Experimental Brain Research (2019) 237:2715–2727
https://doi.org/10.1007/s00221-019-05622-y

RESEARCH ARTICLE

Individual differences in intracortical inhibition predict motor-inhibitory performance

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Received: 8 May 2019 / Accepted: 6 August 2019 / Published online: 17 August 2019

Abstract

Studies in which single- and paired-pulse TMS was applied during motor task performance have shed considerable light on the functional relevance of popular TMS-derived neurophysiological biomarkers such as short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). While it has become well established that corticospinal excitability and intracortical inhibition are modulated during the enactment and cancellation of actions, it has remained unclear as to whether interindividual differences in these neurophysiological markers were associated with an individual's actual ability to restrain and cancel actions. In this study, we found that individual differences in both SICI and LICI were positively associated with relevant performance metrics on the go/no-go task and stop-signal task. Specifically, we found that individuals with greater resting SICI and LICI were faster to respond on go trials of the go/no-go task and were also more accurate at inhibiting their manual responses on both go/no-go and stop-signal tasks. These results are in support of findings from our earlier study and also provide new evidence for a general relationship between individual differences in resting-state GABAergic intracortical inhibitory functioning and motor inhibition.

Keywords Brain Stimulation · Transcranial magnetic stimulation · GABA · Intracortical inhibition · Inhibition · Stop · Go · Cancellation · Restraint

Introduction

Studies in which transcranial magnetic stimulation (TMS) was applied during the go/no-go and stop-signal tasks suggest that the inhibition of a motor response is dependent on a contextual modulation of corticospinal excitability and intracortical inhibition within the primary motor cortex (M1; Duque et al. 2017). For example, provided that an action has been prepared (see Ficarella and Battelli 2019) in 'Go' trials of either task, corticospinal excitability of a relevant effector is incrementally increased in the contralateral M1 prior to the performance of the prepared response (Coxon et al. 2006; Macdonald et al. 2014; Sohn et al. 2002), Conversely, in 'stop' or 'no-go' trials, where a prepared or prepotent action must be inhibited, corticospinal excitability shows a global decrease approximately 140 ms after a cue to 'not go' or 'stop' has been presented (Coxon et al. 2006; Sohn et al. 2002). This drop in excitability appears to temporally coincide with a concurrent increase in gamma aminobutyric acid (GABA) inhibition via fast-acting $GABA_A$ ionotropic receptor activity, assessed by measuring short-interval intracortical inhibition (SICI; Coxon et al. 2006; Sohn et al. 2002). This suggests SICI is a neurophysiological marker of an intracortical inhibitory mechanism within the M1 by which motor commands are inhibited.

GABAergic inhibition also appears to be proactively increased when there is foreknowledge that an action may need to be inhibited (Cirillo et al. 2017; Cowie et al. 2016; Duque et al. 2017; Sohn et al. 2002). However, in this instance, the slower-acting metabotropic $GABA_B$ receptor

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is implicated as long-interval intracortical inhibition (LICI) is increased (McDonnell et al. 2006). In comparison to SICI, LICI is thought to be a neurophysiological marker of a proactive inhibitory process by which unwanted or premature motor responses are attenuated. Taken together, the modulation of SICI and LICI appears to be critical to the successful restraint and cancellation of actions.

Presently, it remains unclear whether individual differences in these intracortical inhibitory neurophysiological markers are related to the accuracy and efficiency by which individuals are able to restrain (i.e., action restraint) and cancel (i.e., action cancellation) actions. While studies in which TMS was applied during task performance have certainly shed light on the functional relevance of SICI and LICI (Duque et al. 2017), they do not necessarily tell us whether individual differences in these markers, which are discernible when assessed at rest (i.e., in a resting state), are related to the quality of the performance of relevant motor functions (e.g., motor inhibition). This is an important avenue of investigation, since most studies which have identified individual- or group-level abnormalities in these markers have typically done so in patient groups where participants were in a resting state (Bütefisch et al. 2005; Hanajima and Ugawa 2000; Kleine et al. 2001; Liepert et al. 2000), rather than during task performance. Indeed, resting-state intracortical inhibition (as per SICI and/or LICI) has been found to be reduced in many disorders where movement is impaired or affected [e.g., Parkinson's disease: (Chu et al. 2009); stroke: (Liepert et al. 2000); Tourette's syndrome: (Ziemann et al. 1997); autism: (Enticott et al. 2013)]. While such studies suggest or imply that reduced intracortical inhibition measured at rest relates to the poorer motor outcomes and/or disorder specific symptomatology, this relationship is not directly assessed in most cases. There is, however, reason to believe that individual differences in these neurophysiological mechanisms do relate to actual motor-related functioning. For example, investigations of intracortical inhibitory functioning (as per SICI and LICI) in aging populations have identified reduced resting-state SICI in older adults, a population with well-documented declines in general motor ability (Opie and Semmler 2014). Still, despite evidence of reduced resting-state SICI, older adults appear to modulate SICI in a manner that is comparable to younger adults (Fujiyama et al. 2011), highlighting a potential limitation in inferring motor-related functioning using simple resting-state measures.

As a direct test of whether individual differences in SICI were related to individual differences in motor stopping performance, we recently conducted a study where resting-state SICI and stop-signal task performance were assessed in a large sample of at-risk gamblers and non-gambling controls (Chowdhury et al. 2018). Here, in support of the view that inhibition within M1 measured at rest explains individual differences in motor specific stopping performance, we found that individuals who had greater resting-state SICI also tended to be faster at cancelling a prepared action on a choice-reaction stop-signal task (i.e., shorter stop-signal reaction times), an effect present in both at-risk gamblers and non-gambling controls. However, as this study only had assessed the relationship between one measure of intracortical inhibition (i.e., SICI) and one form of motor inhibition (i.e., the cancellation of an ongoing action: action cancellation), it remains to be determined whether this relationship is specific to SICI and action cancellation or whether this relationship also extends to LICI and the restraint of prepotent responses (i.e., action restraint).

The present study

The present study sought to explore the relationships between individual differences in M1 inhibition at rest and the quality of a range of stopping behaviours (i.e., accuracy and efficiency of motor inhibition). Here, we measured both resting-state SICI and LICI in participants prior to the performance of two common measures of motor inhibition: The go/no-go task and the stop-signal task. The go/no-go task was used to measure action restraint, while the stop-signal task was used to measure action cancellation. In keeping with the previous work (Chowdhury et al. 2018), we predicted that participants with greater resting-state intracortical inhibition (i.e., SICI and LICI) would also have more accurate and efficient motor-inhibitory performance on the go/no-go task and stop-signal task.

Methods

Participants

Eighteen right-handed young adults ($mean_{age}$ 24.66, SD 3.07, range 20–32) participated in this study (11 females and 7 males). All participants completed a pre-screening questionnaire to ensure they were eligible for TMS. No participants reported having any TMS contraindicators, or having been diagnosed with a neurological or psychiatric disorder. Informed consent was obtained from all participants. No participants reported any negative side-effects during or following TMS. Ethical clearance was received from the Deakin University Human Research Ethics Committee (DUHREC).

Measures

Transcranial magnetic stimulation

Single-pulse TMS and paired-pulse TMS was administered to the left hemisphere of the M1 using a hand-held 70 mm figure-of-eight coil positioned against the scalp using the orthodox method (handle pointing backwards and angled

45° away from the midline). Both single and ppTMS was administered using the same coil, connected to two-Magstim 200[2] (Magstim Co., Whitland, Dyfed, UK) stimulators, combined via a BiStim[2] module. Motor-evoked potentials (MEPs) were recorded from the right-hand first dorsal interosseous (FDI) muscle with self-adhesive EMG electrodes positioned over the muscle belly, the interphalangeal joint of the right index finger (reference), and the ulnar styloid process (ground).

Single-pulse TMS was used to locate the site of the 'hotspot' of the left hemisphere of the M1 that would produce a maximal response in the right FDI. This hotspot was then used for the remainder of the study to elicit MEPs. Resting motor threshold (RMT) was determined and defined as the minimum intensity that produced a peak-to-peak MEP of > 50 µV in at least 5 out of 10 consecutive trials (Kumru et al. 2017). Active motor threshold (AMT) was defined as the lowest stimulation intensity that produced a peak-to-peak MEP of > 200 µV in at least 5 out of 10 trials (Filipović et al. 2009) during ~ 10% of maximal contraction (as assessed by an AD instrument MLT004/ST grip force transducer).

Intracortical inhibition Twenty unconditioned TMS pulses at 120% RMT were delivered at 4-s intervals to provide a baseline measure of corticospinal excitability. Intracortical inhibition was then assessed via two ppTMS paradigms: SICI and LICI. SICI was assessed by delivering a subthreshold conditioning pulse (90% AMT) followed 2 ms later by a suprathreshold test pulse [120% RMT (Enticott et al. 2013)]. LICI was indexed by delivering two suprathreshold (120% RMT) pulses separated by 100 ms (Daskalakis et al. 2008). Ten recordings of SICI and LICI were taken, with 4-s intertrial intervals.

MEPs were first visually inspected to ensure that participants were truly in a resting-state (i.e., did not have EMG activity characteristic of movement in the 300 ms prior to stimulation). No trials contained excessive movement prior to stimulation. MEPs were analyzed by determining their peak-to-peak millivolt (mV) amplitudes. For SICI, each participant's median conditioned peak-to-peak MEP was divided by their respective median unconditioned peak-to-peak MEP measured at baseline. Median conditioned and unconditioned MEPs were used for calculations of SICI (%) and LICI (%) due to the relatively lower number of pulses delivered, and to account for the inherent variability of MEPs (Darling et al. 2006). The resulting value was then multiplied by 100 and subtracted from 100, to represent the percentage of inhibition of the test pulse [SICI (%)]:

$$\text{SICI (\%)} = 100 - \left[\left(\frac{C}{NC}\right) \times 100\right].$$

For LICI, each participant's median peak-to-peak MEP in response to the second TMS pulse (the conditioned pulse) was divided by their median peak-to-peak MEP in response to the first TMS pulse (the non-conditioned pulse). The resulting value was then multiplied by 100 and subtracted from 100 to represent the percentage of inhibition of the second suprathreshold test pulse [LICI (%)]:

$$\text{LICI (\%)} = 100 - \left[\left(\frac{C}{NC}\right) \times 100\right].$$

Motor inhibition

Go/no-go task Participant's ability to perform action restraint was measured using the go/no-go task originally developed by Chikazoe et al. (2008). The task was programmed with E-prime (Version 2.0, Psychology Software Tools, Pittsburgh, PA, USA), and was presented on a 15-in. Acer monitor at eye level. Participants sat approximately 60 cm from the monitor and were provided with a keyboard to respond, centred approximately 6 in. from their midline.

Each trial began with a fixation cross presented for 400 ms followed immediately by a colored circle (10 cm × 10 cm in size) presented for another 400 ms (see Fig. 1a). The color of the circle denoted one of three trial types: frequent-go trial, infrequent-go trial, or no-go trial. Frequent-go, infrequent-go, and no-go trials occurred 75%, 12.5%, and 12.5% of trials, respectively. Frequent-go trials were always represented by white circles, whereas blue and yellow were counterbalanced to represent infrequent-go and frequent-go trials across subjects (Chikazoe et al. 2008; Hirose et al. 2012). For both frequent and infrequent-go trials, participants were instructed to respond as quickly and accurately as possible by depressing the spacebar of the computer keyboard using the distal aspect of their index finger. For no-go trials, participants were instructed to withhold their response.

All participants completed a practice block prior to completing two test blocks. All blocks contained 15 frequent-go trials which were presented at the beginning of each block to allow for task acclimation prior to their performance being recorded. Note that these trials were not included in subsequent analyses and are not part of the total trial counts described below.

Each test block contained 192 trials, consisting of 144 'frequent-go' (75%), 24 infrequent-go (12.5%), and 24 no-go (12.5%) trials. RTs to frequent-go and infrequent-go trials were recorded when a response was made within the stimulus duration (400 ms). Thus, if a response was not recorded in this 400 ms window, it was assumed that the participant had responded during the proceeding fixation cross of the subsequent trial (He et al. 2018). In these instances, RTs for these trials were replaced with the maximum possible RT for go trials (i.e., 400 ms). Go trials with RTs of < 150 ms were excluded from analyses to exclude premature responses (Chikazoe et al. 2008; Hirose et al.

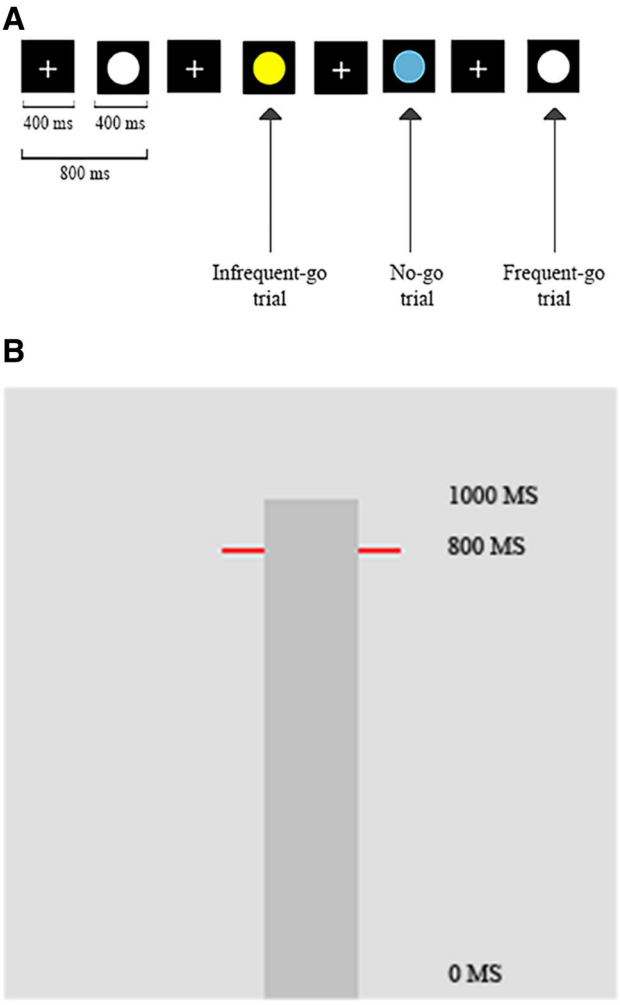

Fig. 1 **a** Visual representation of the go/no-go task used in this study. **b** Visual representation of the stop-signal task used in this study

2012). Mean RTs were then calculated for both frequent-go and infrequent-go trials. For no-go trials, a participant was considered to have accurately completed the trial if they did not depress the spacebar during the duration of the trial. Thus, for each participant, the percentage of accurately inhibited no-go trials was calculated (no-go accuracy).

An action restraint efficiency index (AREI) was then calculated as per Hirose et al. (2012), where a linear regression between RTs on infrequent-go trials and percentage of correct performance on no-go trials was calculated. The regression line was used to represent the performance of the average participant. Thus, participants who scored above the regression line were considered more efficient performers, whereas those who scored below the regression line were considered less efficient. Motor-inhibitory performance on the go/no-go task was indexed by accuracy on no-go trials and AREIs.

Stop-signal task Participant's ability to perform action cancellation was then measured using an anticipated response stop-signal task (Coxon et al. 2006; Coxon et al. 2007; Hermans et al. 2018; Leunissen et al. 2017; Macdonald et al. 2014). The task was presented on the same computer monitor used for the go/no-go task and participants sat at the same approximate distance from the screen. The stimulus display consisted of a fixed, vertically orientated indicator bar (15 cm high × 1 cm wide) centred in the middle of the screen (see Fig. 1b). Participants were instructed to begin a trial by depressing the 0 key of the computer keyboard with the medial aspect of their right index finger. The trial would commence approximately 1 s after the participant had fully depressed the 0 key (discerned by the experimenter, who upon confirming that the participant was ready would initiate each trial). Upon trial commencement, the central indicator bar would fill at a constant velocity from the bottom up (starting at 0 ms) and would finish at the top of the indicator bar (at 1000 ms) if the participant did not lift their finger. A fixed target line was presented 800 ms from the bottom of the indicator bar. Participants were informed that their primary task was to lift their finger from the computer key to stop the rising indicator at the target line as accurately as possible. Trials where the bar did not stop prematurely were referred to as go trials. Participants were also informed that in some of the trials, the indicator bar would stop unexpectedly prior to reaching the target line. These trials were referred to as stop trials. For stop trials, participants were instructed to keep their finger depressed on the computer key.

Stop trial difficulty was increased by delaying the time at which the rising bar stopped within a 'Stop' trial [i.e., the stop-signal delay (SSD)]. As per the horse race model of inhibition (Logan and Cowan 1984), the later the rising indicator bar stopped relative to the start line (i.e. the later the SSD), the more difficult it would be for participants to inhibit their prepared finger lift. SSDs were set at seven different stop-times: 500 ms, 525 ms, 550 ms, 575 ms, 600 ms, 625 ms, and 650 ms from the bottom of the indicator. These SSDs were selected as SSDs resulting in a 50% accuracy rate on stop trials are typically thought to index moderate task difficulty (Verbruggen and Logan 2008 2009, 2009), and our preliminary piloting demonstrated that this point consistently fell between 550 and 575 ms. We used these SSDs as a mid-point for our range of SSDs and expanded our SSDs in two 25 ms increments above 550 ms and below 575 ms to ensure sufficient variation in stop difficulty across trials and to ensure that the stop-signals were not predictable at any one timepoint.

All participants first observed the performance of approximately 15 trials completed by the experimenter. Once the participant had understood the task, they then completed a minimum of 20 randomly selected practice trials. Following practice, participants then completed 450 test trials presented over nine blocks (50 trials per block). Of the 450

trials, 310 were go trials and 140 were stop trials. Of the 140 stop trials, there were 20 trials for each of the seven SSD times.

As with the go/no-go task, go trials with lift times (LTs) of < 150 ms were excluded from analysis to exclude premature responses. Mean LT for go trials were then calculated for each participant by averaging the LT across all go trials. Stop accuracy was determined by calculating the percentage of trials where participants had accurately kept their finger depressed on the computer key when presented with a stop-signal. Stop trials where the SSD was 500 ms, 525 ms, and 650 ms were not included in the calculation of stop accuracy, as there was little variability between participant performance on these SSDs due to ceiling and floor effects (see Fig. 2 below). Participant SSRT was calculated by first using linear interpolation to determine the SSD where the probability of responding was approximately 50% for each participant. This value was then subtracted from the participant's mean 'go' trial LT to determine their individual SSRTs. Shorter SSRTs indicated more efficient action cancellation. Motor-inhibitory performance on the stop-signal task was indexed by stop accuracy and SSRTs.

Design and analysis

All data cleaning procedures and analyses were conducted in R-programming (Version 3.5.0; R Core Team [2013]). Prior to

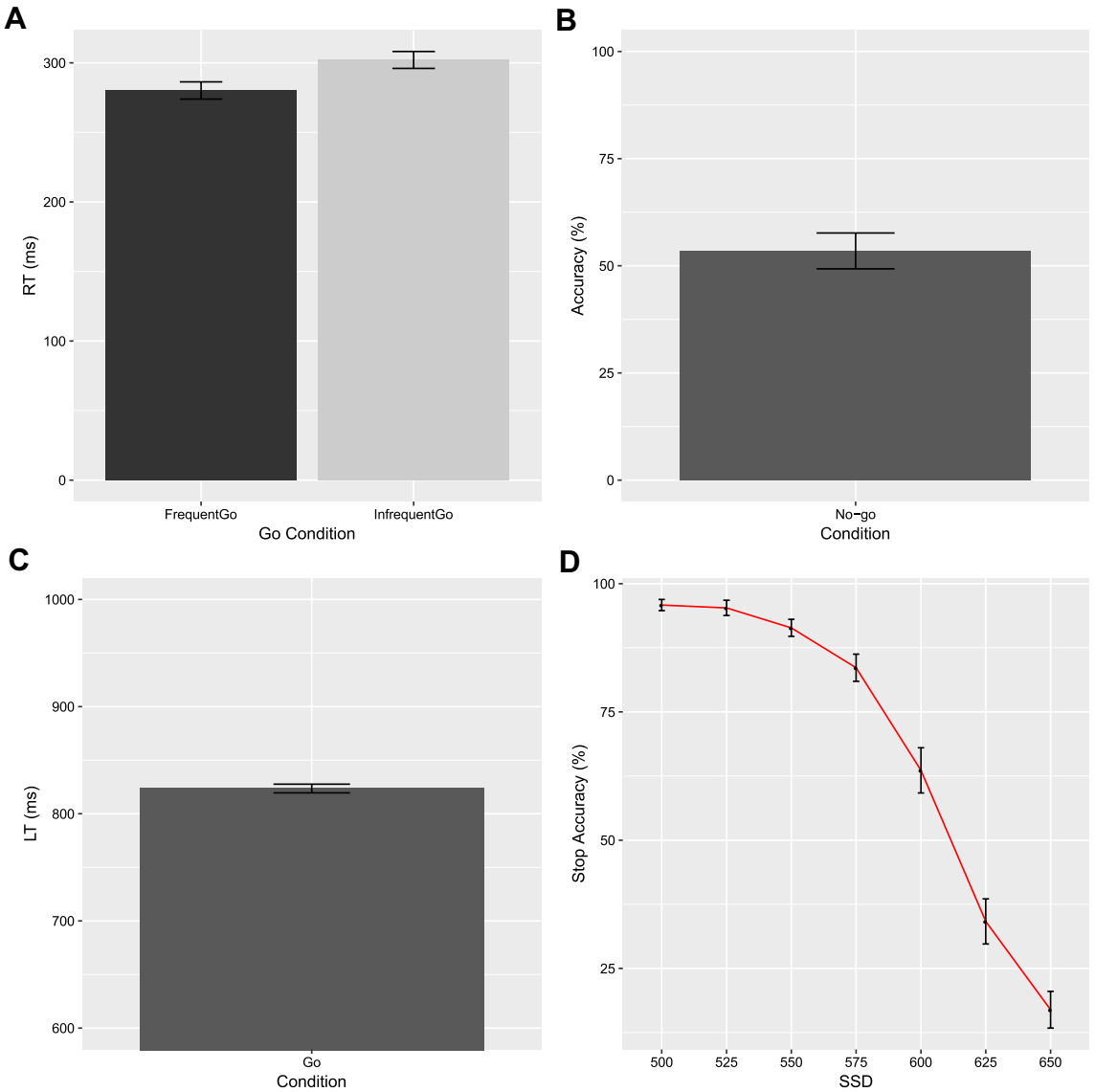

Fig. 2 **a** Mean RTs on frequent and infrequent-go trials on the go/no-go task. **b** Percentage accuracy on no-go trials of the go/no-go task. **c** Mean LTs on go trials of the ARI stop-signal task. **d**. Relationship between total accuracy and SSD. Error bars reflect standard error

analysis, all outcome variables were both visually and statistically examined for violations of normality using density plots and Shapiro–Wilk's tests of normality. Where violations were present, either square root or log transformations were applied to correct for skew. This leads to a square root transformation for resting-state SICI and SSRT, and a log transformation for resting-state LICI. Note that all variables are referred to by their untransformed name in the results for ease of interpretation. Prior to all correlations, univariate and multivariate outliers were assessed and removed using boxplots and Mahalanobis distances, respectively. This led to the removal of one participant for the correlation between LICI and no-go accuracy on the go/no-go task. All figures used in the results section were created using the R-package: ggplot2 (Wickham and Chang 2008).

We first conducted preliminary analyses to determine whether participants had correctly performed both of the behavioural tasks, as per previous work. To this end, we (1) compared RTs between frequent and infrequent-go trials of the go/no-go task using a paired-samples *t* test and (2) conducted a repeated-measures ANOVA (DV: accuracy; IV: SSD (500, 525, 550, 575, 600, 625, and 650) to ensure that stop accuracy had significantly decreased as a function of SSD on the ARI stop-signal task. We also inspected accuracy on no-go trials of the go/no-go task and LTs of go trials of the ARI stop-signal task.

To assess the relationship between individual differences in resting-state intracortical inhibition and motor-inhibitory performance, a series of Pearson's correlation analyses were conducted to determine whether variables relevant to motor-inhibitory performance (i.e., no-go accuracy, stop accuracy, AREI, and SSRT) was predicted by individual differences in resting-state intracortical inhibition (i.e., SICI and LICI). We also ran exploratory Pearson's correlation analyses between resting CSE, SICI, and LICI with RTs on go trials of both tasks. The purpose of these exploratory analyses was to compare our findings to the results of recent work by Greenhouse et al. (2017), which found that individual differences in tonic local GABA levels in M1, as assessed using magnetic resonance spectroscopy (MRS), predicted resting CSE, which in turn predicted differences in RTs on a delayed response task.

Results

Behavioural data

Preliminary analyses confirm that participants completed both the go/no-go task and ARI stop-signal task appropriately

As discerned from the results of a paired-samples *t* test $t(15) = -8.32$, $p = 0.000$, participants responded faster on frequent-go trials (*M* 280.10, SD 26.25) than infrequent-go trials (*M* 302.07, SD 25.73), an effect consistent with what was observed in earlier work adopting this particular version of the go/no-go task (Chikazoe et al. 2008; Hirose et al. 2012). In the case of performance on no-go trials, participants were unable to accurately restrain their responses on approximately half of the no-go trials (*M* 53.47, SD 17.71), suggesting that there was sufficient inhibitory demand (Wessel 2018). The mean AREI was 0.00, SD 9.81 (see Fig. 2a).

On the ARI stop-signal task, participants were able to release the depressed computer key at a time relatively close to the target line (i.e., 800 ms), with the average LT on go trials being 795.09 (SD 17.29). This indicates that participants were able to comfortably complete the go trials of the task. Importantly, and as expected, as SSDs increased, participants became less accurate at inhibiting their prepared finger lift, $F(6, 108) = 175.98$, $p < 001$. This can be visually discerned by the negative logistic (sigmoidal) curve displayed in Fig. 2b. The average SSRT was 216.82 (SD 16.14).

Neurophysiological data

Resting-state CSE and intracortical inhibition

The average RMT was 47.31 (SD 7.57) of the maximum stimulator output (MSO), while the average AMT was 37.63 (SD 6.81). The mean resting-state MEP (i.e., resting CSE) was 1.38 (SD 0.69), the mean percentage of inhibition of the test pulse was 59.27 (SD 27.22) in the SICI protocol, and the mean percentage of inhibition of the test pulse was 77.83 (SD 18.46) in the LICI protocol.

Correlation analyses

Resting SICI predicts both accuracy of action restraint and action cancellation, while resting LICI only predicts accuracy of action restraint

As hypothesised, there were strong positive correlations between resting SICI and accuracy on both no-go trials of the go/no-go task [$r(16) = 0.51$, $p = 0.030$] and stop trials of the stop-signal task [$r(16) = -0.48$, $p = 0.046$]. There was also a strong positive correlation between resting LICI and accuracy on no-go trials of the go/no-go task [$r(16) = 0.54$, $p = 0.026$]. No relationship between resting LICI and stop accuracy could be discerned [$r(16) = 0.10$, $p = 0.692$] (see Fig. 3).

No discernible relationship between resting CSE and intracortical inhibition with efficiency indices from either task

There were no significant correlations between any of our resting-state TMS-derived measures and either of the efficiency indices. Indeed, resting CSE did not significantly correlate with AREI [$r(16) = -0.12$, $p = 0.625$] or SSRT

[$r(16) = 0.28$, $p = 0.256$]. Resting SICI also did not correlate with AREI [$r(16) = 0.05$ $p = 0.860$] or SSRT [$r(16) = 0.10$, $p = 0.705$], and per CSE and SICI [$r(16) = -0.21$, $p = 0.396$], LICI also did not correlate with either AREI or SSRTs [$r(16) = 0.28$, $p = 0.262$] (see Fig. 4).

Individual differences in resting CSE did not correlate with RTs or LTs on the go/no-go task and ARI stop-signal task

Contary to the results of Greenhouse et al. (2017), resting CSE did not correlate with RTs on either frequent [$r(16) = 0.10$, $p = 0.700$] or infrequent [$r(16) = 0.16$, $p = 0.51$] go trials on the go/no-go task. Resting CSE also did not correlate with LTs on go trials of the ARI stop-signal task [$r(16) = -0.21$, $p = 0.398$] (see Fig. 5).

Individual differences in resting CSE did not correlate with accuracy of action restraint or action cancellation

Unlike resting SICI and LICI, resting CSE did not show any significant or meaningful correlations with the accuracy of action restraint [$r(16) = 0.07$, $p = 0.787$] on the go/no-go task or action cancellation [$r(16) = 0.05$, $p = 0.852$] on the ARI stop-signal task (see Fig. 6).

Individual differences in resting SICI and LICI strongly predict RTs on the go/no-go task but not LTs on the ARI stop-signal task

There were significant, strong positive correlations between resting SICI and RTs on frequent [$r(16) = 0.63$, $p = 0.005$] and infrequent [$r(16) = 0.59$, $p = 0.010$] go trials of the go/no-go task. Interestingly, a similar correlation could not be discerned for LTs of the ARI stop-signal task [$r(16) = 0.27$, $p = 0.283$]. In regard to LICI, there was only a moderate-to-strong significant correlation between resting LICI and RTs on infrequent-go trials of the go/no-go task [$r(16) = 0.48$, $p = 0.046$]. Moreover, while in the expected direction, resting LICI did not correlate with RTs on frequent-go trials [$r(16) = 0.30$, $p = 0.220$] of the go/no-go task or LTs on go trials [$r(16) = -0.21$, $p = 0.394$] of the ARI stop-signal task (see Fig. 7).

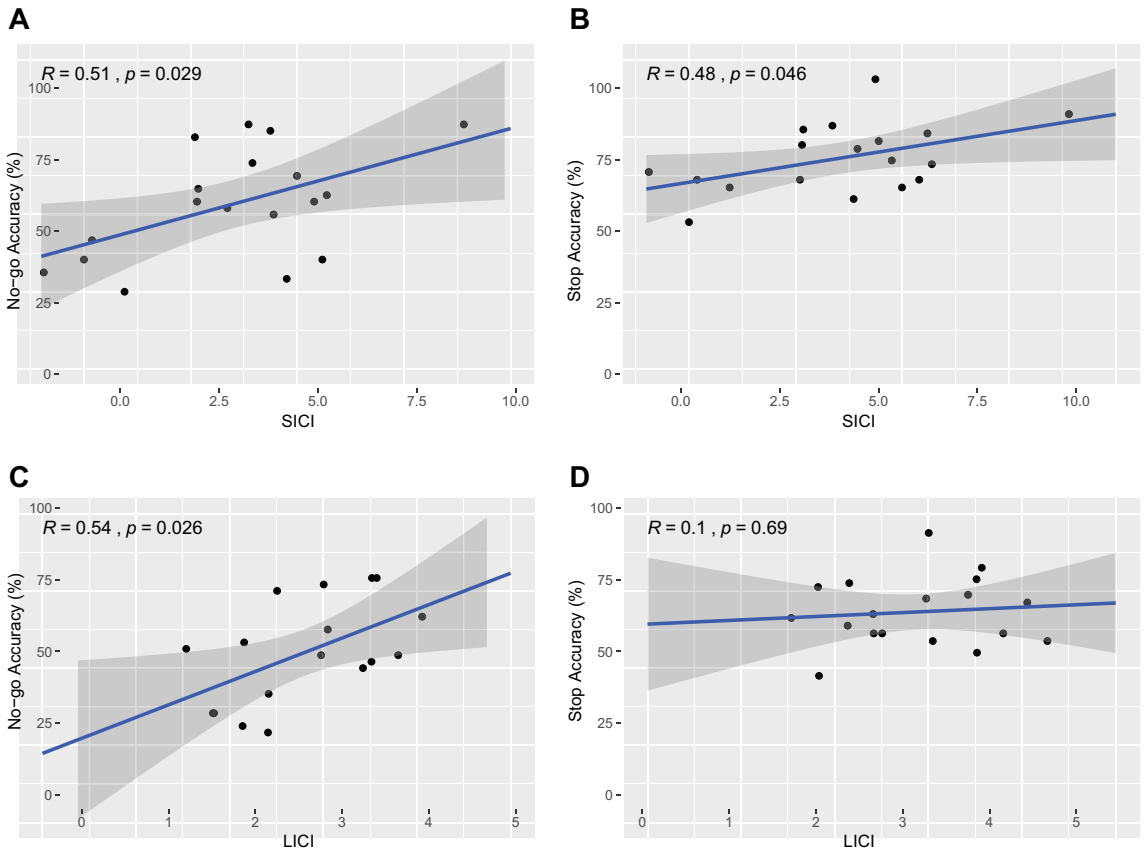

Fig. 3 **a** Linear association between resting SICI and accuracy on no-go trials of the go/no-go task. **b** Linear association between resting SICI and percentage stop accuracy on stop trials of the ARI stop-signal task. **c** Linear association between resting LICI and accuracy on no-go trials of the go/no-go task. **d** Linear association between resting LICI and percentage stop accuracy on stop trials of the ARI stop-signal task. Dark grey areas represent the 95% confidence intervals

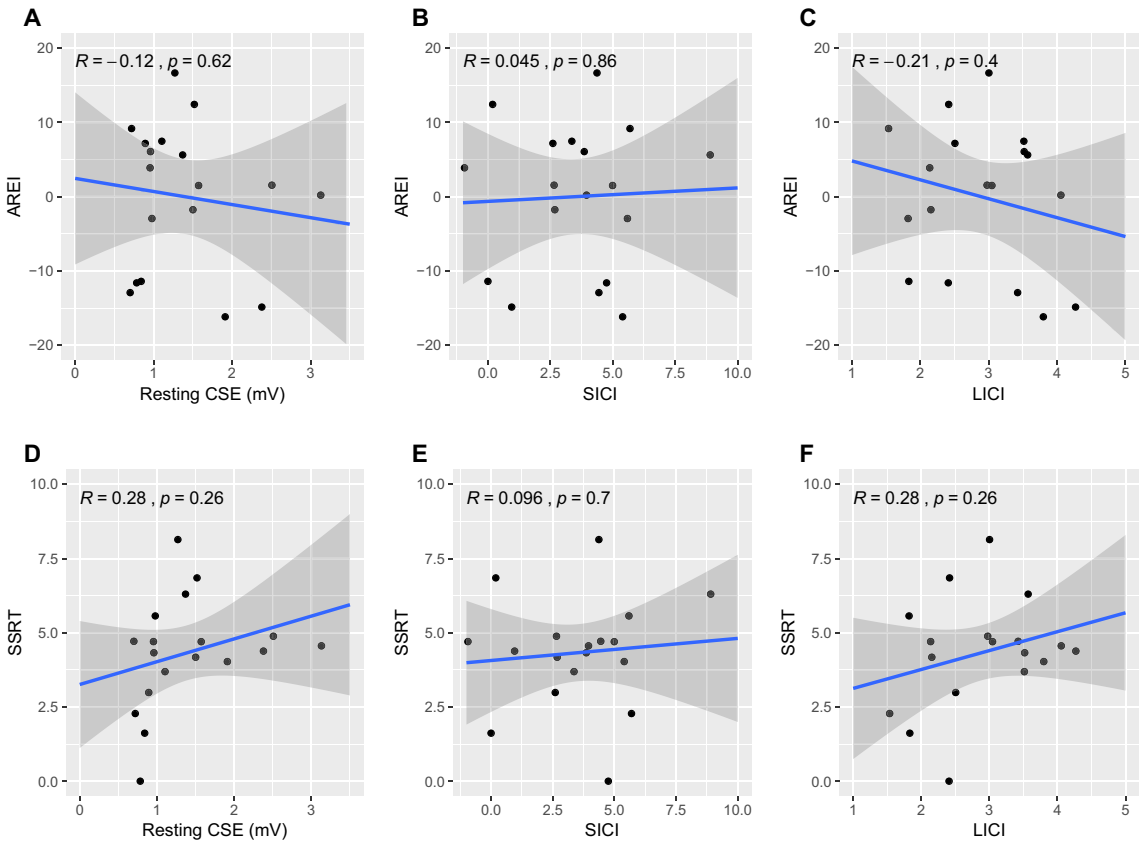

Fig. 4 **a** Linear associations between resting CSE and individual AREI. **b** Linear associations between resting SICI and individual AREI. **c** Linear associations between resting LICI and individual AREI. **d** Linear associations between resting CSE and individual SSRT. **e** Linear associations between resting SICI and SSRT. **e** Linear associations between resting LICI and SSRT. Dark grey areas represent the 95% confidence intervals

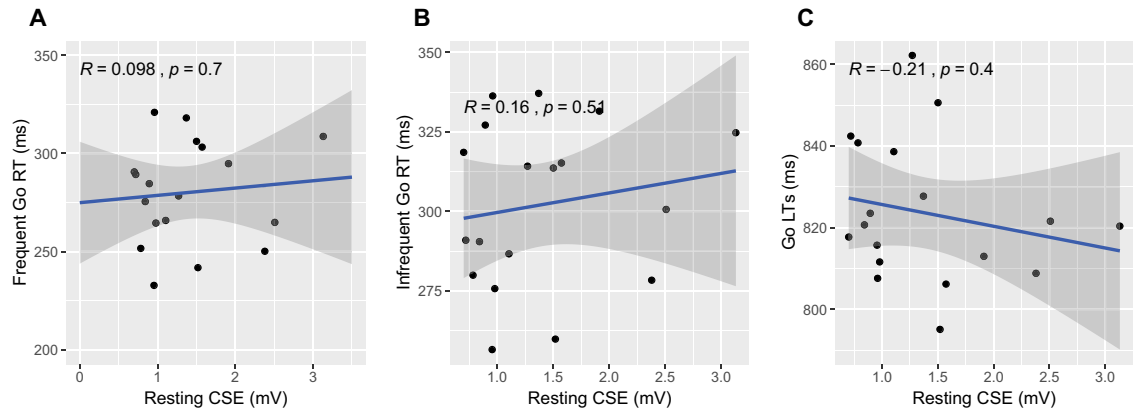

Fig. 5 **a** Linear relationships between resting CSE and RTs on frequent-go trials of the go/no-go task. **b** Linear relationships between resting CSE and RTs on infrequent-go trials of the go/no-go task. **c** Linear relationships between resting CSE and LTs on go trials of the ARI stop-signal task. Dark grey areas represent the 95% confidence intervals

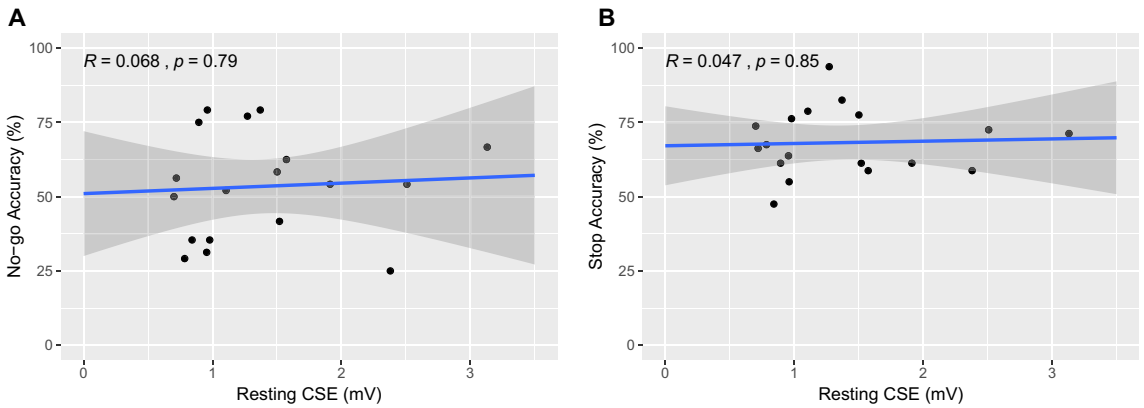

Fig. 6 **a** Linear relationship between resting CSE and the percentage of no-go trials accurately inhibited. **b** Linear relationship between resting CSE and the percentage of stop trials accurately inhibited. Dark grey areas represent the 95% confidence intervals

Discussion

The present study aimed to determine whether individual differences in resting-state intracortical inhibition would be associated with the quality of action restraint and action cancellation. While we were unable to replicate correlations between resting-state SICI and SSRTs found in our previous work (Chowdhury et al. (2018), we found that individual differences in resting-state SICI predicted an individual's ability to accurately perform action restraint and action cancellation. Moreover, and novel to our study, we also found that individual differences in resting-state LICI predicted the accuracy by which individuals could inhibit prepotent responses on the go/no-go task. Thus, building on the results from our earlier study, which had found that individual differences in resting-state SICI predicted the efficiency by which individuals were able to perform action cancellation (Chowdhury et al. 2018), our results suggest that the relationship between resting-state SICI and motor inhibition also extends to the action restraint facet of motor inhibition and LICI. Interestingly, in our exploratory analyses, we also found that individual differences in resting-state SICI and LICI strongly predicted the speed at which individuals could make responses on go trials of the go/no-go task, a finding that is partly consistent with recent work adopting MRS to assess M1 GABA and its relationship to excitability of individual's corticospinal tracts (Greenhouse et al. 2017).

Resting-state intracortical inhibition predicts accuracy of motor inhibition

As hypothesised, participants with greater resting-state intracortical inhibition were more accurate at performing action restraint and action cancellation, reflected by the strong positive correlations between resting-state SICI and LICI, and the percentage of no-go trials and stop trials accurately inhibited. This finding provides complimentary support for the results of our earlier work (Chowdhury et al. 2018). That is, building on from those findings, the results of the present study suggest that the relationship between resting-state measures of intracortical inhibition and motor-inhibitory performance is also present for other facets of motor inhibition (i.e., action restraint as measured by the go/no-go task) and other related measures of intracortical inhibition (i.e., LICI). Taken together, these findings are in support of a more general relationship between intracortical inhibition and motor-inhibitory performance.

Contrary to our expectations, however, no significant or meaningful associations were observed between either of the resting-state intracortical inhibition measures and our motor inhibition efficiency measures. This was indicated by non-significant correlations between SICI and LICI, and the efficiency measures (i.e., AREIs and SSRTs) of the go/no-go task and anticipated response stop-signal task, respectively. These findings are, perhaps, surprising, since our previous work (Chowdhury et al. 2018) had identified a significant association using similar metrics (i.e., resting-state SICI and SSRTs). A potential reason for this incongruence could be due to the difference in the versions of the stop-signal tasks used between the current study and our previous study. Specifically, unlike the anticipated response version of the stop-signal task used in the present study, the Chowdhury et al. (2018) study had employed the more traditional choice-reaction variant of the task. In the choice-reaction stop-signal task, participants were required to inhibit an ongoing choice response in reaction to an auditory stop-signal. This is unlike the anticipated response stop-signal task used in the present study, where participants were required to inhibit

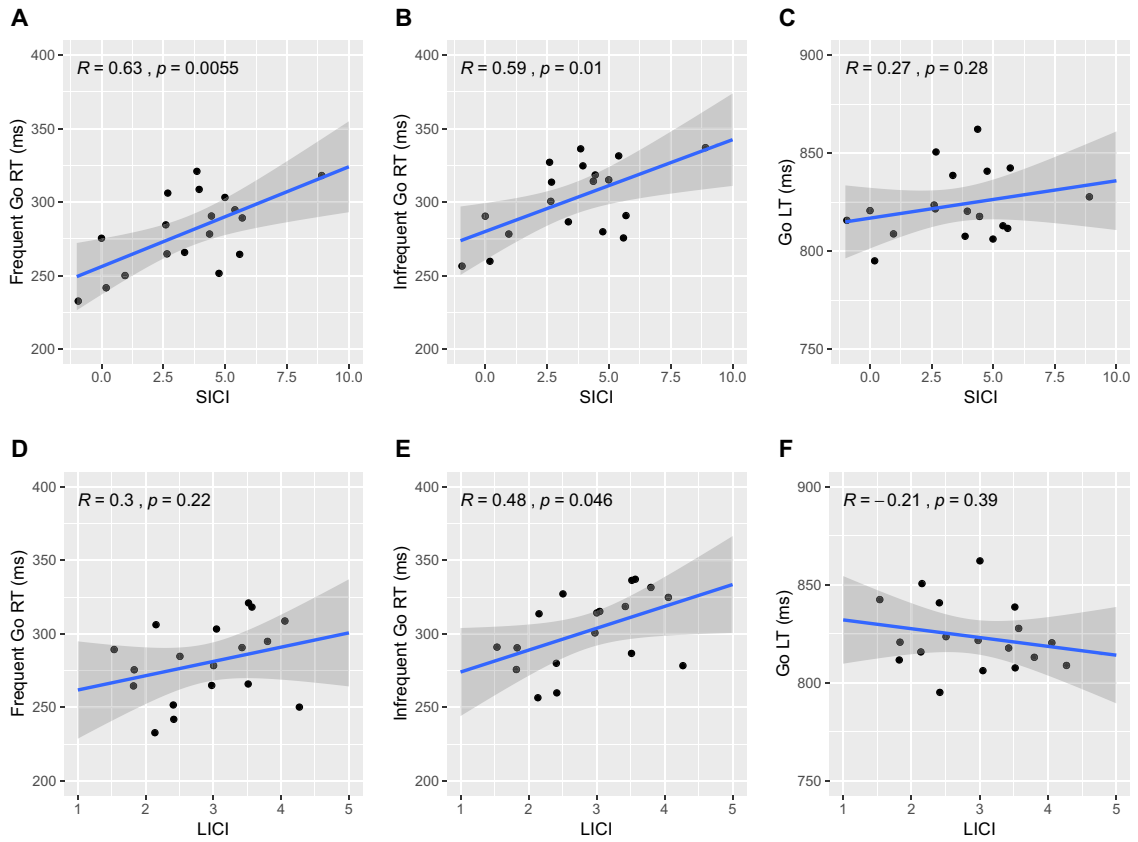

Fig. 7 **a** Linear association between resting SICI and RTs on frequent-go trials of the go/no-go task. **b** Linear association between resting SICI and RTs on infrequent-go trials of the go/no-go task. **c** Linear association between resting SICI and LTs on go trials of the ARI stop-signal task. **d** Linear association between resting LICI and RTs on frequent-go trials of the go/no-go task. **e** Linear association between resting LICI and RTs on infrequent-go trials of the go/no-go task. **f** Linear association between resting LICI and LTs on go trials of the ARI stop-signal task. Dark grey areas represent the 95% confidence intervals

an anticipated action in response to the visual cessation of a rising indicator. The differences in the types of actions being cancelled (i.e., an anticipated response versus a choice response) and the modality of the stop-signal (i.e., an audio versus a visual stop-signal) may provide a possible explanation for the differences in our study findings.

Another potential explanation comes from a recent study conducted by Leunissen et al. (2017), which found that SSRTs estimated from the anticipated response variant of the stop-signal task were far less variable than those estimated from the choice-reaction variant. The authors of the study argued that while the anticipated response task may provide more reliable estimates of individual SSRTs, the reduction in variability of SSRTs may render the anticipated response variant of the stop-signal task less optimal for correlational approaches. Regardless of these discrepancies, the results from the present study and those of our previous study (Chowdhury et al. 2018) both provide compelling support for an association between the resting-state, GABAergic intracortical inhibition indices (i.e., SICI and LICI), and broad motor-inhibitory performance.

Resting-state SICI and LICI predict RTs on go trials of the go/no-go task, but not LTs of the ARI stop-signal task

While our primary aim was to investigate the relationship between individual differences in resting-state intracortical inhibition (i.e., SICI and LICI) and motor-inhibitory performance (i.e., action restraint and cancellation), we had also conducted exploratory analyses to determine whether we were able to replicate the results of a recent study conducted by Greenhouse et al. (2017). Greenhouse et al. (2017) found that individual M1 GABA levels, assessed by MRS, strongly predicted resting CSE, which, in turn, strongly predicted individual differences in RTs on a delayed RT task. While a direct correlation between M1 GABA levels and RTs was not observed, the authors speculated that a higher concentration of M1 GABA could allow for faster responses to be made in reaction to external cues (i.e., due to a more excitable corticospinal pathway). Here, we argue that while our results may initially appear inconsistent with the results of the Greenhouse et al. (2017) study, they are in

part consistent with their suggestion that greater M1 GABA allows for faster RTs.

First, unlike Greenhouse et al. (2017), we were unable to identify a correlation between resting CSE and RTs on either of our tasks. Indeed, while these correlations appear to be in the right direction (i.e., greater resting CSE positively correlated with RTs on frequent and infrequent-go trials of the go/no-go task and negatively with LTs on go trials of the ARI stop-signal task), they were small in effect and far from reaching statistical significance. When assessing the relationships between resting-state intracortical inhibition and RTs, however, our results appear to be somewhat consistent with the suggestion that higher levels of M1 GABA allows for faster RTs. That is, we found that individual differences in resting-state intracortical inhibition strongly correlated with an individual's ability to make speeded responses to frequent and infrequent stimuli. Said differently, the participants with greater resting-state intracortical inhibition were also those who were able to respond faster to frequent and infrequent-go trials on the go/no-go task. It is also worth noting that this relationship was not present between either of the resting-state intracortical inhibition measures and LTs on go trials of the ARI stop-signal task. Here, we would argue that this is, perhaps, not surprising, since LTs on go trials of the ARI stop-signal task do not necessarily reflect an individual's ability to make a 'fast' response as much as it reflects their ability to make an 'accurately timed' response (i.e., while our results suggest that greater resting-state intracortical inhibition predicts individual's ability to make speeded responses, it does not predict their ability to make accurately timed responses).

When taken together, the relationship between resting-state intracortical inhibition and RTs on go trials of the go/no-go task is partly consistent with the suggestion that higher levels of M1 GABA allow for faster RTs (Greenhouse et al. 2017). However, we wish to highlight that our interpretation of how our results align with the suggestions of Greenhouse et al. (2017) should be considered in light of the fact that local GABA levels assessed by MRS are not representatives of the same GABAergic processes that are assessed by paired-pulse TMS paradigms (see Stagg et al. 2011 for a discussion). MRS of GABA is thought to assess the total levels of GABA within a region of interest. An important limitation of MRS of GABA is that it cannot differentiate between tonic levels of GABA within a cell and contributions of synaptic GABA activity. Indeed, the majority of GABA levels are thought to be somatic (Schmidt-Wilcke et al. 2018). In comparison, TMS-derived measures of GABA (i.e., through paired-pulse TMS paradigms) are thought to specifically assess GABAergic action at the receptor level. Thus, while MRS of GABA and paired-pulse TMS measures of inhibition are inherently related, they do not necessarily assess the same construct. In support, many studies assessing GABA within M1 using both MRS and TMS have failed to identify a correlation between individual GABA levels assessed by MRS and intracortical inhibition assessed by paired-pulse TMS protocols (Hermans et al. 2018; Stagg et al. 2011; Tremblay et al. 2012).

The functional relevance of resting-state TMS measures

Since its conception, people have been hopeful for the use of TMS in clinical settings for both diagnostic and remedial purposes (Rossini and Rossi 2007). While repetitive forms of TMS has had success as a mode of treatment for clinical disorders such as depression (Perera et al. 2016) and obsessive compulsive disorder (Tendler and Sisko 2018; Tendler et al. 2018), the utility of single and ppTMS as a diagnostic tool has so far been relatively limited (Rothwell et al. 2009). As we have argued throughout, although studies where TMS was applied during the performance of behavioural motor tasks have certainly shed considerable light on the neural mechanisms underlying the preparation, enactment, and inhibition of actions (see: Cirillo et al. 2017; Cowie et al. 2016; Coxon et al. 2006; MacDonald et al. 2014 for examples), studies which have previously identified abnormalities in these TMS-derived 'biomarkers' in clinical disorders have typically done so when subjects were in a resting state. This was potentially problematic, since prior to the present study and the Chowdhury et al. (2018) study, it had been unclear whether these resting-state, TMS-derived indices were predictive of relevant motor functioning. That is, while SICI and LICI are indeed modulated during motor inhibition, it had not been directly tested whether individual differences in the integrity of these neurophysiological markers could predict the quality of actions which place strong demands on intracortical inhibition (e.g., the restraint and cancellation of action). Taken together with the findings of our earlier work (Chowdhury et al. 2018), the results of the present study are in support of the idea that individual differences in motor-inhibitory ability can indeed be predicted based on individual differences in intracortical inhibition measured at rest.

Limitations and future directions

While the results of our study do indeed suggest a relationship between intracortical inhibition and motor inhibition, a more comprehensive TMS protocol may have shed further insight into this relationship. That is, we had only assessed SICI and LICI at constant stimulation intensities and ISIs. The assessment of SICI and LICI at varying intensities of

the conditioning stimulus [i.e., input/output curves (Ilić et al. 2002)] or test stimulus [i.e., threshold tracking (Samusyte et al. 2018)] may have given us a more comprehensive assessment of the profile of each individual's intracortical inhibitory functioning (and thus its relationship with motor inhibition), and could have potentially produced more reliable estimates than the constant stimulation approach used in the present study. Furthermore, while the ISIs used in the present study are those that are commonly used to assess $GABA_A$ and $GABA_B$ receptor activity (Stagg et al. 2011; Tremblay et al. 2012), there is individual variability in responsivity to different ISIs (Benwell et al. 2006) and different ISIs may potentially probe differing underlying intracortical inhibitory mechanisms (Opie et al. 2017). Future studies investigating the relationship between intracortical inhibitory functioning and relevant motor behaviours should aim to do so using a more comprehensive TMS protocol, encompassing a wider variety of stimulation intensities and ISIs.

Further investigations should aim to determine whether a relationship also exists for other popular resting-state TMS measures such as interhemispheric inhibition (IHI) and other relevant motor behaviours such as the selective enactment and inhibition of bimanual actions. Indeed, like SICI and LICI, IHI has also been often applied during task performance to assess temporal changes in transcallosal inhibition during selective and non-selective bimanual actions (Duque et al. 2007; Hinder et al. 2018). Moreover, IHI has similarly been found to be in deficit when measured in a resting state in clinical groups where bimanual motor control is known to be impaired (Manson et al. 2006; Nelson et al. 2010). To our knowledge, however, there are no available studies which have directly investigated the possible relationship that may exist between individual differences in resting-state IHI and bimanual task performance.

Conclusion

In summary, the present study confirms the hypothesis that resting-state intracortical inhibition measures (i.e., SICI and LICI) are indeed predictive of the quality of stopping performance. While earlier studies had shown that both SICI and LICI were increased when actions had to be restrained or cancelled, our results suggest that interindividual differences in SICI and LICI taken in a resting state are significantly associated with the accuracy by which one is able to perform both action restraint and action cancellation. Taken together, these findings provide support for the use of resting-state measures of intracortical inhibition as a potential biomarker of reduced motor inhibition (and indeed, other relevant motor functions) in research and clinical settings.

Author contributions JLH was involved in the conceptualisation, data collection, and written preparation of the final manuscript. IF, JC, W-PT, and PE were involved in the conceptualisation and written preparation of the final manuscript. PB was involved in the data collection and written preparation of the final manuscript. CH was involved in supervision of the overall project, and contributed to the conceptualisation, data collection, and written preparation of the final manuscript.

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