Cortical Silent Period reflects individual differences in action stopping performance

Mario Paci[1], Giulio Di Cosmo[1], Francesca Ferri[1,2*] & Marcello Costantini[2,3*]

1. Department of Neuroscience, Imaging and Clinical Science, "G. d'Annunzio" University of Chieti-Pescara, Italy.
2. Institute for Advanced Biomedical Technologies, ITAB, University "G. d'Annunzio", Chieti, Italy.
3. Department of Psychological, Health, and Territorial Sciences, "G. d'Annunzio" University of Chieti-Pescara, Italy.

* Joint last authors

Corresponding author:
Mario Paci
Department of Neuroscience, Imaging and Clinical Science, "G. d'Annunzio"
University of Chieti-Pescara, Italy.
Via Luigi Polacchi 11, 66100 Chieti
Phone: +39 0871 3556910
Fax: +39 08713556930
E-mail: mario.paci@unich.it

Running title: Cortical and behavioral inhibition

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

Abstract

Inhibitory control is the ability to suppress unwanted actions. At the behavioral level, this ability can be measured via the Stop-Signal Task (stop-signal reaction time, SSRT). At the neural level, Transcranial Magnetic Stimulation provides electrophysiological measures of motor inhibition within the primary motor cortex (M1), such as the Cortical Silent period (CSP), a biomarker of proactive intracortical inhibition mainly mediated by $GABA_B$ receptors. Individual differences in this biomarker might contribute to behavioral differences in inhibitory control. Hence, we explored the relationship between intracortical inhibition and behavioral inhibition. Levels of intracortical inhibition were determined by measuring the length of individuals' CSP, while inhibitory capacities were assessed by the SSRT. We found a significant positive correlation between CSP and SSRT, namely that individuals with greater $GABA_B$ergic-mediated proactive inhibition seems to perform worse in inhibiting behavioral responses. These results suggest that individual differences in intracortical inhibition are mirrored by differences in motor-inhibitory ability.

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, Greenhouse, Labruna, & Ivry, 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 & Schachar, 2010), eating disorders (Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016), substance abuse disorders (Lipszyc & Schachar, 2010; Smith, Mattick, Jamadar, & Iredale, 2014) and obsessive-compulsive disorder (Milad & Rauch, 2012).

At the behavioral level, one of the most reliable paradigms employed for measuring response inhibition is the Stop Signal Task (Logan & Cowan, 1984). This task allows estimating individuals' ability to suppress a response already initiated, as it measures the temporal dynamics underlying successful response inhibition (Logan & Cowan, 1984; Logan, Schachar, & Tannock, 1997; Logan, Van Zandt, Verbruggen, & Wagenmakers, 2014; Verbruggen et al., 2019; Verbruggen, Logan, & Stevens, 2008). This task 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%), shortly after the go signal, a subsequent stop signal appears 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 stop-signal delay varies as a function of participants performance, decreasing after each unsuccessful stop trial and increasing after each successful one, until reaching a 50% success rate (staircase tracking procedure, see Logan et al., 1997; Verbruggen et al., 2019). Although the latency of response inhibition cannot be measured directly, a computational model allows measuring the temporal dynamics underlying this process, namely the Stop Signal Reaction Time (SSRT) (Verbruggen et al., 2019). Overall, SSRT can be conceptualized as the temporal measure of the latency of the stop process, namely of the time required to efficiently inhibit a response. As such, it reflects the duration of the whole stop process (Matzke, Verbruggen, & Logan, 2018; Verbruggen, Chambers, & Logan, 2013). Specifically, the SSRT provides a precise index of the duration of the whole chain of processes involved in response inhibition, hence the longer the SSRT the lower the efficiency of inhibitory control (Hilt & Cardellicchio, 2018; Verbruggen et al., 2013; Verbruggen et al., 2019). Interestingly, SSRT is highly variable across the normal population and reaches extreme values in clinical conditions

including ADHD and OCD (Lipszyc & Schachar, 2010). 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 & Ivry, 2009; Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010; Greenhouse, King, Noah, Maddock, & Ivry, 2017; Greenhouse, Oldenkamp, & Aron, 2012; Greenhouse, Saks, Hoang, & Ivry, 2015; Greenhouse, Sias, Labruna, & Ivry, 2015; Hasbroucq et al., 1999; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; Pascual-Leone et al., 1992; Starr, Caramia, Zarola, & Rossini, 1988). Different TMS-EMG protocols can be used to measure levels of intracortical inhibition within 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). 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 $GABA_A$ neurotransmission (Coxon, Stinear, & Byblow, 2006; Di Lazzaro et al., 2000; Paulus et al., 2008; Sohn, Wiltz, & Hallett, 2002). This parameter is measured by comparing the amplitude of the paired-pulses test stimulus with the amplitude of a single-pulse 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 by $GABA_B$ 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, Orekhov, & Ziemann, 2006; Paulus et al., 2008; Sanger, Garg, & Chen, 2001). 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 (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

$GABA_B$ergic inhibition within M1, mainly mediated by $GABA_B$ receptors (Cardellicchio, Dolfini, Hilt, Fadiga, & D'Ausilio, 2019; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 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.

To date few studies (Chowdhury et al., 2018; He et al., 2019) have investigated whether and to what extent SICI and LICI predict individual differences in the efficiency of the inhibitory processes. However, no studies have investigated whether the temporal aspect of intracortical inhibition, as indexed by the CSP, relates to the temporal dynamic of response inhibition as indexed by the SSRT. This is the aim of the current study.

Materials and methods

Participants

27 (11 M) Twenty-seven right-handed naïve participants (11 males, mean age = 27.84; SD = 3.8; range = 23-38) with normal or corrected-to-normal vision took part in the present study. One participant (female) was later excluded from further analysis 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 tangent to the scalp following the orthodox method, namely tangent to the scalp with the handle pointed backwards and angled 45□ degrees from the midline, perpendicular to the central sulcus. The optimum scalp position for stimulation was identified by maneuvering the coil until eliciting the maximum amplitude Motor-evoked potentials (MEPs) in the contralateral FDI muscle. Once chosen and marked the hotspot, individuals' resting motor threshold (RMT) was then 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 □V 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.

Intracortical Inhibition. Levels of $GABA_B$ergic-related of corticospinal inhibition were assessed via a single pulse TMS paradigm, namely by measuring the length of the cortical silent period (CSP). CSP is a cessation of background muscle activity following a TMS pulse delivered during tonic muscular contraction (Epstein et al., 2012; Rossini et al., 2015). 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 contraction, maintaining a static hand posture and a constant level of muscle activity. Throughout the whole procedure, participants were looking at a blank computer screen, while their level of muscle contraction was constantly monitored by the experimenter via constant online data inspection. Prior to the experimental session, participants took

part in a preliminary training session in order to learn to perform and retain constantly the appropriate level of FDI contraction, receiving EMG visual feedback displayed on the computer monitor. The experimental session started only after participants reached an adequate level of control in maintaining the correct amount of EMG activity. Each single-pulse TMS stimulations was delivered with an inter-stimulus interval jittered between 8 and 15 ms in order to avoid any habituation effect. Trials were rejected if the participant displayed any pronounced head movement prior to or during the stimulation. After a preliminary data visual inspection and rejection, only the first fifteen among the remained trials were included for further offline analysis.

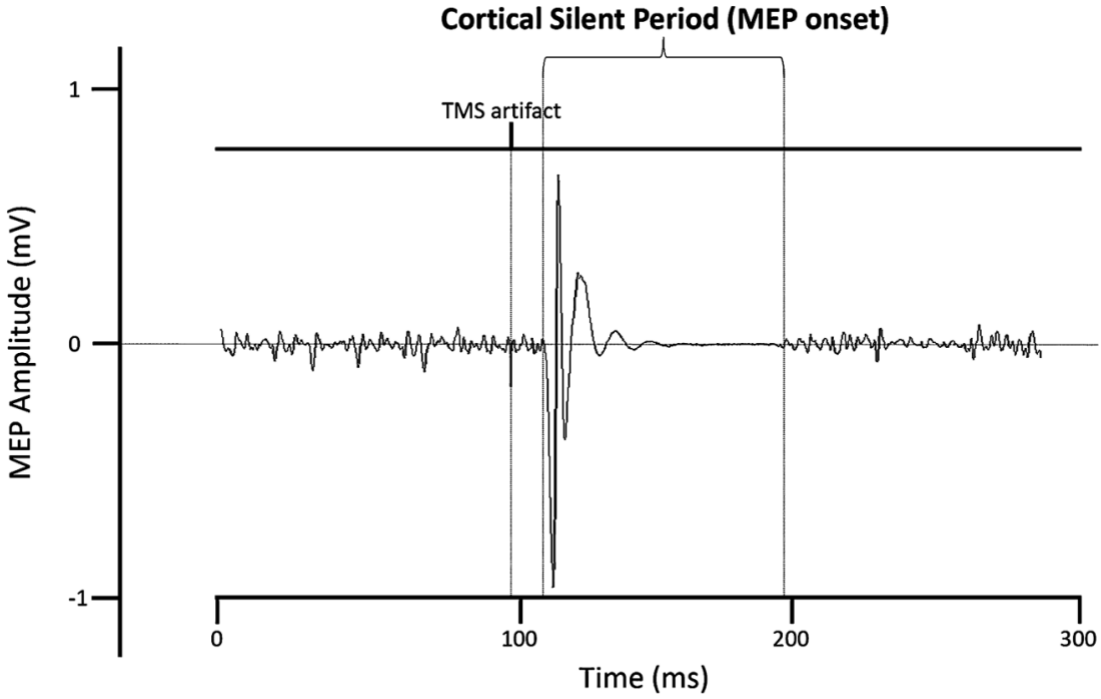


Fig. 1 - Representative traces of the FDI's cortical silent period at 120% maximal voluntary contraction.

Behavioral level – Motor Inhibition. To measure motor inhibiton at the behavioural level we employed the Stop signal task (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Verbruggen et al., 2019; Vince, 1948). This task measures the participants' ability to suppress unwanted or inappropriate actions and impulses and allows the estimation of the temporal dynamics underlying response inhibition, namely the stop-signal reaction time (SSRT). This task requires participants to perform a speeded response go task while accurately discriminating between two different go stimuli, except being ready to suppress any response when a subsequently stop signal is displayed. Specifically, in the present study participants were instructed to discriminate 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 one fourth 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. In go trials, go stimuli lasted 1 second, 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 s. 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, converging [p(respond|signal)] ≅ .50. Specifically, according with the horse race model of inhibition (Logan and Cowan 1984), increasing the delay between the go and the stop stimuli (the SSD) makes response inhibition as well as the task itself more difficult. However, the latency of response inhibition cannot be measured directly, because successful response inhibition leads to the absence of any observable response. Nevertheless, the stop signal task provide a reliable estimation of the time required for successful motor inhibition, namely the stop-signal reaction time (SSRT). Overall, SSRT is an index of the overall latency of the chain of processes involved in response inhibition, including the detection of the stop signal itself. There are different methods to estimate SSRT from the results of stop-signal task. In the present study, we used a non-parametric approach, estimating SSRT using the integration method (e.g. Verbruggen et al., 2019). Crucially, results either violating the horse-race model (reaction time on unsuccessful stop trials > reaction time on go trials) or with a p(respond|signal) too far from ≅ .50 were rejected.

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 (CH) 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 Neuropsychology Laboratory of ITAB, Chieti (CH) 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. Prior to the task, 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. Before the starting the experiment, participants were provided with detailed instructions. The task included an initial

practice block providing feedback for each trial. Trial-by-trial feedback was not provided later in the actual experimental blocks. The whole experiment comprised 1 practice block of 32 trials and, 5 experimental blocks of 96 trials each. In each block 25% of the trials were stop trials, and the direction of the arrows was counterbalanced. Each trail started with a fixation cross (Intertrial interval 4 second), followed by either a go stimulus only (go trial) or a go stimulus and a subsequent stop stimulus (stop trial). In go trials, go stimuli lasted 1 second, 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). Between each block, participants were allowed to take a short break, and received a global feedback summarizing their performance over the previous block. 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 SSRT and cortical silent period, we ran a regression analysis between individual SSRT and CSP. Moreover, to test the robustness of the relationship we computed skipped parametric (Pearson) correlations (Wilcox, 2004) using the Robust Correlation toolbox (Pernet, Wilcox, & Rousselet, 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, Becchio, & Cavallo, 2018) to test whether participants' SSRT could reliably predict the CSP. 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

The sample size of 27 was calculated by using G.Power software (v3.1.9.6) (Faul, Erdfelder, Lang, & Buchner, 2007; Faul, Erdfelder, Buchner, & Lang, 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 0.95. However, one participant (female) was later excluded from correlational analysis because she met the exclusion criteria set a-priori for the behavioral task.

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 because violated the horse-race model (reaction time on unsuccessful stop trials > reaction time on go trials). The individuals' SSRT was estimated following a non-parametric approach using the integration method with replacement of go omissions, reckoned as more reliable than the alternatives integration method with exclusion of go omissions, integration method with adjustment of p(respond|signal), and mean method (Verbruggen et al., 2013; Verbruggen et al., 2019). Raw data were processed via a customised R software (version 3.6.2) for Windows, the code for the analysis was provided by (Verbruggen et al., 2019). The average SSRT was 215 (SD 19.76). The table below (Table.1) shows the average of the main measures of the Stop Signal Task, namely SSRT, SSD, Go reaction time (nthRT), and successful stopping reaction time (sRT).

	SSRT (ms)	SSD (ms)	nthRT (ms)	sRT(ms)
Mean	214.86	309.59	524.45	475.31
SD	19.76	119.62	110.63	90.72

Table 1 - Means and Standard Deviations for all the measures on the Stop Signal Task.

Neurophysiological data

CSPs duration was extracted offline using Signal 6.04 software (Cambridge Electronic Design, Cambridge, UK). 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. Analysis of CSPs was conducted manually, and CSPs duration was always verified and extracted via visual inspection. The average length of each individual CSPs 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 140 ms (SD = 26.94).

Correlation analysis

The linear correlation between the SSRT and the CSP was significant (Pearson r(26) = .59; p = 0.002; CI = [0.27 0.77], figure 3, panel a) and such relationship survived robust correlation (skipped Pearson

r = 0.76; CI = [0.54 0.88]). 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(26) = 0.50, *p* = 0.009, figure 3, panel b). Overall, higher levels of $GABA_B$ergic-related intracortical inhibition in M1 predicted worse inhibitory control capacities.

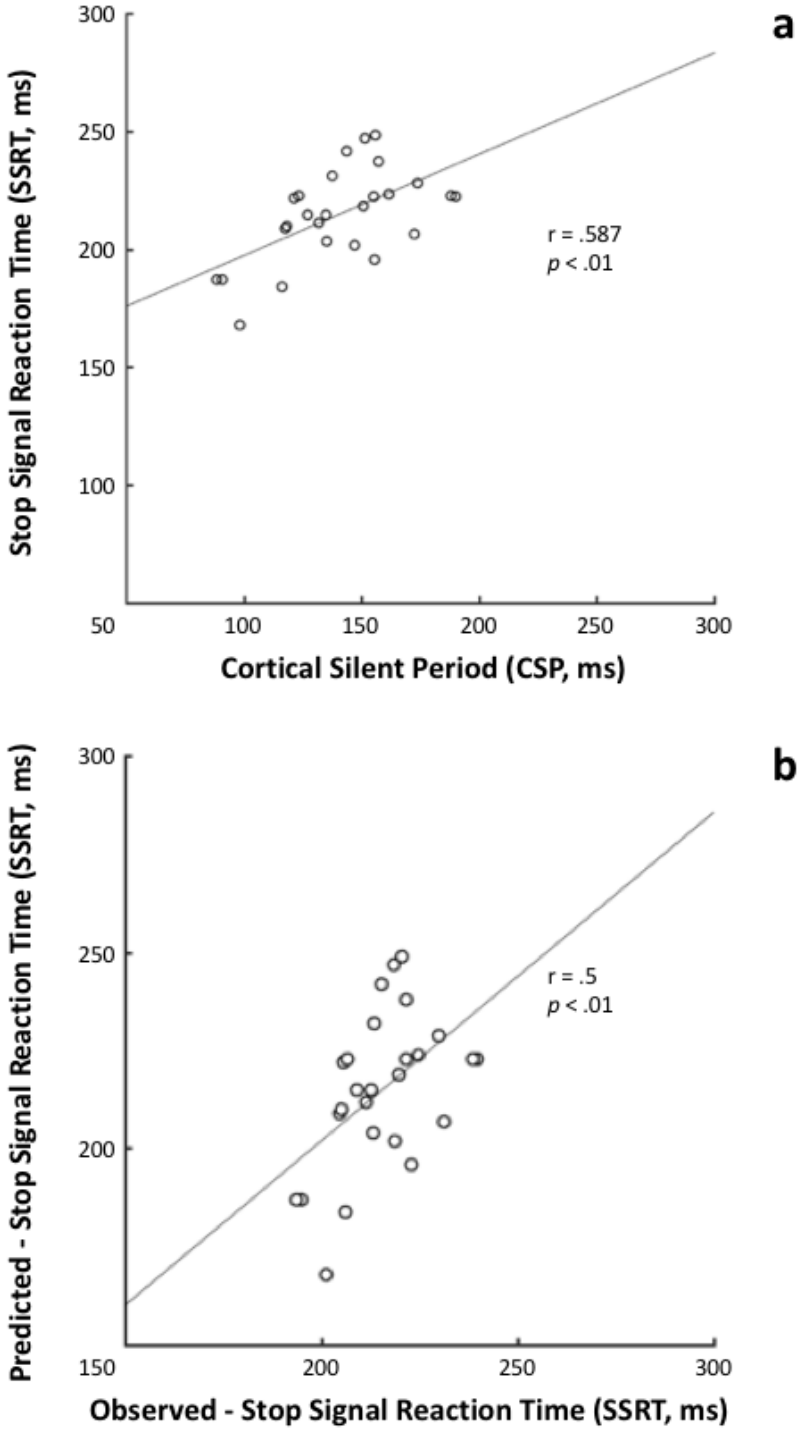


Fig. 3 – a. Linear association between cortical silent period (CSP) and Stop Signal Reaction Time (SSRT). – **b.** Leave one out cross-validation analysis showing d a significant correlation between the model-predicted and observed SSRT values.

Discussion

The present study was aimed at investigating whether individual differences in the temporal aspect of intracortical inhibition at rest might act as a neurophysiological trait marker predicting individual response inhibition capacities. Our results revealed a clear relationship between the length of cortical silent period (CSP) at rest and the stop signal reaction time, obtained from the Stop Signal Task. In particular, individuals with longer CSP at rest 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, Lönnecker, & Paulus, 1995; Ziemann, Lönnecker, Steinhoff, & Paulus 1996; Ziemann et al., 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 rest CSP might provide a valid trait marker to predict 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). However, the specific relation between intracortical inhibition and behavioral individual differences in inhibitory control performance has been poorly investigated.

So far, two studies (Chowdhury et al., 2018; He et al., 2019) have already 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 et al. (2018) 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.

At a first glance, Chowdhury et al. (2018)' results might appear in contradiction with those reported in the present study, but this is not the case. Indeed, 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. The stop signal requires participants to suppress the ongoing response (Wessel, 2018; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 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, Lavric, Chambers, & Verbruggen, 2016), it always engages a combination of both proactive and reactive inhibitory components (Elchlepp, Lavric, Chambers, & Verbruggen, 2016). Keeping this in mind, the negative correlation between SICI's strength and SSRT found by Chowdhury et al. (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 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. Specifically, results of paired-pulse TMS measurements revealed that the amplitude of SICI seems to be higher during successful reactive action stopping, suggesting that these particular sub-processes of motor inhibition might be mainly mediated by $GABA_A$ergic inhibitory activity (Hermans et al., 2018). Hence, it is possible that the negative correlation between SICI's strength and SSRT found by Chowdhury et al. (2018) reflects how levels of fast $GABA_A$ergic reactive inhibition in M1 influence action stopping performance. Conversely, proactive components underlying action stopping are mainly mediated by slow $GABA_B$ergic inhibition (Cowie, MacDonald, Cirillo, & Byblow, 2016; Hermans et al., 2019). Given the proactive nature of $GABA_B$ergic inhibition in action stopping, and that both LICI and CSP could be treated as markers of $GABA_B$-mediated inhibition, we suggest that the positive correlation between CSP's length and SSRT we presented here might reflect the relationship between individuals' levels of $GABA_B$ergic proactive inhibition in M1 and their action stopping performance. 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 & Bucci, 2016; van Hulst et al., 2018; Zandbelt, van Buuren, Kahn, & Vink, 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). Once this apparent contradiction has been

cleared, our results and Chowdhury et al. (2018)'s results not only corroborate each other as part of the same complement, but altogether they also further support the idea that TMS-derived biomarkers might provide a reliable methodology to predict behavioral individual differences in motor inhibition.

References

Bartholdy, S., Dalton, B., O'Daly, O. G., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. *Neuroscience & Biobehavioral Reviews*, *64*, 35-62.

Benis, D., David, O., Lachaux, J. P., Seigneuret, E., Krack, P., Fraix, V., Chabardès, S., & Bastin, J. (2014). Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson's disease. *Neuroimage*, *91*, 273-281.

Cardellicchio, P., Dolfini, E., Hilt, P. M., Fadiga, L., & D'Ausilio, A. (2020). Motor cortical inhibition during concurrent action execution and action observation. *NeuroImage*, *208*, 116445.

Chowdhury, N. S., Livesey, E. J., Blaszczynski, A., & Harris, J. A. (2018). Variations in response control within at-risk gamblers and non-gambling controls explained by GABAergic inhibition in the motor cortex. *Cortex*, *103*, 153-163.

Cowie, M. J., MacDonald, H. J., Cirillo, J., & Byblow, W. D. (2016). Proactive modulation of long-interval intracortical inhibition during response inhibition. *Journal of Neurophysiology*, *116*(2), 859-867.

Coxon, J. P., Stinear, C. M., & Byblow, W. D. (2006). Intracortical inhibition during volitional inhibition of prepared action. *Journal of neurophysiology*, *95*(6), 3371-3383.

Di Lazzaro, V., Oliviero, A., Meglio, M., Cioni, B., Tamburrini, G., Tonali, P., & Rothwell, J. C. (2000). Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clinical neurophysiology*, *111*(5), 794-799.

Duque, J., Greenhouse, I., Labruna, L., & Ivry, R. B. (2017). Physiological markers of motor inhibition during human behavior. *Trends in neurosciences*, *40*(4), 219-236.

Duque, J., & Ivry, R. B. (2009). Role of corticospinal suppression during motor preparation. *Cerebral cortex*, *19*(9), 2013-2024.

Duque, J., Lew, D., Mazzocchio, R., Olivier, E., & Ivry, R. B. (2010). Evidence for two concurrent inhibitory mechanisms during response preparation. *Journal of Neuroscience*, *30*(10), 3793-3802.

Elchlepp, H., Lavric, A., Chambers, C. D., & Verbruggen, F. (2016). Proactive inhibitory control: A general biasing account. Cognitive Psychology, 86, 27-61.

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods, 39(2), 175-191.

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. Behavior research methods, 41(4), 1149-1160.

Greenhouse, I., King, M., Noah, S., Maddock, R. J., & Ivry, R. B. (2017). Individual differences in resting corticospinal excitability are correlated with reaction time and GABA content in motor cortex. Journal of Neuroscience, 37(10), 2686-2696.

Greenhouse, I., Oldenkamp, C. L., & Aron, A. R. (2012). Stopping a response has global or nonglobal effects on the motor system depending on preparation. *Journal of neurophysiology*, *107*(1), 384-392.

Greenhouse, I., Saks, D., Hoang, T., & Ivry, R. B. (2015). Inhibition during response preparation is sensitive to response complexity. *Journal of neurophysiology*, *113*(7), 2792-2800.

Greenhouse, I., Sias, A., Labruna, L., & Ivry, R. B. (2015). Nonspecific inhibition of the motor system during response preparation. *Journal of Neuroscience*, *35*(30), 10675-10684.

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron*, *55*(2), 187-199.

Hasbroucq, T., Osman, A., Possamaï, C. A., Burle, B., Carron, S., Dépy, D., Latour, S., & Mouret, I. (1999). Cortico-spinal inhibition reflects time but not event preparation: neural mechanisms of preparation dissociated by transcranial magnetic stimulation. *Acta psychologica*, *101*(2-3), 243-266.

He, J. L., Fuelscher, I., Coxon, J., Chowdhury, N., Teo, W. P., Barhoun, P., Enticott, P., & Hyde, C. (2019). Individual differences in intracortical inhibition predict motor-inhibitory performance. *Experimental brain research*, *237*(10), 2715-2727.

Hermans, L., Leunissen, I., Pauwels, L., Cuypers, K., Peeters, R., Puts, N. A., Edden, R. A. E., & Swinnen, S. P. (2018). Brain GABA levels are associated with inhibitory control deficits in older adults. *Journal of Neuroscience*, *38*(36), 7844-7851.

Hermans, L., Maes, C., Pauwels, L., Cuypers, K., Heise, K. F., Swinnen, S. P., & Leunissen, I. (2019). Age-related alterations in the modulation of intracortical inhibition during stopping of actions. *Aging (Albany NY)*, *11*(2), 371.

Hilt, P. M., & Cardellicchio, P. (2018). Attentional bias on motor control: is motor inhibition influenced by attentional reorienting?. *Psychological research*, 1-9.

Koul, A., Becchio, C., & Cavallo, A. (2018). Cross-validation approaches for replicability in psychology. *Frontiers in Psychology*, *9*, 1117.

Lappin, J. S., & Eriksen, C. W. (1966). Use of a delayed signal to stop a visual reaction-time response. *Journal of Experimental Psychology*, *72*(6), 805.

Leocani, L., Cohen, L. G., Wassermann, E. M., Ikoma, K., & Hallett, M. (2000). Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. *Brain*, *123*(6), 1161-1173.

Lipszyc, J., & Schachar, R. (2010). Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. *Journal of the International Neuropsychological Society*, *16*(6), 1064-1076.

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological review*, *91*(3), 295.

Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological science*, *8*(1), 60-64.

Logan, G. D., Van Zandt, T., Verbruggen, F., & Wagenmakers, E. J. (2014). On the ability to inhibit thought and action: General and special theories of an act of control. *Psychological review*, *121*(1), 66.

Matzke, D., Verbruggen, F., & Logan, G. D. (2018). The Stop-Signal Paradigm. Stevens' Handbook of Experimental Psychology and Cognitive Neuroscience, 5, 1-45.

Mayer, A. R., Hanlon, F. M., Dodd, A. B., Yeo, R. A., Haaland, K. Y., Ling, J. M., & Ryman, S. G. (2016). Proactive response inhibition abnormalities in the sensorimotor cortex of patients with schizophrenia. *Journal of Psychiatry & Neuroscience: JPN*, *41*(5), 312.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2006). The role of GABA B receptors in intracortical inhibition in the human motor cortex. *Experimental brain research*, *173*(1), 86-93.

Meyer, H. C., & Bucci, D. J. (2016). Neural and behavioral mechanisms of proactive and reactive inhibition. *Learning & Memory*, *23*(10), 504-514.

Milad, M. R., & Rauch, S. L. (2012). Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends in cognitive sciences*, *16*(1), 43-51.

Paulus, W., Classen, J., Cohen, L. G., Large, C. H., Di Lazzaro, V., Nitsche, M., Pascual-Leone, A., Rosenow, F., Rothwell, J. C., & Ziemann, U. (2008). State of the art: pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. *Brain stimulation*, *1*(3), 151-163.

Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., Brasil-Neto, J., Cohen, L. G., & Hallett, M. (1992). Effects of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual and somatosensory stimuli. *Brain*, *115*(4), 1045-1059.

Pernet, C. R., Wilcox, R. R., & Rousselet, G. A. (2013). Robust correlation analyses: false positive and power validation using a new open source matlab toolbox. *Frontiers in psychology*, *3*, 606.

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., Di Lazzaro, V., Ferreri, F., Fitzgerald, P. B., George, M. S., Hallett, M., Lefaucheur, J. P., Langguth, B., Matsumoto, H., Miniussi, C., Nitsche, M. A., Pascual-Leone, A., Paulus, W., Rossi, S., Rothwell, J. C., Siebner, H. R., Ugawa, Y., Walsh, V., Ziemann, U., (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an IFCN Committee. *Clinical Neurophysiology*, *126*(6), 1071-1107.

Sanger, T. D., Garg, R. R., & Chen, R. (2001). Interactions between two different inhibitory systems in the human motor cortex. *The Journal of physiology*, *530*(2), 307-317.

Smith, J. L., Mattick, R. P., Jamadar, S. D., & Iredale, J. M. (2014). Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. *Drug and alcohol dependence*, *145*, 1-33.

Sohn, Y. H., Wiltz, K., & Hallett, M. (2002). Effect of volitional inhibition on cortical inhibitory mechanisms. *Journal of Neurophysiology*, *88*(1), 333-338.

Starr, A., Caramia, M., Zarola, F., & Rossini, P. M. (1988). Enhancement of motor cortical excitability in humans by non-invasive electrical stimulation appears prior to voluntary movement. *Electroencephalography and clinical neurophysiology*, *70*(1), 26-32.

van Hulst, B. M., de Zeeuw, P., Vlaskamp, C., Rijks, Y., Zandbelt, B. B., & Durston, S. (2018). Children with ADHD symptoms show deficits in reactive but not proactive inhibition, irrespective of their formal diagnosis. *Psychological medicine*, *48*(15), 2515-2521.

Verbruggen, F., Aron, A. R., Band, G. P., Beste, C., Bissett, P. G., Brockett, A. T., Brown, J. W., Chamberlain, S. R., Chambers, C. D., Colonius, H., Colzato, L. S., Corneil, B. D., Coxon, J. P., Dupuis, A., Eagle, D. M., Garavan, H., Greenhouse, I., Heathcote, A., Huster, R. J., Jahfari, S., Kenemans, J. L., Leunissen, I., Li, C. S. R., Logan, G. D., Matzke, D., Morein-Zamir, S., Murthy, A., Paré, M., Poldrack, R. A., Ridderinkhof, K. R., Robbins, T. W., Roesch, M., Rubia, K., Schachar, R. J., Schall, J. D., Stock, A. K., Swann, N. C., Thakkar, K. N., van der Molen, M. V., Vermeylen, L., Vink, M., Wessel, J. R., Whelan, R., Zandbelt, B. B., Boehler, C. N., (2019). A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. *Elife*, *8*, e46323.

Verbruggen, F., Chambers, C. D., & Logan, G. D. (2013). Fictitious inhibitory differences: how skewness and slowing distort the estimation of stopping latencies. *Psychological science*, *24*(3), 352-362.

Verbruggen, F., Logan, G. D., & Stevens, M. A. (2008). STOP-IT: Windows executable software for the stop-signal paradigm. *Behavior research methods*, *40*(2), 479-483.

Vince, M. A. (1948). The intermittency of control movements and the psychological refractory period. *British Journal of Psychology*, *38*(3), 149.

Wilcox, R. (2004). Inferences based on a skipped correlation coefficient. *Journal of Applied Statistics*, *31*(2), 131-143.

Wessel, J. R. (2018). Surprise: a more realistic framework for studying action stopping?. *Trends in cognitive sciences*, *22*(9), 741-744.

Werhahn, K. J., Kunesch, E., Noachtar, S., Benecke, R., & Classen, J. (1999). Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *The Journal of physiology*, *517*(2), 591-597.

Zandbelt, B. B., Bloemendaal, M., Hoogendam, J. M., Kahn, R. S., & Vink, M. (2013). Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. *Journal of Cognitive Neuroscience*, *25*(2), 157-174.

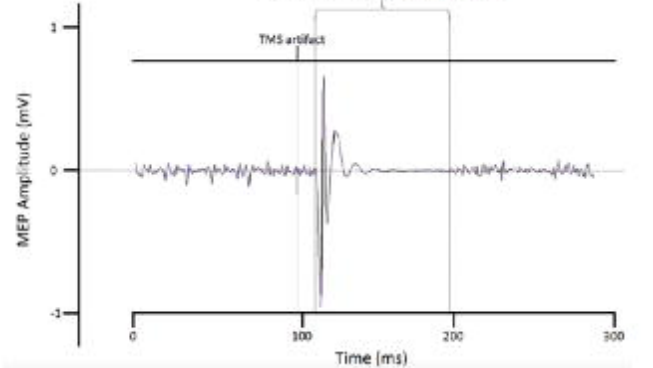
Zandbelt, B. B., van Buuren, M., Kahn, R. S., & Vink, M. (2011). Reduced proactive inhibition in schizophrenia is related to corticostriatal dysfunction and poor working memory. *Biological psychiatry*, *70*(12), 1151-1158.

Ziemann, U. L. F. (2013). Pharmaco-transcranial magnetic stimulation studies of motor excitability. In *Handbook of clinical neurology* (Vol. 116, pp. 387-397). Elsevier.

Ziemann, U., Lönnecker, S., & Paulus, W. (1995). Inhibition of human motor cortex by ethanol A transcranial magnetic stimulation study. *Brain*, *118*(6), 1437-1446.

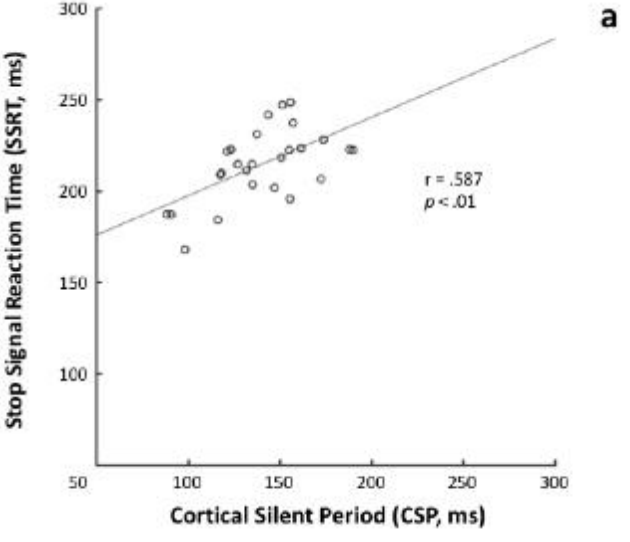
Ziemann, U., Lönnecker, S., Steinhoff, B. J., & Paulus, W. (1996). The effect of lorazepam on the motor cortical excitability in man. *Experimental brain research*, *109*(1), 127-135.

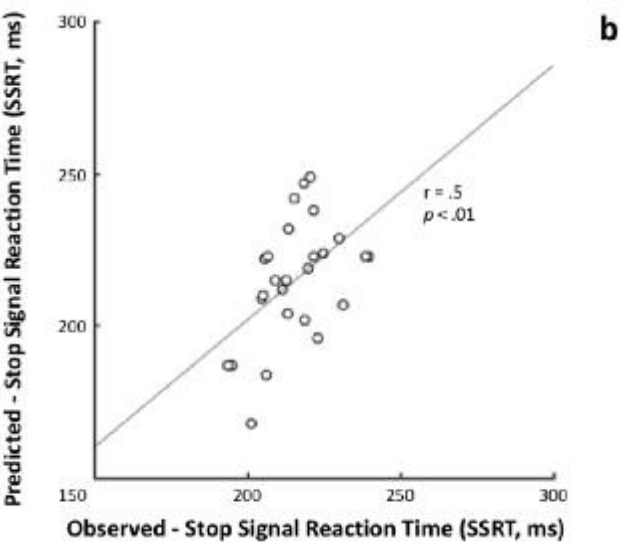
Ziemann, U., Reis, J., Schwenkreis, P., Rosanova, M., Strafella, A., Badawy, R., & Müller-Dahlhaus, F. (2015). TMS and drugs revisited 2014. *Clinical Neurophysiology*, *126*(10), 1847-1868.


Cortical Silent Period (MEP onset)
TMS artifact
MEP Amplitude (mV)
1
0
-1
0
100
200
300
Time (ms)

	SSRT (ms)	SSD (ms)	nthRT (ms)	sRT(ms)
Mean	214.86	309.59	524.45	475.81
SD	19.76	119.62	110.63	90.72


'Go Trial'
Fixation Cross
Go stimulus
Fixation Cross
Response OR
MAX RT (1s)
ITI 4s
'Stop Trial'
Fixation Cross
Stop signal
Go stimulus
Fixation Cross
Response OR
MAX RT (1s) - SSD
SSD
ITI 4s


a
Stop Signal Reaction Time (SSRT, ms)
300
250
200
150
100
50
100
150
200
250
300
Cortical Silent Period (CSP, ms)
r = .587
p < .01


b
Predicted - Stop Signal Reaction Time (SSRT, ms)
Observed - Stop Signal Reaction Time (SSRT, ms)
300
250
200
150
200
250
300
r = .5
p < .01