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Cortical silent period reflects individual differences in action stopping performance

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Inhibitory control is the ability to suppress inappropriate movements and unwanted actions, allowing to regulate impulses and responses. This ability can be measured via the Stop Signal Task, which provides a temporal index of response inhibition, namely the stop signal reaction time (SSRT). At the neural level, Transcranial Magnetic Stimulation (TMS) allows to investigate motor inhibition within the primary motor cortex (M1), such as the cortical silent period (CSP) which is an index of $GABA_B$-mediated intracortical inhibition within M1. Although there is strong evidence that intracortical inhibition varies during action stopping, it is still not clear whether differences in the neurophysiological markers of intracortical inhibition contribute to behavioral differences in actual inhibitory capacities. Hence, here we explored the relationship between intracortical inhibition within M1 and behavioral response inhibition. $GABA_B$ergic-mediated inhibition in M1 was determined by the duration of CSP, while behavioral inhibition was assessed by the SSRT. We found a significant positive correlation between CSP's duration and SSRT, namely that individuals with greater levels of $GABA_B$ergic-mediated inhibition seem to perform overall worse in inhibiting behavioral responses. These results support the assumption that individual differences in intracortical inhibition are mirrored by individual differences in action stopping abilities.

Inhibitory control is a central executive function that allows to temporarily withhold or completely suppress inappropriate or unintended responses, even after these are already initiated. This ability plays a pivotal role in everyday life because behaving in a goal-directed manner constantly requires a quick and efficient regulation of our impulses and responses[1]. Lacking an efficient inhibitory control may result in a number of different dysfunctional behaviors, as evidenced in several medical and psychiatric conditions[2] such as attention-deficit/hyperactivity disorder[3], eating disorders[4] substance abuse disorders[5] and obsessive–compulsive disorder[6].

At the behavioral level, one of the most reliable paradigms employed for measuring response inhibition is the Stop Signal Task[7–10] (SST). This task allows estimating individuals' ability to suppress a response already initiated, as it measures the temporal dynamics underlying successful response inhibition[8,9,11–13]. Performance in this task is highly variable across the normal population and reaches abnormally longer values in clinical conditions[2] including attention-deficit hyperactivity disorder[3] (ADHD) and obsessive compulsive disorder[6] (OCD), as well as Gambling Disorder[14]. Hence finding biomarkers of response inhibition is desirable.

At the neural level, Transcranial Magnetic Stimulation (TMS) has been widely employed to investigate the electrophysiological markers of motor inhibition in the brain[1,15–23]. Different TMS-EMG protocols can be used to measure levels of intracortical inhibition within the primary motor cortex (M1). Specifically, intracortical inhibition can be quantified either from the intensity of Short-interval intracortical inhibition (SICI, $GABA_A$-mediated inhibition) and Long-interval intracortical inhibition (LICI, $GABA_B$-mediated inhibition), obtained with two different paired-pulses procedures, or from the duration of the cortical silent period (CSP, $GABA_B$-mediated inhibition), measured following specific single pulse procedures[24–26]. The CSP is a cessation in the background voluntary muscle activity induced by a single suprathreshold TMS pulse delivered on M1 during tonic contraction of the target muscle[24,25,27] (Fig. 1). In particular, absolute CSP is obtained by measuring the time interval between the offset of the MEP and the restoration of the muscle activity, and it is expressed in milliseconds (ms). The first part of the CSP (50–75 ms) is thought to be partially influenced by spinal cord inhibition contributions,

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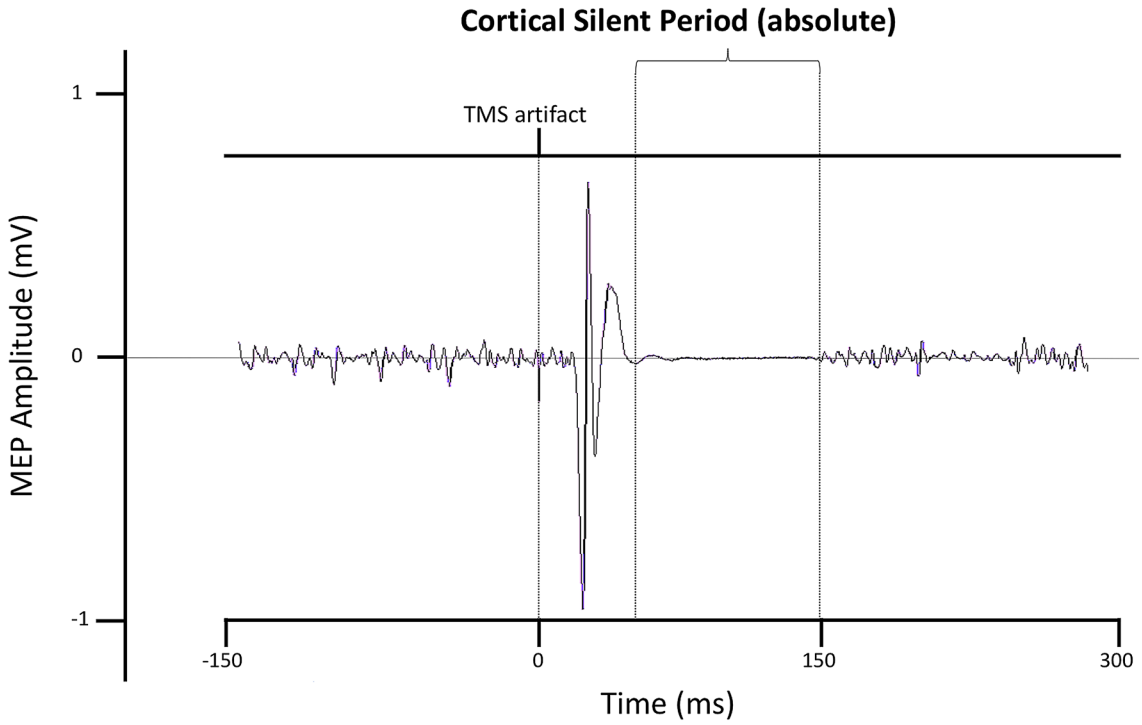

Figure 1. Representative traces of the FDI's cortical silent period at 30% maximal voluntary contraction (MVC).

while its latter part is entirely mediated by motor cortical postsynaptic inhibition[24,25]. Overall, the duration of the CSP is considered an index of the levels of slower inhibitory postsynaptic potentials $GABA_B$ inhibition within M1[25,28]. Crucially, while SICI and LICI provide an amplitude measure of intracortical inhibition, the CSP provides a temporal measure of this process. Hence, even though both LICI and CSP could be treated as markers of $GABA_B$-mediated inhibition, these two measures do not overlap, as they reflect different aspects[29,30]. Specifically, LICI is an electric potential difference expressed in millivolts which represents the magnitude of inhibition, while CSP represents the duration of intracortical inhibition.

Given the complementary nature of these different measures, several works have already tried to employ TMS during the SST to probe the fluctuations in the levels of corticospinal and intracortical inhibition within M1 associated with concurrent action preparation and action stopping[31]. Interestingly, studies in which TMS was delivered online on participants during the SST revealed that behavioral motor inhibition is deeply influenced by the ongoing electrophysiological modulation of corticospinal motor excitability and inhibition within M1[31,32]. For example, in go trials, action preparation induces a significant progressive increase in the levels of corticospinal excitability in the contralateral M1[18,32–34] (≈130–175 ms after the onset of the go signal), while during stop trials action inhibition induces both a widespread decrease in corticospinal excitability[33] (≈140 ms after the onset of the stop signal) and, concurrently, a significant increase in SICI.

Overall, the ongoing modulation of corticospinal excitability and intracortical inhibition within M1 appears to be critical to the successful restraint and cancellation of actions. Nevertheless, it is still unclear whether individual differences in these neurophysiological markers of intracortical inhibition might be related to actual behavioral individual differences in inhibitory control efficiency[14,35]. Recently, quite a few studies[14,35–42] have investigated whether and to what extent individual levels of resting-state SICI and LICI measured offline might reflect individual differences in the efficiency of the inhibitory process, indexed by the length of the Stop Signal Reaction Time (SSRT). Taken together, these studies support the hypothesis that trait-like individual differences in the neurophysiological markers of intracortical inhibition (and SICI in particular) can predict an individual's actual behavioral motor inhibition capacities[14]. Hence, TMS-derived measures of intracortical inhibition might be effectively employed as biomarkers of motor inhibition performance. However, to date, no studies have investigated whether the CSP's duration, measured offline, might also be considered a viable biomarker of motor inhibition, notwithstanding this being the only TMS-based parameter measured as a time interval. This is the aim and the novelty of the current study.

Results

Behavioral data. Raw data were processed via a customized R software (version 3.6.2) for Windows, using the code for the analysis provided by Verbruggen and Colleagues[9]. The average SSRT was 215 ms (SD = 20.6 ms). The table below (Table 1) shows the average and SD of the main measures obtained from the Stop Signal Task: Stop Signal Reaction Time (SSRT), Stop Signal Delay (SSD), RT on go trials (goRT), probability of responding

Stop Signal Task	Mean ± SD
SSRT	215 ms ± 21
SSD	318 ms ± 117
goRT	546 ms ± 105
p(respond|signal)	49% ± 1
sRT	480 ms ± 89
miss	2% ± 3
acc	99.6% ± 0.4

Table 1. Descriptive statistics of the Stop Signal Task. Values in the table represent means and standard deviations of the descriptive statistics of the Stop Signal Task. Legend: SSRT = Stop Signal Reaction Time; SSD = Stop Signal Delay; goRT = RT on go trials; p(respond|signal) = probability of responding on a stop trial; sRT = RT of go responses on unsuccessful stop trials; miss = probability of go omissions; acc = accuracy rate on go trials.

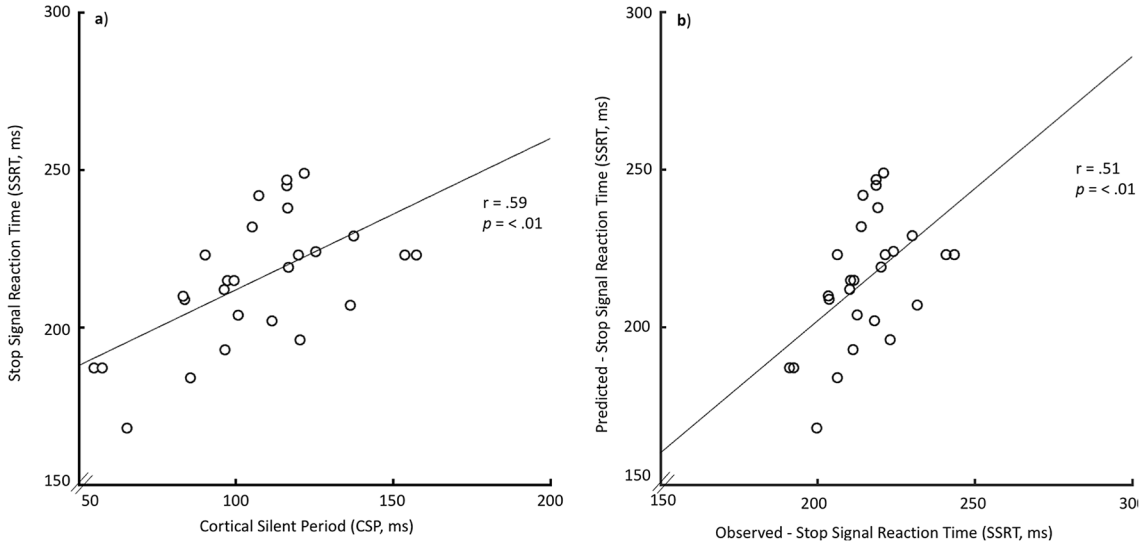

Figure 2. (**a**) Linear association between cortical silent period (CSP) and Stop Signal Reaction Time (SSRT). (**b**) Leave one out cross-validation analysis showing a significant correlation between the model-predicted and observed SSRT values.

on a stop trial [p(respond|signal)], RT on unsuccessful stop trials (sRT), probability of go omissions (miss), and accuracy rate on go trials (acc).

Neurophysiological data. The CSP duration was defined as the time elapsed between the offset of the MEP and the time at which the post-stimulus EMG activity reverted to the pre-stimulus level (absolute CSP). The analysis of CSPs was carried out using Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK). Overall, the mean CSP duration was 106 ms (SD = 26 ms). Average MEP amplitude was 0.49 mV (SD = 0.29 mV), while MEP duration was 35 ms (SD = 2 ms). The average rMT was 55% of the maximum stimulator output (ranging from 48 to 61%, SD = 4%).

Correlation analysis. Four Pearson correlations were carried out to look for the relationships between SSRT and the relevant TMS-derived neurophysiological variables (CSP, rMT, MEP amplitude, MEP duration). These correlations were tested against a Bonferroni-adjusted alpha level of 0.012 (0.05/4). The linear correlation between the CSP and the SSRT was significant (Pearson r (25) = 0.59; $p = 0.001$; CI = [0.25 0.92], Fig. 2a) and survived robust correlation (skipped Pearson r (25) = 0.59; $p = 0.001$; CI = [0.34 0.77]). Most importantly, the results of the leave-one-out cross-validation analysis showed a significant correlation between the model-predicted and observed SSRT values (r(25) = 0.51; $p = 0.007$, Fig. 2b). There was no significant correlation between SSRT and any of the other relevant TMS-derived neurophysiological variables (Table 2).

Discussion

The present study aimed at investigating whether individual differences in the temporal aspect of intracortical inhibition might act as a neurophysiological trait marker reflecting individual response inhibition capacities. Our results revealed a clear relationship between the duration of the cortical silent period (CSP) and the stop

	rMT	MEP (mV)	MEP (ms)	CSP
SSRT	r(25) = .07; p = .716	r(25) = .24; p = .239	r(25) = .269; p = .175	r(25) = .587; p = .001**

Table 2. Correlations between the TMS-derived neurophysiological parameters and SSRT. Values in the table represent Pearson correlation coefficient and significance of the Pearson correlations between each significant TMS-derived Neurophysiological parameter and the SSRT. Legend: rMT = Resting Motor Threshold; MEP (mV) = Motor Evoked Potential amplitude; MEP (ms) Motor Evoked Potential duration; CSP = Cortical Silent Period (absolute); SSRT = see Table 1; ** = correlation is significant at the 0.01 level (2-tailed).

signal reaction time (SSRT), obtained from the Stop Signal Task (SST). In particular, individuals with longer CSP performed worse at the Stop Signal Task, as indexed by longer SSRT, compared to individuals with shorter CSP. The duration of CSP is a neurophysiological marker of the levels of intracortical inhibition within M1[24,25]. Lengthening of the CSP is observed after disruption of motor attention by sedative drugs such as ethanol or benzodiazepines. Indirect pharmacological evidence supports a largely $GABA_B$-mediated origin of the CSP[43–46]. On the other hand, SSRT is a precise index of the duration of the whole chain of processes underlying response inhibition, and so a longer SSRT indicates lower levels of inhibitory control, while a shorter SSRT denotes a better response inhibition. Therefore, our results suggest that CSP might provide a valid trait bio-marker of the quality of action restraint and response inhibition, namely individual inhibitory control capacities.

In general, the relationship between ongoing corticospinal brain activity and behavioral motor functioning has been extensively investigated[31]. Recently, quite a few studies[14,35–42] have investigated the relationship between offline TMS-derived GABA-ergic inhibitory biomarkers (resting-state SICI, LICI) and behavioral motor-inhibitory efficiency. In particular, in their study Chowdhury and colleagues[14] showed a negative correlation between individual $GABA_A$-ergic intracortical motor inhibition (measured via SICI's amplitude) and SSRT's length, indicating that subjects with stronger resting state SICI tend to be faster at inhibiting their responses, and so better at action stopping.

Hence, our results complemented those reported by Chowdhury and colleagues[14]. Indeed, intracortical inhibition is not modulated through a single process, but it is the synergic result of the interaction between two functionally distinct neural populations mediating either short-lasting ionotropic $GABA_A$ postsynaptic inhibition or long-lasting metabotropic $GABA_B$ postsynaptic inhibition. Such two mechanisms are indexed by SICI and LICI/CSP respectively[47,48].

According to the resulting model of interaction between these different cortical inhibitory systems, LICI and CSP do not only inhibit cortical outputs via postsynaptic $GABA_B$ receptors, but they even selectively suppress SICI via presynaptic $GABA_B$ receptors, causing an overall reduction of GABA release[26,49–51]. This $GABA_B$ mediated suppression of $GABA_A$ effects has been corroborated by converging evidence from in vitro studies[47,52], as well as pharmacological and TMS studies both at rest and during voluntary movement[26,30,51,53]. Hence, not only SICI and LICI/CSP are mediated by different neural circuits, but the latter can inhibit the first, and so SICI inhibition might result not only from the actual activity of SICI circuits but also as a consequence of increasing $GABA_B$-mediated inhibition[51]. Given that CSP is regulated by a $GABA_B$-mediated inhibitory network and that longer CSPs are considered an index of upregulated intracortical inhibition[54], we hypothesize that stronger $GABA_B$-ergic circuits, indexed by longer CSP, might unbalance intracortical inhibition during action stopping, resulting in a global reduction of SICI-mediated reactive inhibition and so in a longer SSRT. Interestingly, a similar detrimental effect of CSP's upregulation has been recently associated with eating disorders, and specifically with Binge Eating Disorder[55]. Keeping this in mind, the negative correlation between SICI's strength and SSRT found by Chowdhury and Colleagues[14] and the positive correlation between CSP and SSRT reported here might originate from the same overall inhibitory mechanism. Indeed, it is entirely plausible that these two correlations reflect the opposite effects of these two distinct neural populations mediating different inhibitory sub-processes during action stopping, and so that stronger levels of $GABA_B$ inhibition might unbalance intracortical inhibition diminishing the $GABA_A$-mediated inhibition during action stopping, resulting in worse performance and consequently in a longer SSRT.

Overall, our results suggest that the duration of CSP measured off-task should be considered as a neurophysiological inhibitory biomarker reflecting individual response inhibition capacities, and specifically that individuals with longer CSP performed worse at action stopping (longer SSRT), compared to individuals with shorter CSP (shorter SSRT). Our results also support the idea that TMS-derived biomarkers might provide a reliable methodology to investigate behavioral individual differences in motor inhibition.

Methods

Participants. Twenty-seven 27 (11 males, mean age = 27.84 years; SD = 3.8; range = 23–38) right-handed (self-reported) naïve participants with normal or corrected-to-normal vision took part in the present study. The sample size of 27 was calculated by using G Power software[56,57] (v3.1.9.6) analysis assuming an effect size (r) of 0.62 (based on Chowdhury and Colleagues[14]), an acceptable minimum level of significance (α) of 0.05, and an expected power (1-β) of 0.80.

During the recruitment stage, participants were preliminarily screened for history of neurological disorders and current mental health problems, as well as for hearing and visual difficulties, and completed a questionnaire to check whether they were eligible for a TMS-based study. None of the participants here included reported neither having TMS contraindicators nor having been diagnosed with any psychiatric or neurological disorder, as self-reported. Participants provided written informed consent before taking part in the study. None of the

participants reported any negative side effects during or after the TMS procedure. The whole study took place at ITAB (Institute for Advanced Biomedical Technologies) in Chieti and lasted 1 h and 15 min on average. The study was approved by the Ethics Committee of the "G. d'Annunzio" University of Chieti-Pescara and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Measures. *EMG recording preparation.* The surface EMG signal was recorded from the right First Dorsal Interosseous (FDI) hand muscle using three self-adhesive EMG electrodes connected to a CED Micro 1401 (Cambridge Electronic Design, Cambridge, UK). Before electrode placement, recording areas were wiped using an alcohol swab and a pad with abrasive skin prep. Three electrically conductive adhesive hydrogels surface electrodes were then placed along with the target areas of the right hand. Specifically, the positive electrode was placed over the FDI muscle, the negative electrode was placed on the outer side of the thumb knuckle, and the ground electrode was placed on the ulnar styloid process. EMG raw signals were amplified (by a factor of 1000), digitized at a sampling rate of 8 kHz, and filtered using an analogical online band-pass (20 Hz to 250 Hz) and a 50 Hz notch filter. EMG recordings were then stored on a computer for offline analysis with Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK).

Transcranial magnetic stimulation. Before TMS administration, participants wore a hypoallergenic cotton helmet which was used to mark the exact location of the FDI hotspot over the left primary motor cortex (M1). Single-pulse monophasic TMS was delivered over the left primary motor cortex using a double 70 mm Alpha coil connected to BiStim[4] Magstim stimulators (Magstim, Whitland, UK) to induce a posterior-anterior current flow in the brain. The coil was positioned tangentially to the scalp following the orthodox method[27], with the handle pointed backward and angled 45 degrees from the midline, perpendicular to the central sulcus. The FDI optimal scalp position for stimulation was identified by maneuvering the coil around the left M1 hand area in steps of 1 cm until eliciting the maximum amplitude motor-evoked potentials (MEPs) in the contralateral FDI muscle using slightly suprathreshold stimuli. Once identified and marked the hotspot on the helmet, coil position was fastened through mechanical support, and its position was constantly monitored by the experimenter. Participants were asked to avoid any head movement throughout the whole TMS session and were also firmly cushioned using ergonomic pads. Afterward, individuals' resting motor threshold (rMT) was estimated by consistently adjusting the stimulator to find the lowest percentage of the maximum stimulator output necessary to elicit MEPs with a peak-to-peak amplitude of more than 50 μV during muscle relaxation in 5 out of 10 trials[27]. For each participant, rMT was used to determine the specific intensity of TMS suprathreshold stimulation, which was set at 120% of this individual value. This level of stimulation intensity is considered appropriate for studying CSP[57,58].

Intracortical inhibition. Individuals' CSP was assessed delivering 20 suprathreshold pulses at 120% of rMT while participants were performing an opposition pinch grip at 30% of their FDI's maximal voluntary isometric contraction (MVC) and maintaining both a static hand posture and a constant level of muscle activity. Individuals' MVC was used as the reference contraction to normalize the muscular activity between subjects[59,60] and it was determined by averaging the mean peak-to-peak amplitude of the EMG signal (μV) recorded across three trials lasting 3 s each. Before measuring MVC, the experimenter emphasized to the participants the importance of performing at their best and of trying to keep the contraction stable during EMG recording. Once determined participants' MVC, the level of muscular activation was constantly monitored by the experimenter via online data inspection throughout the whole TMS session. Before the TMS session, each participant took part in a short preliminary training session (never longer than 5 min) to learn how to constantly perform and maintain the appropriate level of FDI contraction (30% MVC) while receiving constant EMG visual feedback displayed on the computer monitor. The TMS session (hotspot mapping procedure, resting motor threshold estimation, and actual experimental session) started only after participants became able to reproduce the adequate level of EMG activity requested without the support of the EMG visual feedback. Each single-pulse TMS stimulation was delivered with an inter-stimulus interval jittered between 8 and 15 s to avoid any habituation effect. Coherently with the short duration of the CSP recording session and with the relatively low level of FDI contraction requested (30% MVC), no participant reported experiencing muscle fatigue at any stage of the recording procedure. Trials were rejected if the participant displayed any pronounced head movement before or during the stimulation. For each trial, CSP duration was first quantified as the time between the offset of the MEP and the return of EMG activity to the pre-stimulus level (±2 SD) and then double-checked following a standard procedure[58,61]. CSPs preliminary inspection, analysis, and offline extraction were all carried out using Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK). CSPs were inspected before processing the Stop Signal Task data, and so the inspector was blinded to the relative behavioral results.

Behavioral level—motor Inhibition. To measure motor inhibition at the behavioral level we employed "STOP-IT"[62], a Matlab and Psychtoolbox[63–65] version of the Stop Signal Task. In the beginning, participants were instructed to place their right hand on a specific site of the computer keyboard (the right index finger over the left arrow key and the right ring finger over the right arrow key) and to maintain this position throughout the whole experiment. The task required participants to perform a speeded response go task while discriminating between two different go stimuli, a left-pointing white arrow, and a right-pointing white arrow, responding to both of them as quickly as possible pressing the left arrow key of the computer keyboard with the right index finger and the right arrow key with the right ring finger, respectively (go trials). However, in 25% of the trials (stop trials), the white go arrow would turn blue after a variable delay (stop signal delay (SSD)), indicating to the participants to withhold their response, whether possible (Fig. 3). Crucially, the instructions provided with the

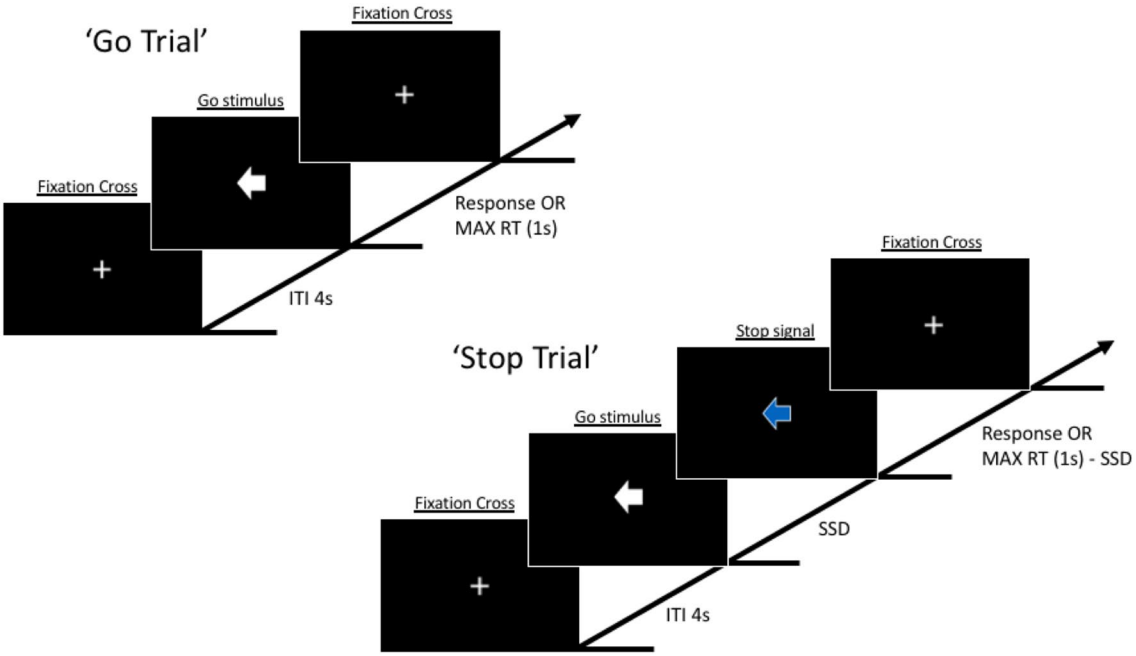

Figure 3. Visual representation of the sequence of events in the Stop Signal Task employed in the present study.

task explicitly emphasized that in half of the stop trials the stop signal would appear soon after the go stimulus, making response inhibition easier, while on the other half of these trials the stop signal would be displayed late making response inhibition difficult or even impossible for the participant. Thus, participants were instructed that the task was difficult and that failing in half of the trial was an inherent characteristic of the task itself. They were also instructed to always try to respond to the go signal as fast and accurately as possible, without withholding their response to wait for a possible stop signal occurrence.

In the go trials, go stimuli lasted 1 s (maximum RT), while in stop trials the combination of the go, the SSD, and the stop signal lasted 1 s in total, with SSD being initially set at 250 ms. Inter-trial interval lasted 4 s. Crucially, after each trial the SSD automatically varied in steps of 50 ms as a function of participants previous stop performance, decreasing after each unsuccessful stop trial and increasing after each successful stop trial, ensuring an overall successful inhibition rate near 50%, and so a $p(\text{respond}|\text{signal}) \cong 0.50$. The task included an initial practice block providing feedback after each trial. Relevant descriptive statistics obtained from the task included: the probability of go omissions, probability of choice errors on go trials, RT on go trials, probability of responding on a stop trial, Stop Signal Delay, Stop Signal Reaction Time, RT of go responses on unsuccessful stop trials. The Stop Signal data collected from each participant were screened according to the following outlier rejection criteria[66]: (1) probability of responding on stop trials < 40% or > 60%; (2) probability of go omissions > 25%; (3) probability of choice errors on go trial > 10%; (4) violation of the independent race model (RT of go responses on unsuccessful stop trials > RT on go trials); (5) either negative SSRT or SSRT < 50 ms. These exclusion criteria were adopted because they help to ensure that participants followed the instruction and got engaged throughout the task[66]. One participant was excluded for matching exclusion criteria (4) and replaced with another one. In the present study, we used a non-parametric approach for SSRT's estimation using the integration method with the replacement of go omissions with the maximum goRT[9]. Overall, the whole task comprised 1 practice block of 32 trials (8 stop trials) and 5 experimental blocks of 96 trials (24 stop trials) each. Between blocks, participants were reminded about the instructions and provided with block-based feedback on their performance.

Procedure. Participants took part in either the TMS session or the behavioral task, administered in random order on the same day with a 10 min break between them. The TMS session took place in the TMS/EMG laboratory of ITAB for about 35 min, following the same procedure already described above for each participant. The behavioral task took place in one of the Data Collecting Booths of the TEAMLab of ITAB for about 40 min. During the behavioral task, participants sat on a comfortable chair in front of a computer monitor with a resolution of 1024 horizontal pixels by 768 vertical pixels, at a distance of approximately 56–57 cm. The tasks were administered on Windows 7 using MATLAB R2016b. The computer monitor refresh rate was set to 60 Hz. Once finished the two parts of the experiment, participants were debriefed.

Data analysis. To investigate the relationship between behavioral and cortical inhibition we look for a possible correlation between SSRT and CSP.

To control for the specificity of the effect, we run a regression analysis between each of the individual Stop Signal Task significant parameters (SSRT, SSD, goRT, sRT, p(respond|signal), acc. ns, miss. ns) and each significant TMS-derived neurophysiological parameter (rMT, amplitude of the accompanying MEP, and duration of CSP).

CSPs inspection and extraction were performed before processing the Stop Signal Task data, and so the inspector was blinded to behavioral results. Moreover, to test the robustness of the relationship we computed skipped parametric (Pearson) correlations[67] using the Robust Correlation toolbox[68] and conducted null hypothesis statistical significance testing using the nonparametric percentile bootstrap test (2000 resamples; 95% confidence interval, corresponding to an alpha level of 0.05), which is more robust against heteroscedasticity compared with the traditional t-test[68]. Then, we employed a leave-one-out cross-validation analysis[69] (i.e., internal validation) to test whether participants' CSP could reliably predict the SSRT. Specifically, at each round of cross-validation, a linear regression model was trained on n-1 subjects' values and tested on the left-out participant. Pearson correlations between observed and predicted SSRT values were used to assess predictive power. All statistical tests were two-tailed. To account for the non-independence of the leave-one-out folds, we conducted a permutation test by randomly shuffling the SSRT scores 5000 times and rerunning the prediction pipeline, to create a null distribution of r values. The *p* values of the empirical correlation values, based on their corresponding null distribution, were then computed.

Data availability

The data analyzed during this study are available from the corresponding author upon request.

Received: 29 March 2021; Accepted: 5 July 2021
Published online: 26 July 2021

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Author contributions

M.P., F.F., and M.C. developed the study concept and design. M.P. and M.G.P. developed the experimental setup. M.P. and G.D.C. performed the behavioral data collection. M.P. performed the TMS data acquisition. M.G.P. provided technical support during data acquisition. M.P. and G.D.C. analyzed the data. M.P. and M.C. interpreted the data. M.P. wrote the manuscript. M.C. contributed to the drafting of the manuscript. All authors contributed to and approved the final manuscript.

Competing interests
The authors declare no competing interests.

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