.4. Transcranial magnetic stimulation

TMS measurement was conducted after the completion of SST. Surface electromyography (EMG) was recorded from the left first dorsal interosseus (FDI) using the Surface EMG for Non-Invasive Assessment of Muscles guidelines for electrode placement [33]. Participants were seated in a comfortable chair with back support. The EMG raw signal was amplified and band-pass filtered (3 Hz to 3 kHz), digitized at a sampling rate of 2048 Hz with a 50 Hz notch filter enabled. EMG data were written to disc for offline analysis.

TMS was performed using a NS5000 Magnetic Stimulator (YIRUIDE Medical Corporation, Wuhan, China). TMS was applied over M1 using a figure-of-eight-shaped coil (70 mm diameter) positioned tangentially 45° from midline to induce a posterior-anterior current in the right hemisphere. Participants were asked to remain static while determining the optimal scalp position for eliciting maximal responses in the contralateral FDI. Resting motor threshold (RMT) was determined experimentally as the lowest stimulation intensity that produced MEPs $\geq$ 50 u V in 50 % of consecutive stimulations at rest [10]. A neuronavigation system (Visor2, ANT Neuro, Hengelo, Netherlands) was used to ensure reliable and consistent coil positioning over the hotspot throughout the experiment. Coil position error was controlled at $<$ 5 mm displacement and $<$ 3° relative to the target [34]. Stimulations were

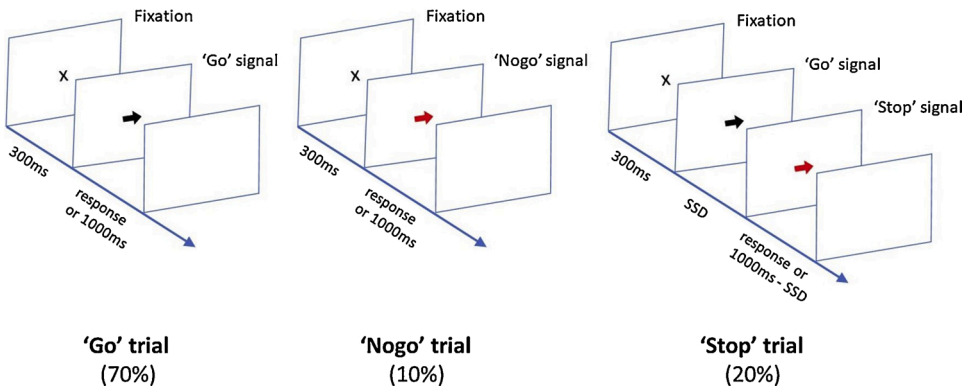

Fig. 1. Schematic illustration of Stop Signal Task. There were three types of trials: 'Go', 'Nogo' and 'Stop'. For each trial, the fixation point was presented for 300 ms. In the 'Go' trials, participants were presented a black arrow and they were asked to press the arrow of the correct direction. In the 'Nogo' trials, participants were asked not to press any key. In the 'Stop' trials, participants were asked to stop pressing any key when they saw the arrow turned red. This figure was inspired by Fig. 1 in Verbruggen et al.'s [35] paper.

delivered at every 5–8 s.

To measure intracortical inhibition and facilitation, either paired-pulse or single-pulse TMS was delivered in 75 trials. There was a total of five conditions of stimuli, including single-pulse condition and four paired-pulse conditions; the TMS parameters for each condition are presented in Table 1. There were 15 trials of each condition conducted in a completely random sequence. An example of unconditioned MEPs (*i.e.*, $MEP_{unconditioned}$) of the single-pulse condition and four paired-pulse conditions is illustrated in Fig. 2. As shown in the figure, the peak-to-peak MEP amplitude of SICI and LICI (*i.e.*, MEP_{SICI} and MEP_{LICI}, respectively) was reduced relative to $MEP_{unconditioned}$, and the peak-to-peak MEP amplitude of ICF and SICF (*i.e.*, MEP_{ICF} and MEP_{SICF}, respectively) was increased relative to $MEP_{unconditioned}$.

2.5. Experimental procedures

This study included two repeat sessions of experiment. In each session, participants were first asked to complete the BIS questionnaires, which was followed by SST. TMS testing was performed after the completion of SST. SICI, ICF, LICI, and SICF were tested followed by TMS parameterization to determine RMT. The second session was conducted after a gap of approximately 2 weeks (range, 12–16 days).

2.6. Data analysis

2.6.1. Data reduction

MEPs were analyzed offline using custom written Matlab scripts (MATLAB R2013b, The MathWorks, Natick, Massachusetts, U.S.A.). EMG data was demeaned and signal averaged over 15 trials per condition. SICI was calculated by the ratio of peak-to-peak amplitudes of $MEP_{SICI}/MEP_{unconditioned}$, and LICI was calculated by the ratio of peak-to-peak amplitudes of $MEP_{LICI}/MEP_{unconditioned}$. Larger values indicate greater disinhibition, and smaller values indicate greater inhibition. ICF was calculated by the ratio of peak-to-peak amplitudes of $MEP_{ICF}/MEP_{unconditioned}$, and SICF was calculated by the ratio of peak-to-peak amplitudes of $MEP_{SICF}/MEP_{unconditioned}$. Larger values indicate greater facilitation, and smaller values indicate weaker facilitation.

The SSRT was estimated using both the mean method and the integration method with Go omission replacement [35]. In the mean method, SSRT (*i.e.*, $SSRT_{mean}$) was calculated by the mean SSD subtracted from the mean reaction time (RT). In the integration method, SSRT (*i.e.*, $SSRT_{integration}$) was calculated by the mean SSD subtracted from the n^{th} Go RT, where n represents a point on the Go RT distribution where the integral of the RT curve is equivalent to P(respond|signal). Go omissions (Go trials on which the participants did not respond before the response deadline) were assigned the maximum RT (*i.e.*, 1000 ms) in order to compensate for the lacking response [35].

Table 1
The TMS parameters for single pulse condition and four paired-pulse conditions.

		S1	S2	ISI
Single pulse	–	120 % RMT	–	–
Paired pulse	SICI	80 % RMT	120 % RMT	2.5 ms
	ICF	80 % RMT	120 % RMT	10 ms
	LICI	120 % RMT	120 % RMT	100 ms
	SICF	120 % RMT	90 % RMT	2.5 ms

S1, first stimulus of the paired pulse; S2, second stimulus of the paired pulse; ISI, interstimulus interval; RMT, resting motor threshold.

2.6.2. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Data were found to meet the normality assumption using the Kolmogorov-Smirnov test and the Shapiro-Wilk test.

We first conducted preliminary analyses to determine whether participants had correctly performed the SST. Based on the horse race model, we compared RTs between Go trials and unsuccessful Stop trials using a paired-sample *t* test for each participant. SSRT was not estimated in participants for whom no significant difference was detected between Go trials and unsuccessful Stop trials [35].

We used Pearson correlation coefficient to assess the test-retest reliability of BIS, SST performance and TMS measures between sessions. Based on previous suggestions [24,36], correlations greater than 0.75 were considered indicative of high test-retest reliability, correlations between 0.5 and 0.75 were considered indicative of moderate test-retest reliability, and correlations less than 0.5 were considered indicative of low test-retest reliability. Paired-sample *t* test was also used to compare each measure between sessions.

To address the relationship between individual differences in resting-state intracortical inhibition and facilitation, SST performance and self-report impulsivity, a series of Pearson correlation analyses were conducted to determine whether variables relevant to SST performance (Go and Nogo accuracy, Stop accuracy, SSRT) and BIS scores were predicted by the individual differences in resting-state intracortical inhibition (SICI and LICI), and facilitation (ICF and SICF). P values < 0.05 were considered indicative of statistical significance.

3. Results

3.1. Self-report impulsivity

Table 2 shows the data for total BIS score and the three subscales, including non-planning impulsiveness, motor impulsiveness, and attentional impulsiveness in the two sessions. Both the total BIS score and the subscales showed high test-retest reliability in the two sessions. There was no significant difference in the total BIS score or subscales between the two sessions (p's > 0.05).

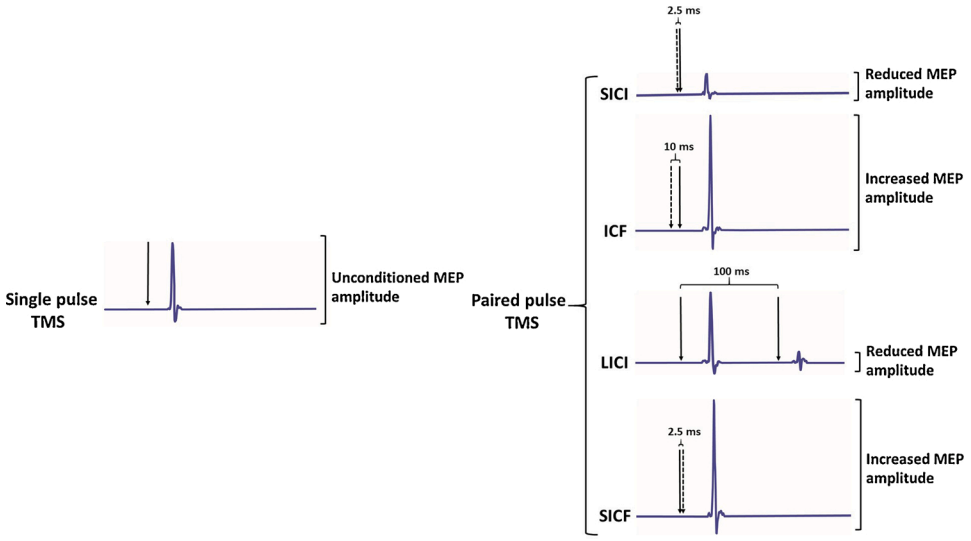

Fig. 2. Illustration of MEPs induced by single and paired-pulse TMS. Solid arrows refer to suprathreshold stimuli, and dashed arrows refer to subthreshold stimuli. The left panel shows the example of a single pulse MEP. The right panel shows examples of SICI, ICF, LICI and SICF, with increased MEP_{ICF} and MEP_{SICF} relative to $MEP_{unconditioned}$, and reduced MEP_{SICI} and MEP_{LICI} relative to $MEP_{unconditioned}$.

Table 2
Self-report impulsivity in the two sessions.

	Session 1	Session 2	*t*-test	significance	correlation	significance
Total BIS Score	33.23 (7.63)	34.04 (8.61)	$t(32) = -1.23$	$p = 0.82$	$r = 0.9$	$p < 0.001$
BIS-Non-Planning	36.67 (10.83)	36.97 (12.85)	$t(32) = -0.22$	$p = 0.82$	$r = 0.8$	$p < 0.001$
BIS-Motor Impulsiveness	26.21 (12.57)	26.82 (12.86)	$t(32) = -0.40$	$p = 0.69$	$r = 0.78$	$p < 0.001$
BIS-Attention	36.82 (9.40)	38.33 (10.31)	$t(32) = -1.55$	$p = 0.23$	$r = 0.85$	$p < 0.001$

Data are presented as mean (standard deviation). Barratt Impulsiveness Scale (BIS) total score and the scores for each subscale are presented.

3.2. Behavioral data of stop signal task

Table 3 shows the data for the SST measures, including Go accuracy, Nogo accuracy, probability of Go omission, reaction time of Go trials and its variability, RT of unsuccessful Stop trials, P (respond|signal), SSD, $SSRT_{mean}$ and $SSRT_{integration}$ in the two sessions. SSRT was not calculated in two participants for whom no significant difference was observed between RT Go trial and RT unsuccessful Stop, which violates the horse race model [35].

For all measures, there was no significant difference between the two sessions (p's > 0.05), except for SSRT calculated by the mean method, which was significantly shorter in session 2 ($p = 0.04$). Most measures showed high test-retest reliability (r's > 0.75), while Go accuracy, probability of Go omission, P (respond|signal) and $SSRT_{integration}$ showed moderate test-retest reliability. $SSRT_{mean}$ showed low test-retest reliability.

3.3. Physiological data

We observed strong evidence of inhibition for SICI and LICI measurements with most participants showing some suppression on paired-pulse trials relative to single-pulse trials. One-sample *t*-tests revealed significant difference when comparing the mean SICI and LICI ratio to a reference value of 1 ($t(32) = -11.79$ and -14.30, respectively, p's < 0.001 in session 1; $t(32) = -7.18$ and -15.16, respectively, p's < 0.001 in session 2). These results suggest significant overall inhibition for SICI and LICI measurements in both sessions.

There was also strong evidence of facilitation for ICF and SICF measurements with most participants showing some facilitation on paired-pulse trials relative to single-pulse trials. One sample *t* tests

Table 3
Behavioral measures on Stop Signal Task in the two sessions.

	Session 1	Session 2	*t*-test	significance	correlation	significance
Go Accuracy (%)	97.09 (2.99)	96.77 (3.87)	$t(32) = 0.46$	$p = 0.65$	$r = 0.7$	$p < 0.001$
Nogo Accuracy (%)	95.14 (6.49)	95.15 (7.10)	$t(32) = -0.22$	$p = 0.82$	$r = 0.8$	$p < 0.001$
P (Go omissions) (%)	1.17 (2.17)	1.66 (3.20)	$t(32) = -1.11$	$p = 0.27$	$r = 0.69$	$p < 0.001$
Go RT (ms)	456.61 (78.60)	468.50 (97.59)	$t(32) = -0.99$	$p = 0.33$	$r = 0.78$	$p < 0.001$
Go RT variability (ms)	104.73 (30.42)	102.65 (34.24)	$t(32) = -0.74$	$p = 0.47$	$r = 0.78$	$p < 0.001$
RT unsuccessful Stop (ms)	401.01(60.78)	420.33 (93.06)	$t(32) = -1.69$	$p = 0.10$	$r = 0.77$	$p < 0.001$
P (respond|signal) (%)	46.82 (7.25)	46.78 (6.47)	$t(32) = -0.08$	$p = 0.94$	$r = 0.73$	$p < 0.001$
SSD (ms)	185.61 (84.60)	212.06 (124.50)	$t(32) = -1.88$	$p = 0.07$	$r = 0.77$	$p < 0.001$
$SSRT_{mean}$ (ms)	271.00(29.09)	256.43 (37.05)	$t(30) = 2.16$	$p = 0.04$	$r = 0.43$	$p = 0.02$
$SSRT_{integration}$ (ms)	250.56(32.80)	240.63 (37.02)	$t(30) = 1.56$	$p = 0.13$	$r = 0.57$	$p = 0.001$

Data are presented as mean (standard deviation). Go Accuracy, accuracy of Go trials; Nogo Accuracy, accuracy of Nogo trials; P (Go omissions), probability of Go omission; Go RT, reaction time of Go trials; Go RT variability, standard deviation of Go RT; RT unsuccessful Stop, reaction time of unsuccessful Stop trials; P (respond|signal), probability of successful Stop trials; SSD, stop signal delay. $SSRT_{mean}$ refers to the SSRT estimated by the mean approach; $SSRT_{integration}$ refers to the SSRT estimated by the integration approach with Go omission replacement.

revealed significant difference when comparing the mean ICF and SICF ratio to a reference value of 1 ($t(32) = 2.98$ and 5.31, p's = 0.005 and <0.001, respectively in session 1; $t(32) = 3.65$ and 6.98, respectively, p's < 0.001 in session 2). These results suggest significant overall facilitation for ICF and SICF measurements in both sessions.

Table 4 shows the paired-pulse TMS data in the two sessions. The test MEP amplitude was comparable between sessions ($p > 0.05$). There was no significant difference in SICI, ICF, LICI or SICF between the two sessions (p's > 0.05). The test-retest reliability was moderate for ICF and LICI and was low for SICI and SICF; however, each TMS parameter showed a significant correlation with each other in the two sessions (p's < 0.05).

3.4. Correlation analyses

There was no significant correlation between BIS scores and TMS parameters in either session (p's > 0.05). There was also no significant correlation between BIS scores and behavioral measures in either session (p's > 0.05).

Fig. 3 shows the scatter plots for each participant's $SSRT_{integration}$ against SICI and SICF in both sessions. In session 1, there was significant positive correlation between SICF and $SSRT_{integration}$ ($r = 0.53$, $p = 0.002$); this indicated that individuals with longer SSRT tend to have stronger SICF. There was significant negative correlation between SICI and $SSRT_{integration}$ ($r = 0.39$, $p = 0.03$); this indicated that individuals with longer SSRT tend to have weaker SICI (*i.e.*, greater disinhibition). In session 2, there was significant positive correlation between SICF and $SSRT_{integration}$ ($r = 0.51$, $p = 0.003$); however, there was no significant correlation between SICI and $SSRT_{integration}$ ($p > 0.05$). On combining data of both sessions, we observed a significant correlation between SICF and $SSRT_{integration}$ ($r = 0.42$, $p < 0.001$), but no significant correlation between SICI and $SSRT_{integration}$ ($p > 0.05$). There was no significant correlation of ICF or LICI with $SSRT_{integration}$ in either session (p's > 0.05).

In session 1, SICF correlated with SICI ($r = 0.45$, $p = 0.009$), while in session 2, SICF did not correlate with SICI ($r = 0.06$, $p = 0.18$). As the interaction between SICI and SICF has been reported before [14,27,28], we also performed partial correlations to eliminate potential interactions between SICI, SICF and $SSRT_{integration}$. In session 1, the correlation between SICF and $SSRT_{integration}$ persisted even after controlling for SICI ($r = 0.45$, $p = 0.012$). After controlling for SICF, the correlation between SICI and $SSRT_{integration}$ did not persist ($r = 0.23$, $p = 0.23$). In session 2, the correlation between SICF and $SSRT_{integration}$ persisted even after controlling for SICI ($r = 0.52$, $p = 0.003$). After controlling for SICF, the correlation between SICI and $SSRT_{integration}$ still did not exist ($r = 0.12$, $p = 0.53$). These results suggest that the correlation between SICI and $SSRT_{integration}$ that was observed in session 1 may be driven by the correlation between SICF and $SSRT_{integration}$. As the interaction between SICI and ICF has been reported [19], we also performed partial correlations between SICI, ICF and $SSRT_{integration}$; however, the results were the same as bivariate correlations.

Fig. 4 shows the scatter plots for each participant's $SSRT_{mean}$ against SICI and SICF in both sessions. In both session 1 and 2, there were significant positive correlations between SICF and $SSRT_{mean}$ (r's = 0.57 and 0.48, and $p = 0.0008$ and 0.0067, respectively). On combining data of both sessions, we observed a significant correlation between SICF and $SSRT_{integration}$ ($r = 0.41$, $p < 0.001$). There was no significant correlation between SICI and $SSRT_{mean}$ in either session (p's > 0.05).

We did not observe any significant correlation between other behavioral measures (*e.g.*, Go accuracy, Nogo accuracy, reaction time and SSD, *etc.*) and TMS parameters (including SICI, ICF, LICI and SICF) in either session (p's > 0.05).

4. Discussion

To the best of our knowledge, this is the first study to systematically investigate the relationship between resting-state intracortical inhibition (*i.e.*, SICI and LICI) or facilitation (*i.e.*, ICF and SICF) and the ability of inhibitory control. We used neuronavigation system throughout the whole TMS testing to ensure stable coil position. We performed all measurements in two independent sessions to test the reliability of the observed correlations. It is worth noting that our results revealed moderate-to-low rest-retest reliability of TMS measures, although each TMS measure obtained in the two sessions showed a significant correlation with each other. The moderate-to-low reliability of paired-pulse TMS measures (*i.e.*, SICI, ICF, and SICF) has also been reported in previous studies [24,37–39]. The variability of TMS measures across sessions may be influenced by several factors, such as inherent changes in cortical excitability, the time of day, and menstrual cycle, *etc.* [24,37]. Because of the moderate-to-low rest-retest reliability of TMS measures, cautions are needed when interpreting the observed correlations between SICI/SICF and SSRT.

Our primary findings are (1) A negative correlation between SICI and SSRT was only revealed in session 1; however, this significant correlation disappeared after statistically controlling for SICF; (2) SICF strongly predicted SSRT in both sessions; (3) No significant correlation was observed between ICF or LICI and SSRT; (4) The reliability of $SSRT_{integration}$ was greater than $SSRT_{mean}$; and (5) No significant correlation was observed between BIS scores and behavioral or physiological measures.

4.1. SICI and SSRT

We observed a negative correlation between SICI and $SSRT_{integration}$ only in session 1, but not in session 2. Importantly, this correlation did not persist after statistically controlling for SICF. Apart from the moderate-to-low test-retest reliability of SICI, the inconsistent relationship between SICI and SSRT was likely accounted for by the relationship between SICF and SSRT. The interaction between SICF and SSRT has been reported before [14,27,28]. Previous studies suggested that SICI can be contaminated by facilitatory components at SICF peaks and is likely to reflect net inhibition resulting from the summation of SICI and SICF [14,27,28]. To estimate the contribution of excess facilitation, studies have recommended measurement of SICF in addition to SICI [27]. However, none of the previous studies investigating the relationship between SICI and SSRT included SICF measurement [19,24–26]; this may explain the inconsistency of their results. In our study, the disappearance of the correlation between SICI and $SSRT_{integration}$ after controlling for SICF suggests that the influence of SICF on SICI should be taken into consideration.

SICI is a $GABA_A$-mediated phenomenon [9] and has been used as a

Table 4
TMS measures in the two sessions.

	Session 1	Session 2	*t*-test	significance	correlation	significance
Test MEP (uV)	712.53 (454.67)	658.66 (516.25)	$t(32) = 0.67$	$p = 0.51$	$r = 0.56$	$p = 0.001$
SICI	0.45 (0.27)	0.57 (0.34)	$t(32) = -1.28$	$p = 0.20$	$r = 0.37$	$p = 0.03$
ICF	1.44 (0.84)	1.70 (1.10)	$t(32) = -1.67$	$p = 0.10$	$r = 0.60$	$p < 0.001$
LICI	0.22 (0.31)	0.15 (0.32)	$t(32) = 1.29$	$p = 0.21$	$r = 0.56$	$p = 0.001$
SICF	1.35 (0.38)	1.60 (0.50)	$t(32) = -1.04$	$p = 0.30$	$r = 0.38$	$p = 0.03$

Data are presented as mean (standard deviation). Test MEP amplitude and four paired-pulse TMS measures are presented.

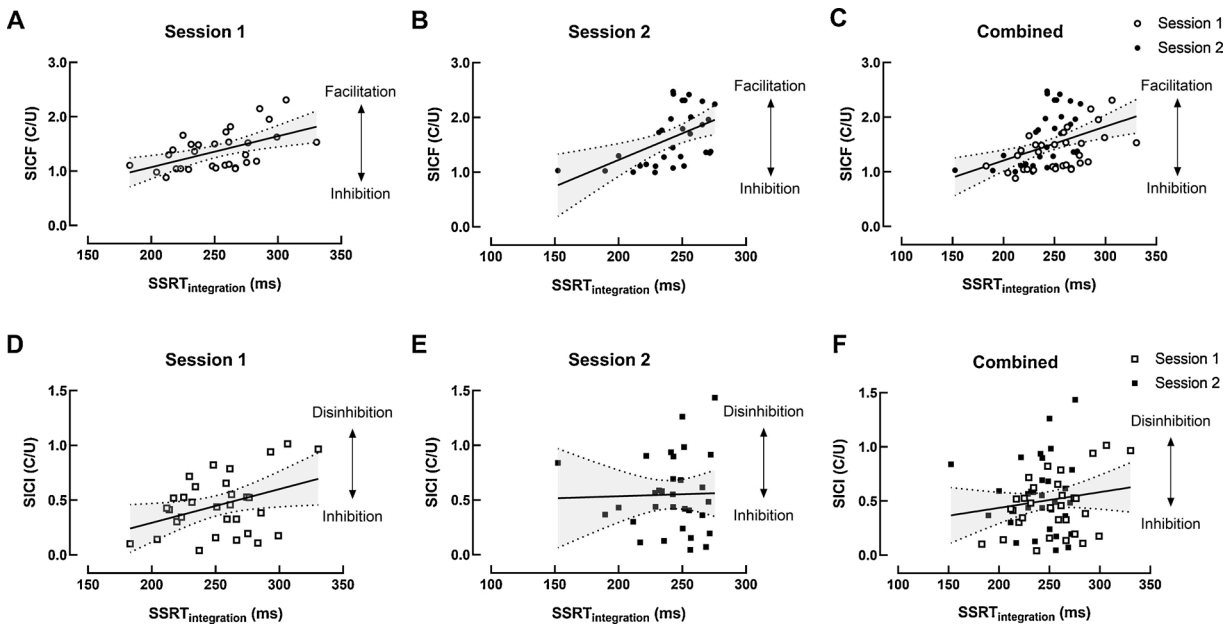

Fig. 3. Correlation between SICI and SICF and $SSRT_{integration}$. There were significant positive correlations between SICF and $SSRT_{integration}$ in both sessions (A and B) and in combined data of the two sessions (C). There was significant negative correlation between SICI and $SSRT_{integration}$ in session 1 (D), but not in session 2 (E) or in combined data of the two sessions (F). The shaded areas indicate the 95 % confidence intervals.

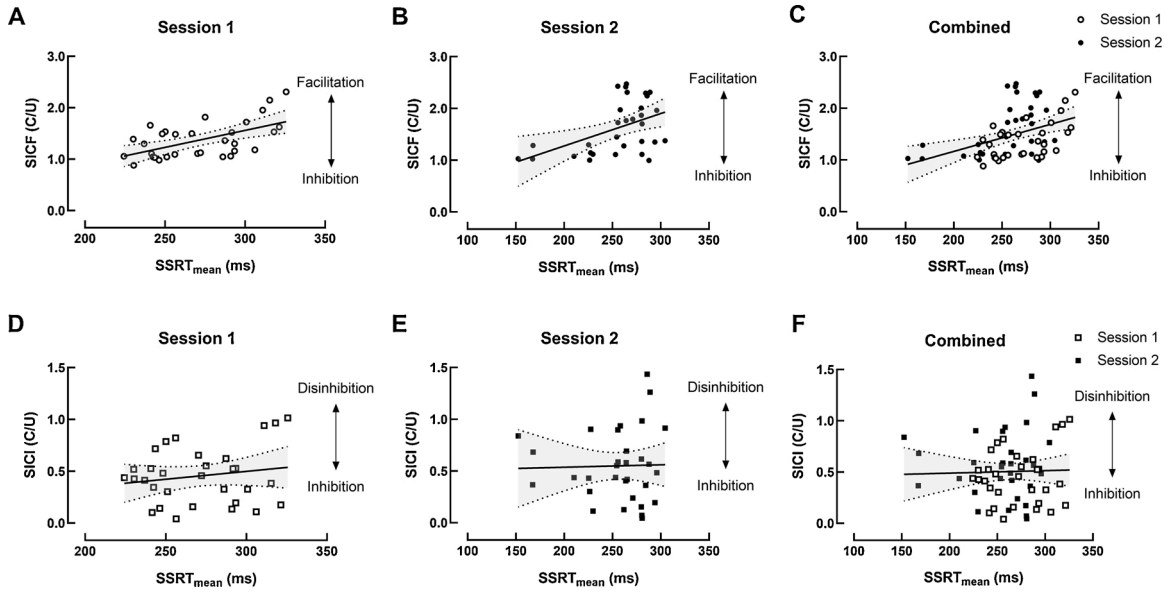

Fig. 4. Correlations between SICI and SICF and $SSRT_{mean}$. There were significant positive correlations between SICF and $SSRT_{mean}$ in both sessions (A and B) and the combined data of the two sessions (C); however, there was no significant correlation between SICI and $SSRT_{mean}$ in either session (D and E) or in the combined data of the two sessions (F). The shaded areas indicate the 95 % confidence intervals.

proxy for the functioning of $GABA_A$-mediated inhibitory neurons [34,40,41]. $GABA_A$-ergic neurons have been suggested to be involved in the process of response inhibition based on the observed modulation of SICI during SST [42]. The lack of consistent relationship between resting-state SICI and SSRT suggests that resting-state SICI may not be a good biomarker of the ability of inhibitory control. Therefore, the functioning of $GABA_A$-mediated neurons may not be specifically related to an individual's ability of inhibitory control, and that other active inhibitory mechanisms may be involved in suppressing the motor command [43].

4.2. *SICF and SSRT*

To the best of our knowledge, this is the first study to investigate the relationship between SICF and inhibitory control. Despite the moderate-to-low test-retest reliability of SICF and SSRT between sessions, our results revealed a robust positive correlation between SICF and SSRT in both sessions, even after controlling for SICI. This result suggests that individuals with stronger resting-state SICF tend to have poorer ability of inhibitory control.

The mechanisms underlying the SICF development are yet to be fully elucidated. It has been proposed that facilitatory interactions of I-waves at the motor cortical level form the basis of SICF [14,28,44].

Suprathreshold first stimulus (S1) leads to a variable and incomplete activation of motor cortical neurons [13], resulting in subliminal depolarization of a subpopulation of cortical neurons. A subsequent subthreshold stimulus (S2) applied at short ISIs causes the subliminally depolarized neurons to reach threshold, thereby facilitating the MEP [14]. There was no facilitation if electrical stimulation was used to elicit S2, suggesting that SICF originates in the cortical level [44]. SICF has three distinct peaks at ISI 1–1.5, 2.4–2.9, and > 4.5 ms [15,45,46]. The observed periodicity of SICF peaks that occur at ~1.5 ms (~660 Hz) is consistent with the I-wave frequency [47], which also supports the cortical origin of SICF [13,14]. Based on results from pharmacological studies, SICF is reduced by $GABA_A$ and dopamine agonist, such as lorazepam and cabergoline, respectively [48], but not modulated by Na^+ agonist, $GABA_B$ antagonist or NMDA receptor antagonist [49,50]. Therefore, SICF may be related to the activities of $GABA_A$-ergic and dopaminergic neurons [48].

Studies have suggested the involvement of both $GABA_A$ and dopamine in the process of response inhibition [3,4,24,43,51,52]. Suppression of an initiated voluntary movement involves a network of cortical and subcortical structures, including inferior frontal cortex, basal ganglia, and supplementary motor cortex, *etc*. [51]. Response inhibition induced by presentation of a Stop signal was suggested to be associated with a fast and global decrease in corticospinal excitability [53–56]. $GABA_A$-ergic intracortical inhibition has been suggested to be involved in the active suppression of corticospinal excitability, based on the observation that SICI was stronger on Stop trials compared with Go trials [42].

However, suppression in motor output requires not only an increase in intracortical inhibition, but also a reduction in excitatory input from thalamus to M1 [43]. Efficient inhibitory performance was suggested to rely on a 'hyperdirect' pathway from the frontal cortex to the subthalamus nucleus (STN) in the basal ganglia, and this provides a mechanism of rapidly shut down motor output [43,51,57–60]. The STN transmits diffuse excitatory projections to the internal segment of the globus pallidus pars interna [61–63], which in turn transmits inhibitory output to thalamus, reducing the excitatory drive to the motor cortex, and thus inhibiting the motor system in a global manner [63–65]. Dopamine was suggested to be an important neurotransmitter in the cortico-basal ganglia network responsible for response inhibition [3,66]. Furthermore, prolonged SSRT was observed in individuals with Parkinson's disease [67]. As Parkinson's disease is characterized by dopamine neuron loss, this observation supports the potential role of dopamine in response inhibition [67].

Our findings revealed that resting-state SICF strongly predicts an individual's ability of inhibitory control. This not only supports the involvement of $GABA_A$ and dopamine in response inhibition, but also provides a potential physiological biomarker for inhibitory control. Our findings may potentially inform new therapeutic strategies for inhibitory control deficits that target both $GABA_A$-ergic and dopaminergic neural pathways. Due to the moderate-to-low reliability of SICF between sessions, the findings of current study should be interpreted with caution. Further studies are required to assess the relationship between SICF and SSRT with larger sample sizes and in other populations (*i.e.*, individuals with psychiatric conditions).

4.3. ICF, LICI and SSRT

In line with a previous study [19], our results did not reveal any significant correlation between resting-state ICF and SSRT. Similarly, in a previous study, no modulation of ICF was observed during Go and Nogo tasks in healthy adults [68]. ICF has been suggested to involve glutamatergic neurotransmissions [11,12]. Collectively, our results and results from previous studies suggest that intracortical glutamatergic interneurons may not be involved in the process of response inhibition.

Consistent with the results of a previous study [25], we did not observe any significant correlation between LICI and SSRT. Sohn et al. [68] observed reduced LICI during both Go and Nogo conditions, suggesting that LICI does not respond selectively to motor inhibition. LICI has been suggested to reflect the activity of $GABA_B$-ergic intracortical interneurons [16–18]. Therefore, it is possible that $GABA_B$-ergic interneurons are only involved in voluntary muscle contraction [68], but not in the process of response inhibition.

4.4. $SSRT_{mean}$ vs. $SSRT_{integration}$

Our results revealed moderate test-retest reliability of $SSRT_{integration}$ and low test-retest reliability of $SSRT_{mean}$. The mean method is currently the most popular approach to estimate SSRT possibly due to its ease of use [35]. The mean method assumes that the mean RT equals SSRT + mean SSD. As the mean RT is strongly influenced by the skewness of the Go RT distribution, $SSRT_{mean}$ is often inaccurate [35]. The integration method entails 'integrating' the RT distribution and identifying the point where the integral equals P(respond|signal); therefore, it is not influenced by the skewness of RT distribution. The use of integration method with Go omission replacement assigned the maximal RT to the Go omission trials and makes the estimated SSRT even closer to the true SSRT [35]. A recent simulation study suggested that the integration method with Go omission replacement is the most reliable and least biased non-parametric approach for estimation of SSRT [35]. Ours is the first clinical study that compares the test-retest reliability of these two methods and our results revealed higher test-retest reliability of $SSRT_{integration}$ than $SSRT_{mean}$. Therefore, the integration method with Go omission replacement is recommended for estimating SSRT compared with the mean method.

4.5. BIS and behavioral or physiological measures

We did not observe any significant correlation between self-report impulsivity (*i.e.*, BIS scores) and SSRT. Lack of correlation between self-report impulsivity questionnaires and behavioral measures has often been reported in previous studies [2,19]. As the impulsivity construct is multidimensional in nature, the lack of correlation could be due to measurement of different aspects of impulsivity. BIS measures non-planning, attention and motor impulsivity, while SSRT only measures motor impulsivity. However, this can only explain the absence of correlation between BIS total score and SSRT, but not the absence of correlation between BIS motor impulsivity subscale and SSRT. The lack of correlation between BIS motor impulsivity subscale and SSRT may be attributable to the subjectivity of self-report questionnaires, which can be biased by the subject's self-perception and past experiences [2].

In line with a previous study [19], we did not observe any significant correlation between BIS scores and intracortical inhibition or facilitation. BIS may not be sensitive enough to differentiate the level of impulsivity, especially in healthy population in whom impulsivity does not spread over a wide range. Further studies are required to investigate whether intracortical facilitation or inhibition can predict an individual's level of impulsivity in other populations, especially in individuals with psychiatric conditions.

4.6. Limitations

One of the limitations is that we used only ISI of 2.5 ms for SICI testing. The ISI that produces the maximal SICI (*i.e.*, optimal ISI) was suggested to vary among individuals; therefore, studies have recommended the use of optimal ISI for each individual or use of multiple ISIs for SICI testing [34,69], especially in individuals with neuropathology in whom there is often considerable variability of optimal ISI [34]. As the present study included only healthy subjects, the variability of optimal ISI should not be large. Furthermore, previous studies suggested that with ISI of 2.5 ms SICI can be elicited in most healthy individuals [34,70,71]; therefore, we used ISI of 2.5 ms for SICI testing. Further studies are required to use individualized ISI or multiple ISIs to measure SICI and to

investigate the relationship between SICI and inhibitory control deficits, especially in individuals with neuropathology.

In the present study, we only measured the second SICF peak (ISI = 2.5 ms), although SICF has three distinct peaks [15,45,46]. Different SICF peaks are likely to be related to interactions of different I-waves [28]. For example, the first SICF peak is likely attributable to the interaction between I2 waves from S1 and I1 waves from S2, while the second SICF peak is likely attributable to the interaction between I3 waves from S1 and I1 waves from S2 [72]. Therefore, different SICF peaks may convey different neurophysiological information and possibly have different relationships with inhibitory control deficits. However, investigating how different ISIs of SICF affect their relationship with inhibitory control performance was beyond the scope of the current study. Further studies are required to measure all three peaks of SICF and investigate the relationship between SICF and the ability of inhibitory control.

Finally, most TMS studies investigating SSRT tested the left motor cortex targeting the right FDI [19,24,25,52] or tested both hemispheres [26], while the current study only tested the right motor cortex targeting the left FDI. In the current study we chose to test the right motor cortex because the right motor cortex has been suggested to be possibly dominant in response inhibition in right-handed adults [26,47], as the GABAergic interneurons in the right motor cortex are more closely connected to key areas in the motor inhibitory network such as right inferior frontal gyrus and right pre-supplementary motor area [26]. We acknowledge that testing only the left motor cortex may prevent direct comparison of our results with those of other studies. Further studies are required to test both hemispheres and to investigate the effect of hemispheric lateralization on the motor inhibitory control.

4.7. Conclusions

Our study systematically investigated the relationship between resting-state intracortical inhibition or facilitation and the ability of inhibitory control. Individual differences in SICF strongly predicted stopping efficiency in two repeat sessions, while the relationship between SICI and SSRT was weak and disappeared after controlling for SICF. Collectively, our results may explain the inconsistency with respect to the relationship between SICI and SSRT in existing literature. Our findings suggest that SICF may be used as a potential physiological biomarker for inhibitory control. Our findings may have clinical implications for disorders associated with inhibitory control deficits.

Funding

This work was supported by the National Science Foundation of China [grant numbers 81772438 (YL), 81974357 (YL), 82072548 (GX) and 81802227 (TL)]; the Guangzhou Municipal Science and Technology Program [grant number 201803010083 (YL)]; the Fundamental Research Funds for the Central University [grant number 2018PY03 (YL)]; National Key R&D Program of China [grant number 2017YFB1303200 (YL)]; Guangdong Basic and Applied Basic Research Foundation [grant number 2020A1515110761 (QD)]; and Guangzhou Postdoctoral Science Foundation (QD).

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We would like to thank all our participants for their interest and time investment.

References

[1] N.S. Chowdhury, E.J. Livesey, A. Blaszczynski, J.A. Harris, Pathological gambling and motor impulsivity: a systematic review with meta-analysis, J. Gambl. Stud. 33 (4) (2017) 1213–1239.
[2] A. Bari, T.W. Robbins, Inhibition and impulsivity: behavioral and neural basis of response control, Prog. Neurobiol. 108 (2013) 44–79.
[3] J.D. Schall, T.J. Palmeri, G.D. Logan, Models of inhibitory control, Philos. Trans. R. Soc. Lond. Ser. B. Biol. Sci. 372 (1718) (2017).
[4] A.R. Aron, From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses, Biol. Psychiatry 69 (12) (2011) e55–68.
[5] M. Lijffijt, J.L. Kenemans, M.N. Verbaten, H. van Engeland, A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? J. Abnorm. Psychol. 114 (2) (2005) 216–222.
[6] J.C. Badcock, P.T. Michie, L. Johnson, J. Combrinck, Acts of control in schizophrenia: dissociating the components of inhibition, Psychol. Med. 32 (2) (2002) 287–297.
[7] P. Skippen, D. Matzke, A. Heathcote, W.R. Fulham, P. Michie, F. Karayanidis, Reliability of triggering inhibitory process is a better predictor of impulsivity than SSRT, Acta Psychol. (Amst.) 192 (2019) 104–117.
[8] R.Q. Cracco, J.B. Cracco, P.J. Maccabee, V.E. Amassian, Cerebral function revealed by transcranial magnetic stimulation, J. Neurosci. Methods 86 (2) (1999) 209–219.
[9] T. Kujirai, M.D. Caramia, J.C. Rothwell, B.L. Day, P.D. Thompson, A. Ferbert, S. Wroe, P. Asselman, C.D. Marsden, Corticocortical inhibition in human motor cortex, J. Physiol. 471 (1993) 501–519.
[10] R. Chen, A. Tam, C. Butefisch, B. Corwell, U. Ziemann, J.C. Rothwell, L.G. Cohen, Intracortical inhibition and facilitation in different representations of the human motor cortex, J. Neurophysiol. 80 (6) (1998) 2870–2881.
[11] J. Liepert, P. Schwenkreis, M. Tegenthoff, J.P. Malin, The glutamate antagonist riluzole suppresses intracortical facilitation, J. Neural Transm. (Vienna) 104 (11–12) (1997) 1207–1214.
[12] U. Ziemann, R. Chen, L.G. Cohen, M. Hallett, Dextromethorphan decreases the excitability of the human motor cortex, Neurology 51 (5) (1998) 1320–1324.
[13] C.V. Rusu, M. Murakami, U. Ziemann, J. Triesch, A model of TMS-induced I-waves in motor cortex, Brain Stimul. 7 (3) (2014) 401–414.
[14] M.A.J. Van den Bos, P. Menon, J. Howells, N. Geevasinga, M.C. Kiernan, S. Vucic, Physiological processes underlying short interval intracortical facilitation in the human motor cortex, Front. Neurosci. 12 (2018) 240.
[15] U. Ziemann, J.C. Rothwell, M.C. Ridding, Interaction between intracortical inhibition and facilitation in human motor cortex, J. Physiol.-Lond. 496 (3) (1996) 873–881.
[16] R. Chen, Interactions between inhibitory and excitatory circuits in the human motor cortex, Exp. Brain Res. 154 (1) (2004) 1–10.
[17] J.F.M. Müller-Dahlhaus, Y. Liu, U. Ziemann, Inhibitory circuits and the nature of their interactions in the human motor cortex–a pharmacological TMS study, J. Physiol. 586 (2) (2008) 495–514.
[18] K.J. Werhahn, E. Kunesch, S. Noachtar, R. Benecke, J. Classen, Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans, J. Physiol. 517 (Pt 2) (1999) 591–597.
[19] N.S. Chowdhury, E.J. Livesey, A. Blaszczynski, J.A. Harris, Variations in response control within at-risk gamblers and non-gambling controls explained by GABAergic inhibition in the motor cortex, Cortex J. Devoted Study Nerv. Syst. Behav. 103 (2018) 153–163.
[20] T. Hoegl, H. Heinrich, W. Barth, F. Losel, G.H. Moll, O. Kratz, Time course analysis of motor excitability in a response inhibition task according to the level of hyperactivity and impulsivity in children with ADHD, PLos One 7 (9) (2012), e46066.
[21] S.W. Wu, D.L. Gilbert, N. Shahana, D.A. Huddleston, S.H. Mostofsky, Transcranial magnetic stimulation measures in attention-deficit/hyperactivity disorder, Pediatr. Neurol. 47 (3) (2012) 177–185.
[22] B.D. Greenberg, U. Ziemann, G. Cora-Locatelli, A. Harmon, D.L. Murphy, J.C. Keel, E.M. Wassermann, Altered cortical excitability in obsessive-compulsive disorder, Neurology 54 (1) (2000) 142–147.
[23] B.D. Greenberg, U. Ziemann, A. Harmon, D.L. Murphy, E.M. Wassermann, Decreased neuronal inhibition in cerebral cortex in obsessive-compulsive disorder on transcranial magnetic stimulation, Lancet 352 (9131) (1998) 881–882.
[24] N.S. Chowdhury, E.J. Livesey, J.A. Harris, Stop signal task training strengthens GABA-mediated neurotransmission within the primary motor cortex, J. Cognit. Neurosci. 32 (10) (2020) 1984–2000.
[25] J.L. He, I. Fuelscher, J. Coxon, N. Chowdhury, W.P. Teo, P. Barhoun, P. Enticott, C. Hyde, Individual differences in intracortical inhibition predict motor-inhibitory performance, Exp. Brain Res. 237 (10) (2019) 2715–2727.
[26] N.S. Chowdhury, E.J. Livesey, J.A. Harris, Contralateral and ipsilateral relationships between intracortical inhibition and stopping efficiency, Neuroscience 415 (2019) 10–17.
[27] S.H. Peurala, J.F. Muller-Dahlhaus, N. Arai, U. Ziemann, Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF), Clin. Neurophysiol. 119 (10) (2008) 2291–2297.
[28] A. Wagle-Shukla, Z. Ni, C.A. Gunraj, N. Bahl, R. Chen, Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex, J. Physiol. 587 (Pt 23) (2009) 5665–5678.
[29] R. Ahdab, S.S. Ayache, P. Brugieres, C. Goujon, J.P. Lefaucheur, Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor,

premotor and prefrontal targets in patients with chronic pain and depression, Neurophysiol. Clin. 40 (1) (2010) 27–36.
[30] J.H. Patton, M.S. Stanford, E.S. Barratt, Factor structure of the Barratt impulsiveness scale, J. Clin. Psychol. 51 (6) (1995) 768–774.
[31] A.C.A. Portugal, A.S. Afonso Jr., A.L. Caldas, W. Maturana, I. Mocaiber, W. Machado-Pinheiro, Inhibitory mechanisms involved in Stroop-matching and stop-signal tasks and the role of impulsivity, Acta Psychol. (Amst.) 191 (2018) 234–243.
[32] F. Verbruggen, G.D. Logan, Long-term aftereffects of response inhibition: memory retrieval, task goals, and cognitive control, J. Exp. Psychol. Hum. Percept. Perform. 34 (5) (2008) 1229–1235.
[33] H.J. Hermens, B. Freriks, C. Disselhorst-Klug, G. Rau, Development of recommendations for SEMG sensors and sensor placement procedures, J. Electromyogr. Kinesiol. 10 (5) (2000) 361–374.
[34] Q. Ding, W.J. Triggs, S.M. Kamath, C. Patten, Short intracortical inhibition during voluntary movement reveals persistent impairment post-stroke, Front. Neurol. 9 (2018) 1105.
[35] F. Verbruggen, A.R. Aron, G.P. Band, C. Beste, P.G. Bissett, A.T. Brockett, J. W. Brown, S.R. Chamberlain, C.D. Chambers, H. Colonius, L.S. Colzato, B. D. Corneil, J.P. Coxon, A. Dupuis, D.M. Eagle, H. Garavan, I. Greenhouse, A. Heathcote, R.J. Huster, S. Jahfari, J.L. Kenemans, I. Leunissen, C.R. Li, G. D. Logan, D. Matzke, S. Morein-Zamir, A. Murthy, M. Pare, R.A. Poldrack, K. R. Ridderinkhof, T.W. Robbins, M. Roesch, K. Rubia, R.J. Schachar, J.D. Schall, A. K. Stock, N.C. Swann, K.N. Thakkar, M.W. van der Molen, L. Vermeylen, M. Vink, J. R. Wessel, R. Whelan, B.B. Zandbelt, C.N. Boehler, A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task, Elife 8 (2019).
[36] P. Davila-Perez, A. Jannati, P.J. Fried, J. Cudeiro Mazaira, A. Pascual-Leone, The effects of waveform and current direction on the efficacy and test-retest reliability of transcranial magnetic stimulation, Neuroscience 393 (2018) 97–109.
[37] B. Boroojerdi, L. Kopylev, F. Battaglia, S. Facchini, U. Ziemann, W. Muellbacher, L. G. Cohen, Reproducibility of intracortical inhibition and facilitation using the paired-pulse paradigm, Muscle Nerve 23 (10) (2000) 1594–1597.
[38] A.M. Hermsen, A. Haag, C. Duddek, K. Balkenhol, H. Bugiel, S. Bauer, V. Mylius, K. Menzler, F. Rosenow, Test-retest reliability of single and paired pulse transcranial magnetic stimulation parameters in healthy subjects, J. Neurol. Sci. 362 (2016) 209–216.
[39] S. Ngomo, G. Leonard, H. Moffet, C. Mercier, Comparison of transcranial magnetic stimulation measures obtained at rest and under active conditions and their reliability, J. Neurosci. Methods 205 (1) (2012) 65–71.
[40] Y.H. Sohn, M. Hallett, Surround inhibition in human motor system, Exp. Brain Res. 158 (4) (2004) 397–404.
[41] R. Chen, D. Cros, A. Curra, V. Di Lazzaro, J.P. Lefaucheur, M.R. Magistris, K. Mills, K.M. Rosler, W.J. Triggs, Y. Ugawa, U. Ziemann, The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee, Clin. Neurophysiol. 119 (3) (2008) 504–532.
[42] J.P. Coxon, C.M. Stinear, W.D. Byblow, Intracortical inhibition during volitional inhibition of prepared action, J. Neurophysiol. 95 (6) (2006) 3371–3383.
[43] J. Duque, I. Greenhouse, L. Labruna, R.B. Ivry, Physiological markers of motor inhibition during human behavior, Trends Neurosci. 40 (4) (2017) 219–236.
[44] U. Ziemann, F. Tergau, E.M. Wassermann, S. Wischer, J. Hildebrandt, W. Paulus, Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation, J. Physiol. 511 (Pt 1) (1998) 181–190.
[45] R. Chen, R. Garg, Facilitatory I wave interaction in proximal arm and lower limb muscle representations of the human motor cortex, J. Neurophysiol. 83 (3) (2000) 1426–1434.
[46] H. Tokimura, M.C. Ridding, Y. Tokimura, V.E. Amassian, J.C. Rothwell, Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex, Electroencephalogr. Clin. Neurophysiol. 101 (4) (1996) 263–272.
[47] V.E. Amassian, M. Stewart, G.J. Quirk, J.L. Rosenthal, Physiological basis of motor effects of a transient stimulus to cerebral cortex, Neurosurgery 20 (1) (1987) 74–93.
[48] U. Ziemann, J. Reis, P. Schwenkreis, M. Rosanova, A. Strafella, R. Badawy, F. Muller-Dahlhaus, TMS and drugs revisited 2014, Clin. Neurophysiol. 126 (10) (2015) 1847–1868.
[49] T.V. Ilic, F. Meintzschel, U. Cleff, D. Ruge, K.R. Kessler, U. Ziemann, Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity, J. Physiol. 545 (1) (2002) 153–167.
[50] M. Inghilleri, A. Berardelli, P. Marchetti, M. Manfredi, Effects of diazepam, baclofen and thiopental on the silent period evoked by transcranial magnetic stimulation in humans, Exp. Brain Res. 109 (3) (1996) 467–472.
[51] C.M. Stinear, J.P. Coxon, W.D. Byblow, Primary motor cortex and movement prevention: where stop meets Go, Neurosci. Biobehav. Rev. 33 (5) (2009) 662–673.
[52] N.S. Chowdhury, E.J. Livesey, J.A. Harris, Individual differences in intracortical inhibition during behavioural inhibition, Neuropsychologia 124 (2019) 55–65.
[53] I. Greenhouse, C.L. Oldenkamp, A.R. Aron, Stopping a response has global or nonglobal effects on the motor system depending on preparation, J. Neurophysiol. 107 (1) (2012) 384–392.
[54] D.S. Majid, W. Cai, J.S. George, F. Verbruggen, A.R. Aron, Transcranial magnetic stimulation reveals dissociable mechanisms for global versus selective corticomotor suppression underlying the stopping of action, Cereb. Cortex 22 (2) (2012) 363–371.
[55] W.P. van den Wildenberg, B. Burle, F. Vidal, M.W. van der Molen, K. R. Ridderinkhof, T. Hasbroucq, Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study, J. Cognit. Neurosci. 22 (2) (2010) 225–239.
[56] J.R. Wessel, H.S. Reynoso, A.R. Aron, Saccade suppression exerts global effects on the motor system, J. Neurophysiol. 110 (4) (2013) 883–890.
[57] A.R. Aron, D.M. Herz, P. Brown, B.U. Forstmann, K. Zaghloul, Frontosubthalamic circuits for control of action and cognition, J. Neurosci. 36 (45) (2016) 11489–11495.
[58] D. Benis, O. David, J.P. Lachaux, E. Seigneuret, P. Krack, V. Fraix, S. Chabardes, J. Bastin, Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson's disease, NeuroImage 91 (2014) 273–281.
[59] W.I. Haynes, S.N. Haber, The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for Basal Ganglia models and deep brain stimulation, J. Neurosci. 33 (11) (2013) 4804–4814.
[60] N. Swann, H. Poizner, M. Houser, S. Gould, I. Greenhouse, W. Cai, J. Strunk, J. George, A.R. Aron, Deep brain stimulation of the subthalamic nucleus alters the cortical profile of response inhibition in the beta frequency band: a scalp EEG study in Parkinson's disease, J. Neurosci. 31 (15) (2011) 5721–5729.
[61] L.N. Hazrati, A. Parent, Striatal and subthalamic afferents to the primate pallidum: interactions between two opposite chemospecific neuronal systems, Prog. Brain Res. 99 (1993) 89–104.
[62] A. Parent, L.N. Hazrati, Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry, Brain Res. Brain Res. Rev. 20 (1) (1995) 128–154.
[63] J.R. Wessel, A.R. Aron, On the globality of motor suppression: unexpected events and their influence on behavior and cognition, Neuron 93 (2) (2017) 259–280.
[64] J.R. Wessel, A. Ghahremani, K. Udupa, U. Saha, S.K. Kalia, M. Hodaie, A. M. Lozano, A.R. Aron, R. Chen, Stop-related subthalamic beta activity indexes global motor suppression in Parkinson's disease, Mov. Disord. 31 (12) (2016) 1846–1853.
[65] A. Nambu, H. Tokuno, M. Takada, Functional significance of the cortico-subthalamo-pallidal' hyperdirect' pathway, Neurosci. Res. 43 (2) (2002) 111–117.
[66] D. Lindenbach, C. Bishop, Critical involvement of the motor cortex in the pathophysiology and treatment of Parkinson's disease, Neurosci. Biobehav. Rev. 37 (10 Pt 2) (2013) 2737–2750.
[67] Z. Ye, E. Altena, C. Nombela, C.R. Housden, H. Maxwell, T. Rittman, C. Huddleston, C.L. Rae, R. Regenthal, B.J. Sahakian, R.A. Barker, T.W. Robbins, J. B. Rowe, Improving response inhibition in Parkinson's disease with atomoxetine, Biol. Psychiatry 77 (8) (2015) 740–748.
[68] Y.H. Sohn, K. Wiltz, M. Hallett, Effect of volitional inhibition on cortical inhibitory mechanisms, J. Neurophysiol. 88 (1) (2002) 333–338.
[69] X. Du, A. Summerfelt, J. Chiappelli, H.H. Holcomb, L.E. Hong, Individualized brain inhibition and excitation profile in response to paired-pulse TMS, J. Mot. Behav. 46 (1) (2014) 39–48.
[70] R. Fisher, Y. Nakamura, S. Bestmann, J. Rothwell, H. Bostock, Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking, Exp. Brain Res. 143 (2) (2002) 240–248.
[71] L. Roshan, G.O. Paradiso, R. Chen, Two phases of short-interval intracortical inhibition, Exp. Brain Res. 151 (3) (2003) 330–337.
[72] R. Hanajima, Y. Ugawa, Y. Terao, H. Enomoto, Y. Shiio, H. Mochizuki, T. Furubayashi, H. Uesugi, N.K. Iwata, I. Kanazawa, Mechanisms of intracortical I-wave facilitation elicited with paired-pulse magnetic stimulation in humans, J. Physiol. 538 (Pt 1) (2002) 253–261.