Cortical Silent Period reflects individual differences in action stopping performance

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Running Head: Cortical and behavioral inhibition

Keywords: Cortical silent period; Motor inhibition; Individual differences; TMS; Stop Signal Task.

Abstract

Inhibitory control is the ability to suppress inappropriate movements and unwanted actions, allowing to behave in a goal directed manner and to regulate impulses and responses. At the behavioral level, the ability to suppress unwanted actions can be measured via the Stop Signal Task, which allows estimating the temporal dynamics underlying successful response inhibition, namely the stop signal reaction time (SSRT). At the neural level, Transcranial Magnetic Stimulation (TMS) provides measures of electrophysiological markers of motor inhibition within the primary motor cortex (M1), such as the Cortical Silent period (CSP). Specifically, CSP's length is a neurophysiological index of the levels of intracortical inhibition within M1, mainly mediated by slow $GABA_B$ receptors. Although there is strong evidence that intracortical inhibition varies during both action initiation and action stopping, it is still not clear whether interindividual differences in the neurophysiological markers of intracortical inhibition might contribute to behavioral differences in actual inhibitory control capacities. Hence, we here explored the relationship between individual differences in intracortical inhibition within M1 and behavioral response inhibition. The strength of $GABA_B$ergic-mediated inhibition in M1 was determined by the length of individuals' CSP, while the ability to suppress unwanted or inappropriate actions was assessed by the SSRT. We found a significant positive correlation between CSP's length and SSRT, namely that individuals with greater levels of $GABA_B$ergic-mediated inhibition within M1 seems 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.

New & Noteworthy

The present study corroborates the hypothesis that interindividual differences in neurophysiological TMS-derived biomarkers of intracortical inhibition provide a reliable methodology to investigate individual response inhibition capacities. To date, this is the first study to show that interindividual differences in the CSP's length measured offline provide a viable biomarker of behavioral motor inhibition, and specifically that individuals with longer CSP performed worse at action stopping, compared to individuals with shorter CSP.

Keywords: Transcranial Magnetic Stimulation; Intracortical Inhibition; Cortical Silent Period; GABA; Stop Signal Task; Inhibitory Control; Action Stopping

Introduction

Inhibitory control is a central executive function which 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 (Duque et al. 2017). Lacking of an efficient inhibitory control may result in a number of different dysfunctional behaviors, as evidenced in several medical and psychiatric conditions such as attention-deficit/hyperactivity disorder (Lipszyc and Schachar 2010), eating disorders (Bartholdy et al. 2016), substance abuse disorders (Lipszyc and Schachar 2010; Smith et al. 2014) and obsessive-compulsive disorder (Milad and Rauch 2012).

At the behavioral level, one of the most reliable paradigms employed for measuring response inhibition is the Stop Signal Task (SST, Lappin and Eriksen 1966; Logan and Cowan 1984; Verbruggen et al. 2019; Vince 1948). This task allows estimating individuals' ability to suppress a response already initiated, as it measures the temporal dynamics underlying successful response inhibition (Logan and Cowan 1984; Logan et al. 1997, 2014; Verbruggen et al. 2008, 2019). The SST requires participants to perform speeded responses to go stimuli, usually arrows pointing either to the left or to the right, by pressing left or right keys, respectively. Crucially, on a minority of trials (e.g., 25% - 30%, stop signal probability), shortly after the go signal, a subsequent stop signal may randomly appear with a variable delay (stop signal delay, SSD). In presence of this stop signal participants are instructed to suppress their response, whenever possible (Verbruggen et al. 2019). After each stop trial the following SSD varies as a function of participants performance, decreasing after each unsuccessful stop trial and increasing after each successful one, in order to achieve a 50% rate in the probability of successful stopping (Logan et al. 1997; Verbruggen et al. 2019). Since successful inhibition always leads to the absence of any observable response, the latency of response inhibition cannot be measured directly. However, by assuming the "independent race" model of inhibition (Logan and Cowan 1984; Verbruggen et al. 2019), the SST allows to measure the individual time required to inhibit a response, namely the Stop Signal Reaction Time (SSRT). In this model action stopping in the SST is the result of a race between two independent and countermanding processes, namely between the ongoing "go process" (measurable by the Go Reaction Time, GoRT) triggered by the "go signal" and the subsequent "stop process" triggered after the relative SSD by the upcoming "stop signal", trying to catch up (Liddle et al. 2009). On stop trials, response inhibition is successful only when the stop process wins the independent race against the go process, namely when the time necessary to finalize the go process (Reaction Time, RT) is larger than the SSRT plus the trial's relative SSD. Overall, SSRT reflects the duration of the whole stop process (Verbruggen et al. 2013) and provides a precise index of the duration of the whole chain of processes involved in response inhibition, and so the longer the SSRT the lower the efficiency of inhibitory control (Hilt and Cardellicchio 2018; Verbruggen et al. 2013, 2019). Interestingly, SSRT is highly variable across the normal population, and reaches abnormally longer values in clinical conditions (Lipszyc and Schachar 2010) including attention-deficit hyperactivity disorder (ADHD) (Oosterlaan et al. 1998) and obsessive compulsive disorder (OCD) (Menzies et al. 2007), as well as Gambling Disorder (Chowdhury et al. 2017). 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 (Duque and Ivry 2009; Duque et al.

2010; Greenhouse et al. 2012, 2015a, 2015b, 2017; Hasbroucq et al. 1999; Leocani et al. 2000; Pascual-Leone et al. 1992; Starr et al. 1988). Different TMS-EMG protocols can be used to measure levels of intracortical inhibition within the primary motor cortex (M1). Specifically, it can be quantified either from the intensity of Short-interval intracortical inhibition (SICI) and of Long-interval intracortical inhibition (LICI), obtained with two different paired-pulses procedures, or from the length of the cortical silent period (CSP), measured following a particular single pulse procedure (Hallett 2007; Paulus et al. 2008; Werhahn et al. 1999). Overall, in paired-pulses protocols a first TMS pulse, the conditioning stimulus (CS), is always followed by a second TMS pulse, the test stimulus (TS), delivered after a variable interstimulus interval (ISI). SICI is thought to reflect fast-acting inhibitory postsynaptic potentials within M1, and it is considered mainly an effect of inotripic $GABA_A$ neurotransmission (Coxon et al. 2006; Di Lazzaro et al. 2000; Paulus et al. 2008; Sohn et al. 2002; Ziemann et al. 1996). This parameter is measured by comparing the amplitude of the paired-pulses test stimulus with the amplitude of a single-pulse motor evoked potential (MEP) and is expressed in mV; the greater the difference, the stronger the $GABA_A$-mediated inhibition. On the other hand, LICI is thought to reflect slow inhibitory postsynaptic potentials within M1, mainly mediated the activity of metabotropic $GABA_B$ receptors, and is measured by comparing the amplitude of the inhibited test stimulus with the amplitude of the conditioning stimulus and is expressed in mV; a greater difference indicates a stronger $GABA_B$-mediated inhibition (McDonnell et al. 2006; Paulus et al. 2008; Sanger et al. 2001; Werhahn et al. 1999). Unlike SICI and LICI, CSP is measured via a single pulse procedure (Hallett 2007; Paulus et al. 2008). 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 (Epstein et al. 2012; Hallett 2007; Paulus et al. 2008; Rossini et al. 2015). This parameter is obtained measuring the time interval between the onset 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 due to spinal cord inhibition contributions, while its latter part is entirely mediated by motor cortical postsynaptic inhibition (Hallett 2007; Paulus et al. 2008). Overall, the length of the CSP is considered an index of the levels of slower inhibitory postsynaptic potentials $GABA_B$ inhibition within M1 (Cardellicchio et al. 2019; Werhahn et al. 1999; Ziemann et al. 2015). 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 both treated as markers of $GABA_B$-mediated postsynaptic inhibition, these two measures do not overlap, as they reflect different aspects. Specifically, despite both these TMS-based paradigms providing an index of intracortical inhibition, LICI represents an electric potential difference expressed in millivolts, while CSP represents the temporal aspect of intracortical inhibition.

Given the complementary nature of these different measures, several works have already tried to combine TMS with the SST in order to probe the fluctuations in the levels of corticospinal and intracortical inhibition within M1 associated with concurrent action preparation and action stopping (see Duque et al. 2017). 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 inhibitability within M1 (Duque et al. 2017). For example, in go trials action preparation induces a significant progressive increase in the levels of cortico-spinal excitability in the contralateral M1 (≈ 130-175 ms

after the onset of the stop signal Coxon et al. 2006; Greenhouse et al. 2012; Macdonald et al. 2014; Majid et al. 2012; van den Wildenberg et al. 2010), while during stop trials action inhibition induces both a widespread decrease in cortico-spinal excitability (≈ 140ms after the onset of the stop signal; Coxon et al. 2006) and, concurrently, a significant increase in the levels of fast-acting inhibitory postsynaptic $GABA_A$-ergic potentials within the contralateral M1, as indexed by variations in SICI levels. Conversely, increasing the stop signal probability and consequently the foreknowledge that a response might need to be stopped seems to proactively strengthen inhibitory postsynaptic $GABA_B$-ergic, setting a general inhibitory tone in M1, as indexed by variations in LICI levels (Cirillo et al. 2017; Cowie et al. 2016; Duque et al. 2017; Hermans et al. 2019). However, $GABA_B$ activity within M1 can be measured not only from LICI's amplitude, but also from the duration of the CSP. This is particularly important in the context of motor inhibition because, unlike LICI, CSP seems to be modulated specifically during volitional inhibition (van den Wildenberg et al. 2010). In particular, CSP not only significantly decrease after go signal presentation, suggesting that response execution is followed by a concurrent drop of $GABA_B$ intracortical inhibition, but it also shows a significant stop-related increase (≈ 134ms after the onset of the stop signal; van den Wildenberg et al. 2010). Moreover, this stop-related increase in the levels of $GABA_B$ intracortical inhibition (and so in the length of the CSP) is followed by a consequent reduction of cortico-spinal excitability (≈ 180ms after the onset of the stop signal), which, in turn, increases the probability of successful stopping (van den Wildenberg et al. 2010).

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 (Chowdhury et al. 2017; He et al. 2019). Recently quite a few studies (Chowdhury et al. 2018, 2019a, 2019b, 2020a, 2020b; He et al. 2019; Hermans et al. 2019) 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 processes, indexed by the length of the SSRT. Taken together, these studies support the hypothesis that trait-like interindividual differences the neurophysiological markers of intracortical inhibition (and SICI in particular) can predict individual's actual behavioral motor inhibition capacities (Chowdhury et al. 2018). Hence, TMS-derived measures of intracortical inhibition might be effectively employed as biomarkers of motor inhibition performance. However, to date no studies have investigated yet whether interindividual differences in the CSP's length measured offline might also candidate as a viable biomarker of motor inhibition, notwithstanding this being the only TMS-based parameter measured as a time interval. This is the aim of the current study.

Materials and methods

Participants

Twenty-seven 27 (11 males, mean age = 27.84; SD = 3.8; range = 23-38) right-handed 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 (v3.1.9.6) (Faul et al. 2007, 2009) analysis

assuming an effect size (r) of .62 (based on Chowdhury et al. 2018), an accepted minimum level of significance (α) of 0.05, and an expected power (1-β) of 0.80. One participant (female) was excluded from correlational analysis and replaced with another one (male) because she met the exclusion criteria set a-priori for the behavioral task.

During the recruitment stage, participants were preliminary screened for history of neurological disorders and current mental health problems, as well as for hearing and visual difficulties, and completed a standard 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. Participants provided their informed consent before taking part in the study. None of the participants reported any negative side-effects during or after TMS procedure. The whole study took place at ITAB (Institute for Advanced Biomedical Technologies) in Chieti, and lasted 1 hour 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. 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). Prior to 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 the target areas on 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 (1000°ø), digitized at a sampling rate of 8 kHz, and filtered using an analogical on-line band-pass (20 Hz to 250 Hz) and a 50 Hz notch filter. EMG recordings were then stored on a computer for online visual display and 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 as a reference to mark the exact location of the FDI hotspot over the left primary motor cortex (M1). Single-pulse TMS was delivered over the left primary motor cortex using a 70 mm figure-of-eight coil connected to two-Magstim 2002 (Magstim, Whitland, UK) integrated into a Bistim2 stimulator. The coil was positioned tangentially to the scalp following the orthodox method (Rossini et al. 2015), with the handle pointed backwards and angled 45 degrees from the midline, perpendicular to the central sulcus. The FDI Optimal Scalp Position (OSP) for stimulation was identified by maneuvering the coil around the left M1 hand area in steps of 0.5 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 a mechanical support and its position 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. Afterwards, individuals' resting motor threshold (RMT) was estimated by consistently adjusting the stimulator output to find the lowest intensity of stimulation necessary to elicit MEPs with a peak-to-peak amplitude of more than 50 μV

during muscle relaxation in approximately 5 out of 10 trials (Rothwell et al. 1999). 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 (Farzan et al. 2013; Giovannelli et al. 2009; Säisänen et al. 2008).

Intracortical Inhibition. Levels of $GABA_B$ergic-related corticospinal inhibition were assessed via a single pulse TMS paradigm, namely by measuring the length of the cortical silent period (CSP). 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 (Burden 2010; Mathiassen et al. 1995) and it was determined by averaging the mean peak-to-peak amplitude of the EMG signal (μV) recorded across three trials lasting 3 seconds each. Before measuring MVC, the experimenter emphasized to participants the importance of performing at their best and of trying to keep the contraction as stable during EMG recording. Once determine participants' MVC, the level of muscular activation was constantly monitored by the experimenter via online data inspection throughout the whole TMS session. Prior to the TMS session, each participant took part in a preliminary training session in order to learn to perform and retain constantly the appropriate level of FDI contraction (30% MVC) while receiving a 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 reproduce the adequate level of EMG activity requested even without the support of the EMG visual feedback. Each single-pulse TMS stimulations was delivered with an inter-stimulus interval jittered between 8 and 15 seconds in order to avoid any habituation effect. Trials were rejected if the participant displayed any pronounced head movement prior to or during the stimulation.

Any possible head movement was constantly monitored by the experimenter by comparing coil position with the marked hotspot on the helmet. After the TMS session, we run a preliminary data inspection in order to exclude trials where CSP was not observable or where the pre-stimulus EMG activity (measured as the root mean square amplitude computed from -300 to -25 ms before the onset of TMS pulse) was exceeding the mean EMG activity by ±3SD. For each accepted trial, CSP duration was first quantified as the time between the onset of the MEP and the return of EMG activity to the pre-stimulus level (±2 SD) and then double-checked following a standard procedure (Farzan et al. 2013; Säisänen et al. 2008). CSPs preliminary inspection, analysis, and offline extraction were all was carried out using Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK). Remarkably, CSPs was inspected prior to processing the stop signal task data, and so the inspector was blinded to the relative behavioral results.

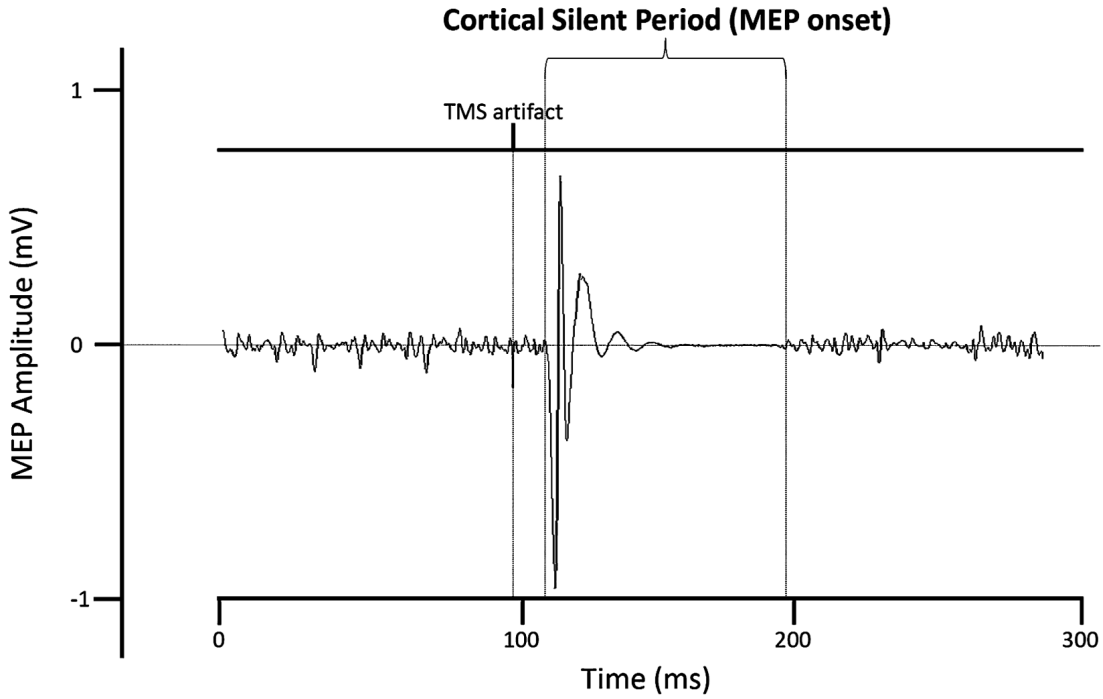

FIG. 1 - Representative traces of the FDI's cortical silent period at 30% maximal voluntary contraction (MVC).

Behavioral level – Motor Inhibition.

To measure motor inhibition at the behavioral level we employed "STOP-IT" (Verbruggen et al. 2013), a Matlab and Psychtoolbox (Brainard 1997; Kleiner et al. 2007; Pelli 1997;) version of the stop signal task. An important methodological consideration is that the decision to employ a unimanual stop signal task was based At the beginning, participants were provided with detailed instructions and 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, on 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. Crucially, the instructions provided with the task explicitly emphasized that on half of the stop trials the stop signal would appear soon after the go one 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 in nature and that failing in half of the trial was an inherent characteristic of the task itself. They were also instructed to always trying to respond to the go signal as fast and accurately as possible, without withholding their response in order to wait for a possible stop signal occurrence, because otherwise the program would have progressively delayed the stop signal presentation. These task-related requests were not only clearly explained in the instructions, but also stressed by the experiment prior to starting the task.

In go trials, go stimuli lasted 1 second (MAX RT), while in stop trials the combination of the go and the stop stimuli lasted 1 second in total (go stimulus duration = SSD; stop stimulus duration = 1 s - SSD), with SSD being initially set at 250 ms. Intertrial interval lasted 4 seconds. 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, ensuring an overall successful inhibition rate near 50%, and so a p(respond|signal) ≅ .50. The task included an initial practice block providing feedback for each trial. Relevant descriptive statistics obtained from the task included: probability of go omissions (miss.ns), probability of choice errors on go trials (acc.ns), RT on go trials (goRT), probability of responding on a stop trial [p(respond|signal)], Stop Signal Delay (SSD), Stop Signal Reaction Time (SSRT), RT of go responses on unsuccessful stop trials (sRT). The Stop Signal data collected from each participant were screened according with the following outlier rejection criteria (see Congdon et al. 2012): (1) [p(respond|signal)] <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 (sRT > goRT); (5) either negative SSRT or SSRT < 50 ms. These exclusion criteria were adopted because they help ensuring that participants followed the instruction and got engaged throughout the task (Congdon et al. 2012). In the present study, we used a non-parametric approach for SSRT's estimation using the integration method with replacement of go omissions with the maximum goRT (see Verbruggen et al. 2019). SSRT was calculated subtracting the mean SSD from the n^{th}goRT, with n being the point in the GoRT distribution whose integral is equivalent to the mean p(respond|signal). 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 a block-based feedback including information about their mean RT, number of go omissions, and p(respond|signal).

FIG. 2 - Visual representation of the of the stop signal task used in the present study.

Procedure

Prior to taking part into the study, all participants were screened for history of neurological disorders and current mental health problems, as well as for hearing and visual difficulties, and completed a standard questionnaire to check whether they were eligible for a TMS-based study, which were administered following a specific procedure. Each participant was then asked to provide basic demographic information (age and sex), received a brief explanation about the purpose of the study, and provided informed consent. Afterwards, participants took part in either the TMS session or the behavioral task, administered in a random order on the same day with a 10 minutes break between them. The TMS session took place in the TMS/EMG Laboratory of ITAB, Chieti for about 35 minutes, 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, Chieti for about 40 minutes. 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 XP using MATLAB R2016b. The whole experiment (TMS session + behavioral session) lasted approximately 1h and 15m. Once finished the two parts, participants were debriefed.

Data Analysis

To investigate the relationship between behavioral and cortical inhibition, we ran a regression analysis between individual stop signal task significant parameters (SSRT, SSD, goRT, sRT, p(respond|signal), acc.ns, miss.ns) and CSP. We were particularly interested in looking for a possible correlation between SSRT and CSP. Remarkably, CSPs inspection and extraction were performed prior to 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 (Wilcox 2014) using the Robust Correlation toolbox (Pernet et al. 2012) 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 (Pernet et al. 2012). Then, we employed a leave-one-out cross-validation analysis (i.e., internal validation) (Koul et al. 2018) 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.

Results

Behavioral data

Preliminary analyses confirm that 26 out of 27 participants completed the stop-signal task appropriately. Only one participant was excluded from further data analysis and replaced with another one because she met the exclusion criteria set a-priori for the behavioral task (she violated

the horse-race model, sRT > goRT, see above). 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 (2019). The average SSRT was 215 ms (SD 20.6). The table below (Table.1) shows the average and SD of the main measures obtained from the Stop Signal Task, namely Stop Signal Reaction Time (SSRT), Stop Signal Delay (SSD), RT on go trials (goRT), probability of responding on a stop trial [p(respond|signal)], RT on unsuccessful stop trials (sRT), probability of go omissions (miss.ns), and probability of choice errors on go trials (acc.ns).

Table 1 – Descriptive statistics of the Stop Signal Task.

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.ns	2% ± 3
acc.ns	99.6% ± 0.4

Values are Means ± Standard Deviations of the main 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.ns = probability of go omissions; acc.ns = probability of choice errors on go trials.

Neurophysiological data

The CSP duration was defined as the time elapsed between the onset of the MEP and the time at which the post-stimulus EMG activity reverted to the pre-stimulus level. The analysis of CSPs were carried out using Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK), and CSPs duration was always ultimately double-checked via visual inspection prior offline extraction. The average length of each individual CSP was treated as an index of the strength of $GABA_B$ergic-mediated activity in M1 (longer CSP = stronger $GABA_B$ergic-mediated activity). Overall, mean CSP duration was 141 ms (SD = 26). Average relative MEP amplitude was 0.49 mV (SD = 0.29).

Correlation analysis

The linear correlation between the CSP and the SSRT was significant (Pearson r(27) = .60; *p* = .0009; CI = [0.36 0.77], figure 3, panel a) and such relationship survived robust correlation (skipped Pearson r (27) = .60; CI = [0.36 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(27) = .52; *p* = .005, figure 3, panel b). There was no correlation between the relative MEP amplitude and the SSRT (Pearson r(27) = .24; *p* = .239). Overall, higher levels of $GABA_B$ergic-related intracortical inhibition in M1 predicted worse inhibitory control capacities.

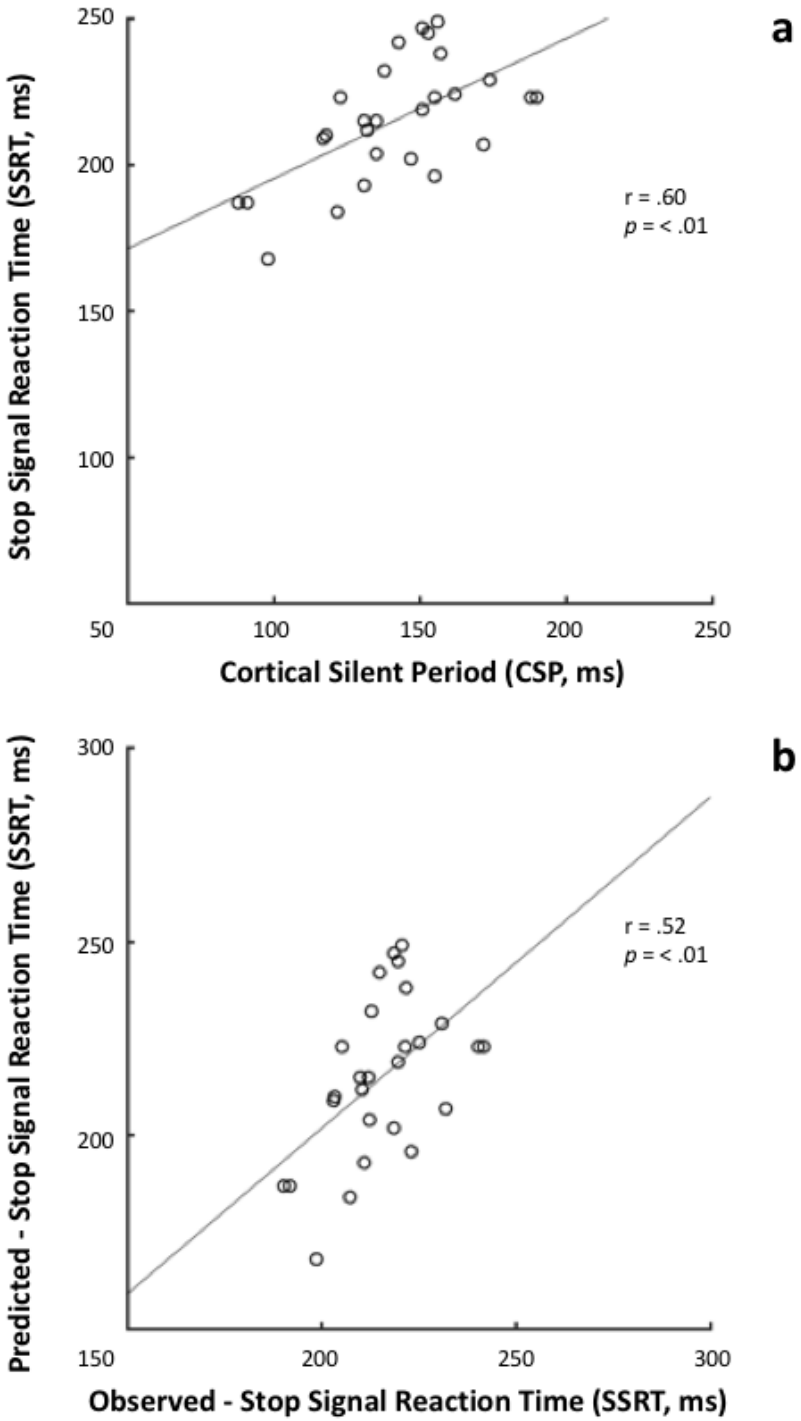

FIG. 3 – **a.** Linear association between cortical silent period (CSP) and Stop Signal Reaction Time (SSRT). – **b.** Leave one out cross-validation analysis showing a significant correlation between the model-predicted and observed SSRT values.

Discussion

The present study was 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 length of cortical silent period (CSP) and the stop signal reaction time, obtained from the stop signal task. 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 (Hallett 2007; Paulus 2008). 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 (Ziemann 2013; Ziemann et al. 1995, 1996, 2015). 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 (Duque et al. 2017). Recently, quite a few studies (Chowdhury et al. 2018, 2019a, 2019b, 2020a, 2020b; He et al. 2019; Hermans et al. 2019) have investigated the relationship between offline TMS-derived GABAergic inhibitory biomarkers (resting-state SICI, LICI) and behavioral motor-inhibitory efficiency. In particular, in their study Chowdhury and Colleagues (2018) showed for the first time 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. At a first glance, Chowdhury and Colleagues (2018)' results might appear in contradiction with those reported in the present study, but this is not the case.

Indeed, the balance between intracortical inhibition and facilitation processes play a key role in modulating cortical outputs in general, and action stopping as well is the results of the complex interactions between inhibitory and excitatory circuits within M1 (Sanger et al. 2001). Moreover, intracortical inhibition itself 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 $GABA_A$ ionotropic postsynaptic inhibition or long-lasting $GABA_B$ metabotropic postsynaptic inhibition, mediating SICI and LICI/CSP respectively (McCormick 1992; Deisz 1999).

Crucially, the mechanism of interactions between these distinct neural circuits underlying these different inhibitory processes, as well as their time courses, have been extensively investigated both during voluntary movement and at rest (Chen 2004; Chu et al. 2008). According with 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 (Chu et al. 2008; Craig and McBain 2014; Sanger et al. 2001; Werhahn et al. 1999). This $GABA_B$ mediated suppression of $GABA_A$ effects has been corroborated by converging evidence from in vitro studies (Davies et al. 1990; Deisz 1999), as well as from pharmacological and TMS studies both at rest and during voluntary movement (McDonnell et al. 2006; Ni et al. 2007; Sanger et al. 2001; Werhahn et al. 1999). 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 activity of SICI circuits itself, but also as a consequence of increasing $GABA_B$-mediated inhibition (Sanger et al. 2001). Given that CSP is regulated by a $GABA_B$-mediated inhibitory network and that longer CSPs are considered an index of upregulated intracortical inhibition (Chaves et al. 2019), 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 (Antunes et al. 2020). Interestingly, a similar detrimental effect of CSP upregulation has been recently associated with eating disorders, and specifically with Binge Eating Disorder (Antunes et al. 2020). Keeping this in mind, the negative correlation between SICI's strength and SSRT found by Chowdhury and Colleagues (2018) is only apparently contradictory with the positive one between CSP's length and SSRT we showed in this study. Indeed, it is entirely plausible that these two correlations reflect the opposite effects of these two distinct neural populations mediating different inhibitory sub-process 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 a worse performance and consequently in a longer SSRT.

Another possible explanation for the aforementioned apparent contradiction, albeit more speculative, is that these two correlations simply reflect different components of action stopping, namely reactive and proactive inhibition. The stop signal task is an inhibitory control paradigm in which participants are always explicitly instructed that, in stop trials, a subsequent stop signal could appear shortly after the go signal onset (Wessel 2018; Zandbelt et al. 2013). Therefore, throughout the whole task participants are continuously engaged in trying to suppress their actions, when needed. As a consequence, they are also inevitably inclined to consider each trial as a potential stop-trial, anticipating the eventuality of having to withhold their response. Such proactive inhibition intensifies before the onset of the stop signal, while reactive inhibition is triggered by the stop signal detection, prompting the actual inhibitory response (Wessel 2018). Crucially, proactive inhibition might significantly alter action stopping at both behavioral and neural level, affecting stimuli detection, as well as action selection and execution (Elchlepp et al. 2016; Wessel 2018). Hence, despite the Stop Signal Task being primarily designed for investigating reactive inhibition (Elchlepp et al. 2016), it always engages a combination of both proactive and reactive inhibitory components (Elchlepp et al. 2016). Indeed, it is entirely plausible that these two correlations reflect different components of action stopping, namely reactive and proactive inhibition. Given that successful motor inhibition relies on distinct reactive and proactive components, we suggest that SICI and CSP should be considered as neurophysiological inhibitory biomarkers of these two sub-processes, respectively. The idea that proactive and reactive inhibitory abilities can be dissociated is supported by clinical conditions including schizophrenia and ADHD (Benis et al. 2014; Meyer and Bucci 2016; van Hulst et al. 2018; Zandbelt et al. 2011). Indeed, while the former seems to suffer more from proactive inhibitory deficits (van Hulst et al. 2018; Zandbelt et al. 2011), the latter seems to suffer more from reactive inhibitory deficits (Mayer et al. 2016).

Overall, our results clearly revealed that the length CSP measured off-task should be considered as 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.

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