J Neurophysiol 125: 648–660, 2021.
First published January 13, 2021; doi:10.1152/jn.00571.2020

american physiological society

JNP JOURNAL OF NEUROPHYSIOLOGY

RESEARCH ARTICLE

Higher Neural Functions and Behavior

Paired-pulse TMS and scalp EEG reveal systematic relationship between inhibitory $GABA_a$ signaling in M1 and fronto-central cortical activity during action stopping

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Abstract

By stopping actions even after their initiation, humans can flexibly adapt ongoing behavior to changing circumstances. The neural processes underlying the inhibition of movement during action stopping are still controversial. In the 90s, a fronto-central event-related potential (ERP) was discovered in the human EEG response to stop signals in the classic stop-signal task, alongside a proposal that this "stop-signal P3" reflects an inhibitory process. Indeed, both amplitude and onset of the stop-signal P3 relate to overt behavior and movement-related EEG activity in ways predicted by the dominant models of action-stopping. However, neither EEG nor behavior allow direct inferences about the presence or absence of neurophysiological inhibition of the motor cortex, making it impossible to definitively relate the stop-signal P3 to inhibition. Here, we therefore present a multimethod investigation of the relationship between the stop-signal P3 and GABAergic signaling in primary motor cortex, as indexed by paired-pulse transcranial magnetic stimulation (TMS). In detail, we measured short-interval intracortical inhibition (SICI), a marker of inhibitory $GABA_a$ activity in M1, in a group of 41 human participants who also performed the stop-signal task while undergoing EEG recordings. In line with the P3-inhibition hypothesis, we found that subjects with stronger inhibitory GABA activity in M1 also showed both faster onsets and larger amplitudes of the stop-signal P3. This provides direct evidence linking the properties of this ERP to a true physiological index of motor system inhibition. We discuss these findings in the context of recent theoretical developments and empirical findings regarding the neural implementation of motor inhibition.

NEW & NOTEWORTHY The neural mechanisms underlying rapid action stopping in humans are subject to intense debate, in part because recordings of neural signals purportedly reflecting inhibitory motor control are hard to directly relate to the true, physiological inhibition of motor cortex. For the first time, the current study combines EEG and transcranial magnetic stimulation (TMS) methods to demonstrate a direct correspondence between fronto-central control-related EEG activity following signals to cancel an action and the physiological inhibition of primary motor cortex.

GABA; motor inhibition; paired-pulse TMS; P3 event-related potential; stop-signal task

INTRODUCTION

Inhibitory control of movement is a key cognitive control function implemented by the human brain, which allows humans to cancel actions even after their initiation. The neurophysiological underpinnings of inhibitory control are still subject of controversial debate. Neuroimaging studies have identified a distributed network of frontal and basal ganglia brain regions that is activated by sudden signals to stop an action [1, 2; see reviews by Aron et al. (3), Levy and Wagner (4), Chambers et al. (5), and Wager et al. (6)]. There is now widespread agreement that the exact timing of activity within that brain network, rather than the magnitude of its activity alone, is paramount to the successful

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Submitted 24 September 2020 / Revised 29 December 2020 / Accepted 10 January 2021

implementation of motor inhibition (7–9). This notion is consistent with early behavioral and theoretical work on the stop-signal paradigm, which holds that successful stopping of movement is achieved through a race between inhibitory control process(es) (triggered by a signal to stop an action) and the processes governing movement initiation and execution (10, 11). Although there is no overtly observable response on successful stop trials, the assumptions of this "horse-race" model allow the calculation of a latent variable—"stop-signal reaction time" (SSRT)—which expresses the latency of the inhibitory process (12). Shorter SSRTs reflect a faster, more efficient stop-process that allows actions that are even further along in their initiation to be successfully stopped. With some modifications (13, 14), this horse-race model of inhibitory control in the stop-signal task (SST) is still widely accepted today. Since a key implication of the horse-race model is that the timing of the "stop"-process influences the success of action stopping, studying the neural underpinnings of inhibitory control necessitates the usage of methods with sufficient temporal resolution, such as electroencephalography (EEG).

Early work using EEG in healthy humans has resulted in the suggestion that the fronto-central P3 event-related potential (ERP) following stop signals may reflect the inhibitory process in the stop-signal task (15). Strong support for this notion came from subsequent work (16), in which the latency of the stop-signal P3 was found to index stopping success: within subjects, the stop-signal P3 peaked earlier on successful compared with failed stop trials. This property reflects a direct correspondence between the features of the stop-signal P3 and the predictions of the race model. However, controversy remained. Specifically, several authors argued that since the peak of the fronto-central P3 occurs after SSRT, it is unlikely that the process signified by this neurophysiological signal is critical to the success of motor inhibition (17–19). A later study, however, used single-trial analyses to show that the "onset" of the fronto-central stop-signal P3 (instead of its peak) not only occurs early enough to fall within the pre-SSRT time period, but is also highly positively correlated with SSRT—that is, subjects with a faster onset of the stop-signal P3 also show shorter SSRTs (9). Although this latter association has since been independently replicated (20), the association between the stop-signal P3 and inhibitory processing still remains controversial. One argument is that additional ERPs, including ERPs that predate the P3 and likely reflect attentional processes, also correlate with SSRT (20, 21). In addition to this debate focusing on the electrophysiology of stopping, the fundamental assumptions underlying the SSRT computation have also recently been called into question themselves, with some authors arguing that SSRT systematically overestimates the latency of the stopping process, specifically because the classic SSRT computation does not take into account trials in which the inhibitory control process is not triggered at all (22, 23). Moreover, SSRT, just like any index derived from overt reaction times, has the notable limitation that the delay between the first measurable sign of an overt response (i.e., the initial contraction of a muscle in the EMG) and the button press itself is not taken into account (e.g., 24). Taken together, the notion that SSRT should be used as the ultimate benchmark to evaluate the involvement of specific neural indices in action stopping has become more controversial itself.

In light of these recent criticisms of SSRT, some more recent neuroscientific studies have turned away from this latent behavioral variable and toward evaluating purported EEG indices of inhibitory control in direct relation to the (neuro)physiological activation of the motor system. The motor system is the final stage of the neural system in which the "go"-side of the horse-race underlying action stopping will manifest, and motor activity can therefore function as a precise indicator of how much inhibitory control is or was necessary to stop a given action. Therefore, motor activity can be related to trial-to-trial estimates of potential inhibitory control signatures, and that relationship can then be scrutinized vis-à-vis the predictions of the horse-race model. Using such approaches, two recent studies have provided notable support for the classic interpretation of the fronto-central P3 as an index of inhibitory control processes. In one example, the lateralized readiness potential, an index of late-stage motor preparation observable in EEG recordings over sensorimotor cortex, was used to show that successfully stopped trials with more residual motor activity also showed larger stop-signal P3 ERPs (25). In other words, successfully cancelled actions that were more advanced (and hence required more inhibitory control to cancel) were accompanied by a larger stop-signal P3. In another study, force recordings were used to provide further evidence along the same lines. Specifically, Nguyen et al. (26) found that on failed stop trials (i.e., trials with a stop signal in which the go-response was not successfully stopped) larger P3 amplitudes were found when the erroneous response was produced with reduced force. This suggests that trials in which the incorrectly executed response showed stronger residual signs of partial inhibition were also accompanied by larger stop-signal P3 amplitudes.

Studies such as these can provide unique insights into the dynamics of action stopping, since they do not have to rely on SSRT to evaluate the potential neurophysiological concomitants of the processes underlying the horse-race. However, even those studies cannot provide a direct proof of the proposition that the P3 (or any other EEG signature) directly relates to the physiological inhibition of the motor system. As EEG does not offer insights into the physiological excitation or inhibition of the neuronal populations underlying the scalp signal, EEG-derived signatures, such as ERPs, cannot resolve whether an observed reduction of a motor process is truly due to the activity of inhibitory processes at the neural level. Therefore, to investigate whether specific EEG indices are truly related to the actual physiological inhibition of the motor system, EEG needs to be supplemented with other methods.

Notably, the combination of transcranial magnetic stimulation (TMS) and electromyography (EMG) provides a well-established method that allows this exact type of measurement. Specifically, when single pulses of TMS are applied to motor representations in primary motor cortex (M1), they result in overtly observable amplitude deflections in EMG recordings from the associated muscle. These deflections, called motor-evoked potentials (MEP), index the net corticospinal excitability of the associated motor tract (27). In addition, more advanced TMS methods make use of paired-pulse protocols to directly index the activity of local inhibitory γ-aminobutyric acid (GABA) neuron populations in M1 (28,

29). GABA is the primary inhibitory neurotransmitter in the brain, including in M1 (30, 31) and magnetic resonance spectroscopy has revealed that GABA content in the basal ganglia correlates with the behavioral efficacy in response inhibition (32). In paired-pulse TMS protocols, introducing a "conditioning" pulse before the MEP test pulse results in a reduction of the MEP compared with an unconditioned, single-pulse MEP. Depending on the latency difference between conditioning and test pulses, this relative reduction in the MEP is either called short-interval or long-interval intracortical inhibition (SICI/LICI). SICI is typically observed when the subthreshold conditioning pulse precedes the test pulse by 1–6 ms (28). It is thought that SICI results from the activation of the low-threshold inhibitory system by the conditioning pulse, resulting in the production of inhibitory postsynaptic potentials via fast ionotropic $GABA_a$ receptors (31, 33). LICI, on the other hand, is observed when a suprathreshold conditioning pulse precedes the test pulse by 50–200 ms (34), which is consistent with the slower production of inhibitory postsynaptic potentials produced via metabotropic $GABA_b$ receptors (35, 36). Pharmacological studies have largely supported these ideas for both SICI (37, 38) and LICI (39), with some proposing distinct, but interacting, neuronal circuits as the possible origin (29, 40). SICI and LICI are reduced during volitional movements (41–43) and have been shown to be differentially modulated by specific motor tasks (44, 45). Therefore, SICI and LICI are popular indices of the activity of local $GABA_{a/b}$ receptors in M1 and their relationship to motor behavior.

In line with the proposition that stopping an action would involve the activity of true, physiological inhibition of the motor system, studies using the stop-signal task have also shown that SICI and LICI are related to the behavioral success of stopping. Indeed, increased SICI has been demonstrated in subjects who are required to rapidly inhibit movements (46), whereas LICI has been shown to increase when subjects possess prior knowledge of when they need to inhibit specific movements (47, 48). In other words, $GABA_a$ activity, indexed by SICI, appears to be increased during rapidly exerted, reactive inhibitory control following a stop signal, whereas $GABA_b$ neurons seem to be anticipatorily recruited during situations in which inhibitory control can be proactively deployed toward specific effectors. Indeed, in perhaps the most direct demonstration of the relationship between SICI-indexed $GABA_a$ activity in M1 and stopping behavior, Chowdhury et al. (49) have recently shown that SICI measured at baseline (i.e., in the absence of a task) is directly related to SSRT across subjects. In their study, subjects with stronger SICI at baseline also showed faster SSRTs during the stop-signal task. This shows that the ability to recruit inhibitory neuronal circuitry in M1 is directly related to the ability to stop an action. Although the recent criticism of SSRT as a measurement variable itself (see INTRODUCTION) can also be levied against these findings, the results of Chowdhury et al.'s study do indicate that GABAergic inhibitory neural activity in M1 can potentially be used to probe an individual's ability to physiologically inhibit the motor system, and ultimately, to stop an action. In the current study, we attempt to capitalize on this utility of SICI to directly test whether the stop-signal P3, as a purported index of inhibitory control processing in frontal cortex, is related to the physiological activity of $GABA_a$ neurons in M1.

To this end, we combined the SICI approach of Chowdhury et al. (49) with additional recordings of scalp EEG during the stop-signal task. This was done with the explicit goal of directly relating each subjects' SICI measurement to the two core features of the fronto-central stop-signal P3, which have been proposed to index inhibitory control activity: its onset latency and its amplitude. Doing so achieves two overarching goals: first, using a direct index of the activity of inhibitory neurotransmission in M1 will allow us to evaluate whether the fronto-central stop-signal P3 ERP is related to the physiological inhibition of the motor system. Second, relating two measurements of brain activity that purportedly index inhibitory control without having to rely on a latent behavioral variable (viz., SSRT) would provide a direct validation of both measures and their purported involvement in action stopping using overtly measurable physiological variables.

Based on the aforementioned findings regarding the relationship between SICI, the P3, and stopping behavior, we hypothesized that subjects with stronger $GABA_a$ activity would show faster onset latencies and larger amplitudes of the stop-signal P3. Furthermore, we also collected baseline estimates of LICI to test whether $GABA_b$ activity is related to the behavioral implementation of proactive inhibitory control.

MATERIALS AND METHODS

Data Availability

All data, analysis scripts, and task code can be found on the OSF at https://osf.io/kqr3n/.

Participants

Forty-one healthy adult subjects participated in this study (27 female, 14 male; mean age, 21.6 yr, SD = 3.85, range 18–30; all right-handed). Subjects were recruited either through University of Iowa (UI)'s Department of Psychological and Brain Sciences sign-up system or through a mass recruitment email. Subjects signed written informed consent prior to enrollment and were granted either class credit for their participation or were compensated with $15/h. All procedures were approved by the University of Iowa's Institutional Review Board (No. 201612707, No. 201511709). Before experimentation, all subjects were screened for abnormal (noncorrected) vision or hearing, as well as for contraindications of TMS (50).

Stimulus Presentation

All stimuli were presented on a 19-in. Dell flat screen monitor connected to an IBM-compatible PC running Fedora Linux and MATLAB 2015b. Stimuli were presented using Psychtoolbox 3 (51). Responses were made using a standard QWERTY USB keyboard.

Experimental Task

Our variant of the stop-signal task alternated between blocks of the classic stop-signal paradigm and blocks of a pure-go task (which was identical in layout and timing to the stop-signal blocks but did not include any stop-signals, Fig. 1). In other words, in half of the blocks, subjects performed the standard variant of the stop-signal task, whereas in the other half, they

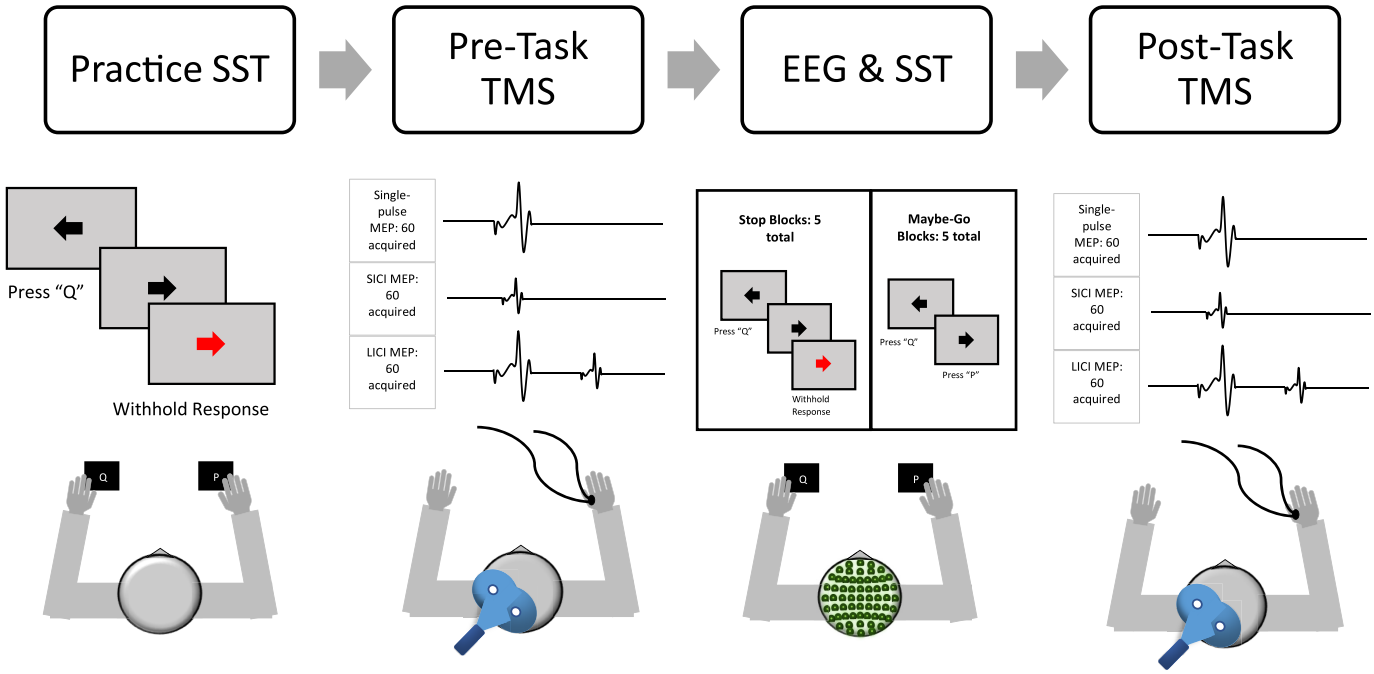

Figure 1. Study design, task diagram, and illustration of the TMS and EEG procedures. MEP, motor-evoked potentials; LICI, long-interval intracortical inhibition; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

performed a task that was exactly the same in layout, but did not include any stop-signals. These pure-go blocks were included in this study to measure proactive control behavior (i.e., reaction time slowing on go-trials in stop- vs. pure-go blocks), in addition to reactive control [for other studies using this comparison, see Chikazoe et al. (52), Jahfari et al. (53), Verbruggen and Logan (11)]. This was done to explore the proposed association between LICI and behavioral indices of proactive inhibitory control (47), a secondary goal of the current study.

Stimuli were presented on a gray background. Each trial began with a black fixation cross (500 ms), followed by a black arrow (go-signal) pointing either left or right, displayed for 1,000 ms. Subjects were instructed to press the "q" key on the keyboard with their left index finger in case of a left-facing arrow and "p" with their right index finger in case of a right-facing arrow. Responses were to be made within the 1,000 ms window during which the stimulus was presented on the screen. Each trial was followed by a 1,500 ms intertrial interval (ITI). If no response was made during the response window, the first 1,000 ms of the ITI included a red "Too Slow!" message presented on the screen. In stop-signal blocks, a stop-signal (i.e., the black go-signal arrow changing to red color) was presented after the go signal on 25% of trials. The stop-signal delay was initially set to 200 ms and was then subsequently adjusted in steps of 50 ms (which were added to the stop-signal delay after successful stop trials and subtracted after failed stop trials) with the goal of achieving an overall *P*(stop) of ~0.5. Participants completed two blocks of practice with the stop-signal task, and then performed 10 total blocks, alternating between stop-signal blocks ("There will be stop-signals. Responding quickly on go-trials and stopping successful on stop-trials are equally important.") and pure-go blocks ("There will be no stop-signals. Respond as fast as possible."). We altered the type of the first block after each subject to counterbalance the order. Two blocks were removed from one participant who was pressing the wrong buttons toward the end of the experiment. To achieve a balanced number of go trials from each task context, each block contained 48 go trials. In addition, the stop-signal blocks contained 16 stop trials. In total, this resulted in 240 go trials from pure-go blocks, 240 go trials from stop-signal blocks, and 80 stop trials per subject.

Procedure

Each subject participated in a one-time experimental visit, lasting ~3 h, which consisted of *1*) practicing the task, *2*) pretask measurements of SICI/LICI, *3*) EEG recording during the task, and *4*) posttask measurements of SICI/LICI (Fig. 1).

TMS Protocol

Each subject had their right hand cleaned using alcohol wipes and an abrasive pad, before two Ag/AgCl electrodes were adhered parallel to the belly of the first dorsal interosseus (FDI) muscle, whereas a third electrode (reference) was placed over the ulnar head. Electrodes were connected to a Grass P511 amplifier (1,000 Hz sampling rate, filters: 30 Hz high-pass, 1,000 Hz low-pass, 60 Hz notch). Amplified data were sampled via a Micro 1401-3 sampler (Cambridge Electronic Design) and visualized/recorded using Signal software (v. 6; Cambridge Electronic Design).

Each subject adorned a Lycra cap before TMS stimulation to mark TMS coil locations during hotspotting. TMS stimulation was performed using a MagStim BiStim^2 system with a 70-mm figure-of-eight coil. The coil was held 45° to the coronal plane, over the left primary motor cortex (M1) of each subject, inducing an anterior-posterior (AP) current (see Fig. 2). Hotspotting was performed while maintaining coil angle,

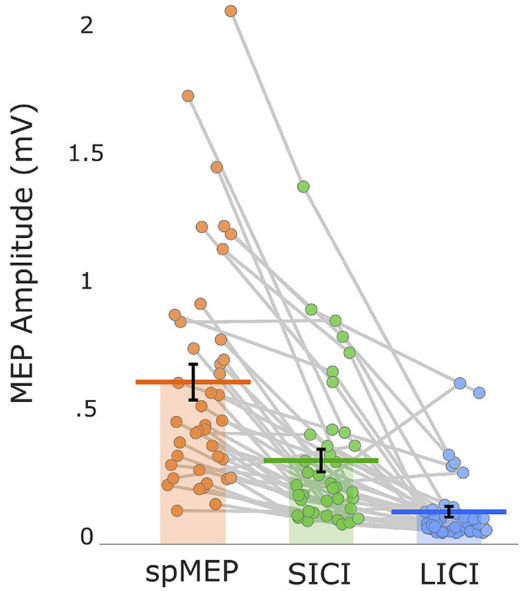

Figure 2. Average motor evoked potentials (MEPs) from all three stimulation conditions. Orange: single pulse unconditioned MEP (spMEP). Green: short-interval intracortical inhibition (SICI). Blue: long-interval intracortical inhibition (LICI). Horizontal lines represent the group mean; the confidence interval represents the standard error of the mean.

to locate the locus of optimal FDI stimulation, which was then marked on the Lycra cap. Resting motor threshold (RMT) was then defined as the minimum intensity required to induce MEPs of amplitudes exceeding 0.1 mV peak to peak in 5 of 10 consecutive probes (27).

Short-/Long-Interval Intracortical Inhibition Protocols

All TMS/EMG data were collected while the participant was at rest. We aimed to quantify both LICI and SICI. Hence, data were collected in 9 blocks of 20 trials; with three blocks dedicated to each measurement (i.e., 3 blocks each of paired-pulse SICI, paired-pulse LICI, and the single-pulse, unconditioned MEP). These blocks were acquired in randomized order. For SICI, the conditioning pulse was sent at 80% RMT and the test pulse sent at 120% RMT, with the interstimulus interval (ISI) set at 2 ms (54). For LICI, both the conditioning and test pulse were sent at 120% RMT with 100 ms ISI (29). Unconditioned, single-pulse MEPs were elicited with a single-pulse at 120% RMT. All MEPs were screened after collection using in-house MATLAB software. Trials were excluded if the root mean square of the prestimulus baseline EMG exceeded 0.1 mv or if either peak (negative or positive) of the MEP was outside the range of −2.99 mV to 2.99 mV. This lead to the retention of 54.9 trials on average for the unconditioned MEP (91.5% retention), 59.3 trials for SICI (98.8% retention), and 54.3 trials for LICI (90.5% retention). SICI and LICI were computed by using a following equation:

$$SICI,\ LICI\ = \frac{Mean\ Paired\ Pulse\ MEP}{Mean\ Single\ Pulse\ MEP}.$$

In other words, each subjects' average MEP in the respective paired-pulse condition (2 ms ISI for SICI, 100 ms ISI for LICI) was normalized by the unconditioned, single-pulse MEP average for the same subject.

When comparing the amplitudes of the MEP before and after the task, it became evident that there was a significant difference between the pre- and posttask MEP amplitudes [poststim MEPs larger; $t(40) = 2.86$, $P < 0.01$]. Therefore, we decided to focus our investigation on the pretask measurements. This was done for two reasons: first, alertness and sleep pressure may affect motor excitability (55, 56). Given that the posttask TMS measurements were collected after an extended period of performing a repetitive behavioral task, those measurements were likely to be affected by these confounding variables, potentially explaining the discrepancy. Second, inhibitory control training itself can also change the amplitude of the MEP in the involved muscles (57). Therefore, we believe the pretask measurements to be a more accurate representation of GABA activity, unaffected by both fatigue and potential inhibitory control training effects.

Behavior Analysis

Within the stop-blocks, go and failed stop-trial reaction time were compared to ensure that the requirements of the horse-race model were met [specifically, failed stop reaction time had to be faster than go-trial reaction time (10)]. Furthermore, P(stop) was investigated to ensure that the stop-signal delay staircase algorithm was effective in achieving an approximate stopping success rate of 0.5. SSRT was calculated from the stop-block data using the integration method with replacement of go-trial omission errors (12). Lastly, to explore the purported relationship between LICI and proactive control behavior, we also computed the response delay effect between stop-signal and pure-go blocks using the following equation:

$$Response\ delay\ effect = \frac{Mean\ SST\ Go\ RT - Mean\ Pure\ Go\ RT}{Mean\ Pure\ Go\ RT}.$$

EEG Recording

EEG data were recorded at a sampling rate of 500 Hz (10 s time-constant high-pass and 1,000 Hz low-pass hardware filter) using a 64-channel active electrode cap connected to an actiCHamp amplifier (BrainProducts, Garching, Germany). The reference electrode was Pz and a ground electrode was placed at Fz.

EEG Preprocessing

EEG data were preprocessed using MATLAB functions and the EEGLab toolbox. Raw EEG data were bandpass filtered (0.5–50 Hz) using a Hamming windowed sinc FIR filter. Following filtering, all participants' continuous EEG data were visually inspected and any segments that included nonstereotypical artifacts were removed. Data were then rereferenced to the common average and submitted to a temporal infomax independent component analysis (ICA) decomposition algorithm (58). The resulting component matrix was visually inspected to identify independent components (ICs) that reflected stereotypical artifacts (blinks and saccades), which were removed from the data by means of selective backprojection.

P3 Onset Calculation

The procedures to calculate the onset of the P3 ERP in each participant were designed to match the methodology of

Wessel and Aron (9). First, one IC was identified from each participant's ICA solution to represent the fronto-central P3. To select this IC, we manually identified candidate ICs that showed maximal IC weights around the fronto-central electrodes (Cz, FCz) in the scalp topographies. We then back projected these candidate ICs into the channel space to compute ERP using epochs time-locked to stop-signal onsets to confirm that there was N2/P3 following stop signals. Using this procedure, we identified a single IC for each participant that fulfilled both criteria.

Subsequently, to validate that these chosen ICs showed the previously demonstrated properties of the P3 in relation to behavior in the SST, we tested *1*) if the onset of the P3 was faster in successful compared with failed stop trials within subjects and *2*) whether the successful stop P3 onset correlated with SSRT across subjects. To this end, the thusly selected IC was back projected into the channel space and the resulting activity was averaged at the fronto-central electrode sites FCz and Cz. Four types of events were time locked (−300–700 ms) for each epoch: successful stop (SS), failed stop (FS), and go trials paired with each type of stopping. Each stop trial was paired with a go trial in which a pseudoevent was generated at the same stop-signal delay. This approach allowed us to compare the stop-related activity with matching time ranges on go trials (9). Within each subject, pairs of stop and matched go trials were compared for each sample point using label shuffling permutation testing (10,000 iterations, $P = 0.01$, corrected for multiple comparisons using the false-discovery rate (FDR) method (59). The onset of P3 was identified by locating the P3 peak latency first, then moving "backward" (i.e., toward the stop signal) until there was no more significant difference between stop and matching go trials. We then compared the P3 onsets of SS versus FS trials using a paired-samples t test. The correlation between the SS P3 onsets and SSRT estimates was tested using Pearson's product-moment correlation coefficient.

Brain-Behavior and Brain-Brain Correlations

All correlations were tested using Pearson's correlation coefficient. To test our main hypothesis, SICI was correlated with the onset latency of the stop-signal P3 across subjects. We predicted a positive correlation, signifying that participants with stronger $GABA_a$ activity (i.e., lower SICI values) would also show faster neural stopping activity (i.e., lower P3 onset values in milliseconds after the stop signal).

Moreover, we correlated each subject's SICI measurement with the amplitude of the trial-averaged ERP of the selected IC (i.e., specifically, its backprojection at channels FCz and Cz), which was quantified for each sample point in the 700 ms time period immediately following the stop signal. This was done to investigate a potential relationship between the amplitude of the P3 (and potential additional fronto-central ERPs represented in the same IC), without making prior assumptions about the latency of the P3. These analyses were performed separately for both the successful and failed stop-trial waveforms. In addition, to explore potential relationships between the amplitude of stop-related ERPs other than the P3, we also performed this very same analysis on both *1*) the EEG signal at the same fronto-central electrodes that was reconstructed using all nonartifact ICs "except" the selected P3 IC, as well as *2*) the EEG signal at the same fronto-central electrodes that were reconstructed using all nonartifact ICs "including" the selected P3 IC. The analysis of these signals was conducted exactly the same way that the sample-to-sample analysis for the P3-IC was conducted.

Furthermore, we attempted to investigate two previously reported associations between SICI/LICI. First, aimed to replicate the previously reported correlation between baseline SICI and SSRT (49). Second, we correlated the response delay effect (i.e., the purported behavioral marker of proactive inhibitory control) with the LICI measurement, as previous research has shown that LICI strength is modulated by task related expectations of stopping (47).

RESULTS

Behavior

In the stop-signal blocks, all participants showed slower go RT (mean = 554 ms; SD = 119) compared with failed stop trial RT (mean = 488 ms; SD = 114), indicating that all data were consistent with that assumption of the horse-race model. Mean P(stop) was 0.53 (SD= 0.05; 0.45–0.71), which validated the effectiveness of the staircase procedure. Mean SSRT was 237 ms (SD = 31). The mean response delay effect between stop signal and pure-go blocks was 0.41 (SD = 0.27; mean pure go RT: 393 ms, SD: 50; mean SST go RT: 554 ms; SD: 119).

SICI and LICI

Across all subjects, the mean unconditioned single-pulse MEP amplitude was 0.60 mV (SD: 0.45). The SICI conditioned paired-pulse MEP was 0.30 (SD: 0.29), which presents a significant reduction from the single-pulse MEP [$t(40) = 6.46$, $P = 5.33 \times 10^{-8}$), reflecting the presence of SICI. The mean reduction of the MEP due to SICI conditioning pulses was 48.6%, and SICI was numerically present in 39 out of 41 subjects (nominal SICI MEP/MEP ratio < 1). The average LICI conditioned paired-pulse MEP was 0.10 (SD: 0.13), which presents a significant reduction from the single-pulse MEP [$t(40) = 7.68$, $P = 1.07 \times 10^{-9}$), reflecting the presence of LICI. The mean reduction of the MEP due to LICI conditioning pulses was 82%, and LICI was found in 40 out of 41 subjects (nominal LICI MEP/MEP ratio < 1). The MEP results can be found in Fig. 2.

Validation of P3 Component Selection

Replicating Wessel and Aron (9), the P3 onset on successful stop trials occurred significantly earlier compared with failed stop trials [$t(40) = 7.17$; $P < 0.001$, Cohen's $d = 1.12$) and was positively correlated with SSRT ($r = 0.35$, $P = 0.028$; one participant removed from sample due to Cook's distance $>$ 4/N). These properties, alongside the grand-average ERP waveform of the selected components, can be found in Fig. 3.

SICI–P3 Correlations

In line with our primary hypothesis, SICI and the onset of the fronto-central stop-signal P3 were positively correlated ($r = 0.37$, $P = 0.017$), in other words, subjects that showed

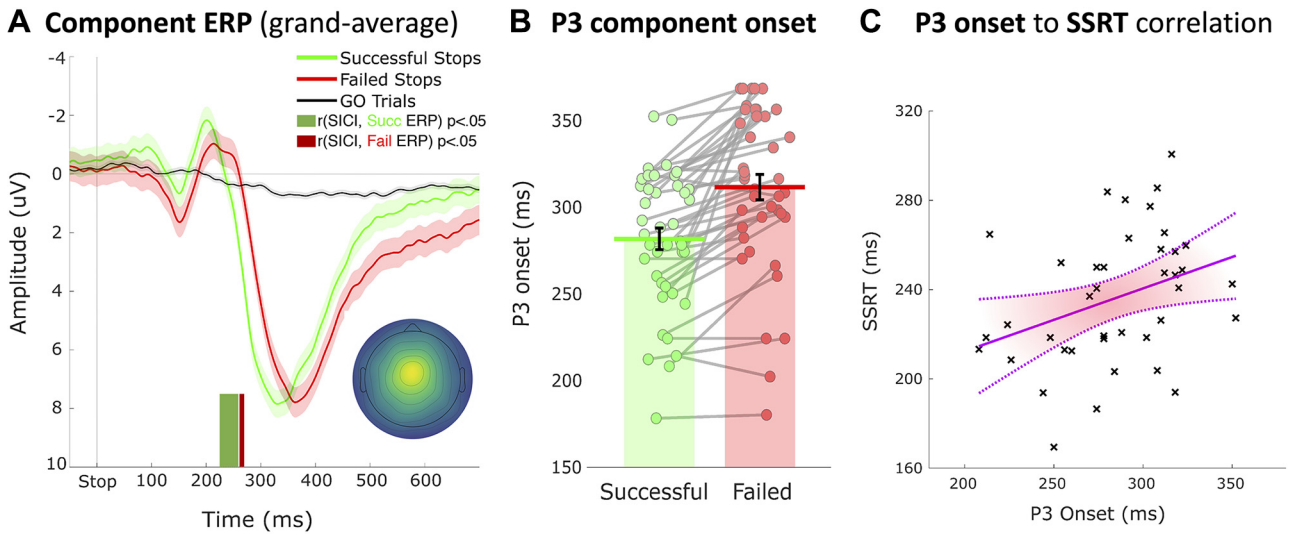

Figure 3. Validation of the selected component reflecting the stop-signal P3 ERP. *A*: grand-average of the back-projected channel ERP at fronto-central electrodes (Cz and FCz), separately for successful and failed stop trials. *Inset*: mean component topography (rectified at Cz/FCz). Green and red bars on the bottom of the plot highlight significant periods in which the ERP amplitude correlated with SICI. *B*: results of the single-trial based P3 onset identification. P3 onset was significantly earlier for successful vs. failed stop trials. *C*: positive correlation between P3 onset latency (in ms) and SSRT (in ms), alongside confidence interval. ERP, event-related potential; LICI, long-interval intracortical inhibition; SICI, short-interval intracortical inhibition; SSRT, stop-signal reaction time.

greater $GABA_a$ activity in M1 (lower SICI values) also showed faster fronto-central P3 ERPs (lower P3 onset values, Fig. 4). This correlation remained significant (P = 0.013) when the outlier from the P3-SSRT correlation (Fig. 3) was removed from the analysis (there was no reason to exclude this data point here as the data from that subject did not show Cook's $d > 4/N$ in this analysis). Moreover, although we used a Pearson's correlation to assess this relationship to replicate Chowdhury et al. (49), SICI was not normally distributed. However, the correlation remained significantly positive even when tested with the nonparametric Kendall's τ coefficient (P = 0.041, one-sided), which does not require normally distributed data. Finally, a control analysis revealed that this relationship cannot be accounted for by the amplitude of the unconditioned single-pulse MEP alone, as there was no significant correlation between the amplitude of the single-pulse MEP and P3 onset (r = 0.041, P = 0.8).

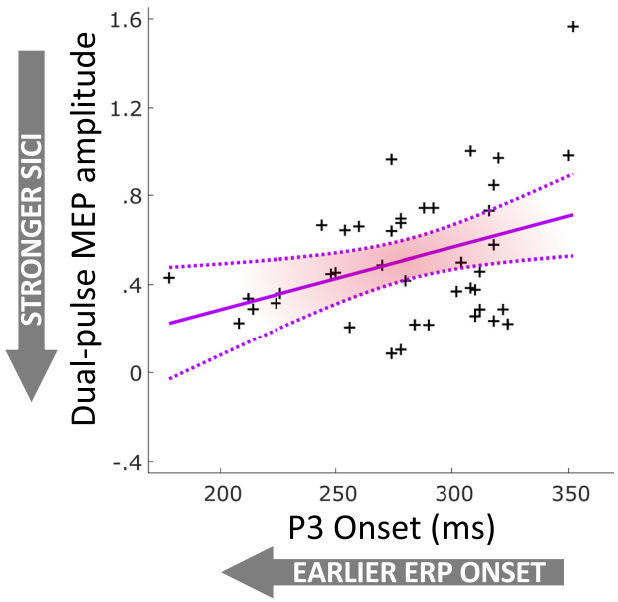

Figure 4. P3 onset and SICI are positively correlated across subjects; subjects with faster P3 onset (lower ms values) also show stronger SICI effects (lower paired-pulse MEP amplitudes). Magenta solid line shows best fit, dotted line shows the confidence interval. ERP, event-related potential; MEP, motor-evoked potential; SICI, short-interval intracortical inhibition.

In addition, our sample-to-sample amplitude analysis showed that SICI was correlated with stop-related activity of the selected independent component on both successful (significant time period: 228–260 ms after the stop signal) and failed stop trials (significant time period: 264–268 ms after the stop signal; Fig. 3*A*). No other time period showed a significant correlation with SICI (neither in the selected independent component, nor in the ERP that remained after removal of that component, nor in the "regular" ERP that was reconstructed using all nonartifact-independent components, Fig. 5). This was tested using the same sample-to-sample testing method that was used to identify the P3-SICI relationship in Fig. 3. No sample in either of the conditions (successful or failed stop trials) showed any significant correlation in any of the signal configurations (all nonartifact ICs, all nonartifact ICs minus the P3 IC, P3 IC only). In an attempt to visualize the absence of ERP-SICI correlations in response to a reviewer suggestion, Fig. 5 highlights the resulting correlations for manually selected mean amplitude measurements in select time ranges of the overall nonartifact ERP that included visible stop signal-related ERP components in the successful stop-trial waveform. However, the reader is again reminded that, just like the main analysis in Fig. 3, this analysis was actually performed on each individual sample point [and moreover, not just on the all-nonartifact-IC ERP that is depicted in Fig. 5, but also on the ERP of the selected P3 IC (cf., Fig. 3, which shows no significant correlations for either condition outside of the P3 time range), as well as the ERP of all nonartifact ICs minus the P3 (not depicted)]. As it is

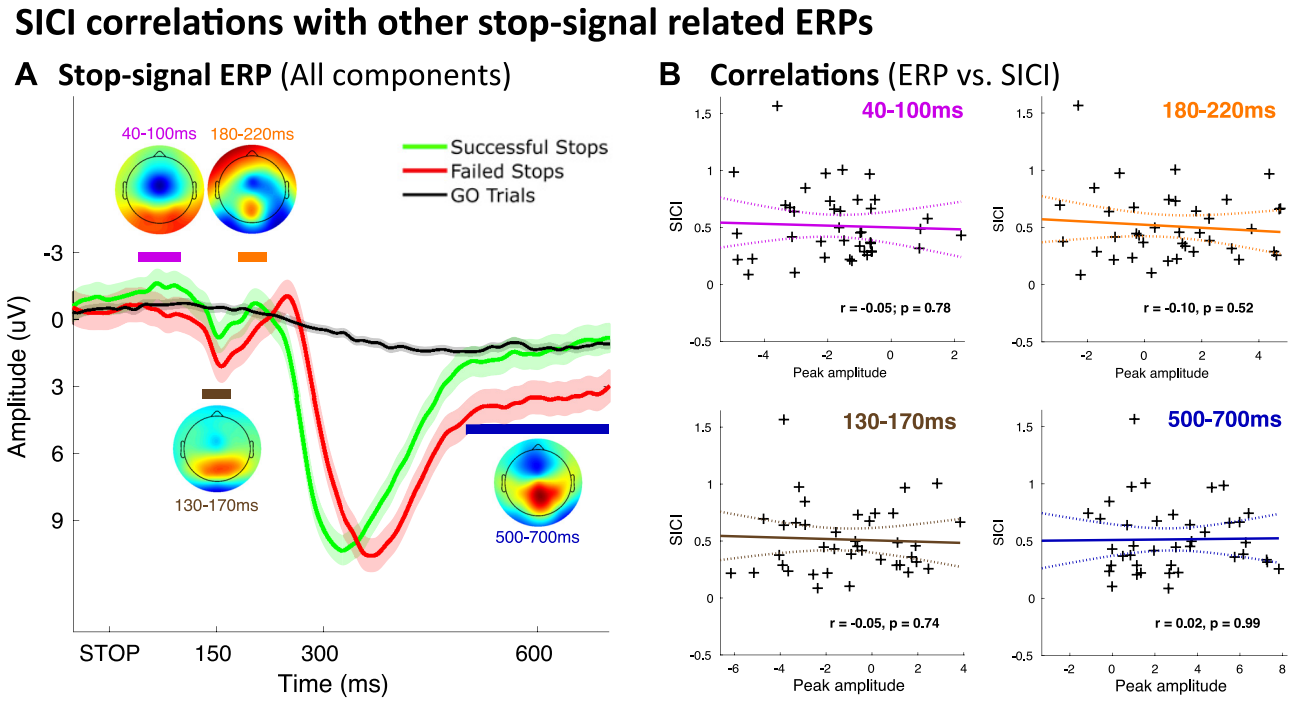

Figure 5. *A*: no other stop-signal related event-related potential (ERP) component showed a positive amplitude correlation with short-interval intracortical inhibition (SICI; unlike the P3, which showed a significant correlation, cf., Fig. 3). *B*: the results of the analysis performed on the mean amplitude of any visible voltage components in the successful stop-trial stop-signal locked ERP that was reconstructed using all nonartifact independent components from the independent component analysis back-projected at fronto-central electrodes (Cz and FCz). Neither this ERP, nor the ERP that was reconstructed using just the selected P3 independent component (cf., Fig. 3), nor the ERP that was reconstructed after removal of the P3 independent component (but retaining all others) showed any significant correlations between the successful stop-trial ERP and SICI at any time point after the stop signal.

impossible to conveniently visualize the absence of a correlation for several hundreds of individual time points across three signal configurations and two trial conditions, we have manually chosen time ranges that showed visible morphological features in the successful stop-trial waveform of the overall nonartifact ERP, averaged the activity therein, and plotted the resulting correlations alongside that same ERP (Fig. 5).

SICI/LICI–Behavior Correlations

Contrary to our expectations, we did not find any relationship between SICI/LICI and behavior. Specifically, we did not find a significant correlation between SICI and SSRT ($r = 0.02$, $P = 0.92$). Moreover, we did not find a significant relationship between LICI and the proactive response delay effect ($r = 0.21$, $P = 0.19$).

DISCUSSION

In the current study, we combined EEG recordings and paired-pulse TMS to investigate the relationship between a physiological indicator of $GABA_a$ activity in primary motor cortex (SICI) and a purported neural index of an inhibitory control process underlying action stopping (the fronto-central stop-signal P3). Based on previous findings that suggest a relationship between a subject's baseline M1 $GABA_a$ activity and their ability to stop an action (46, 48, 49), as well as on the purported role of the fronto-central P3 as a neural index of cortical processes underlying this ability (15), we hypothesized to find a direct cross-subject correspondence between SICI and the properties of the P3 to stop signals. The hypothesis confirmed was as follows: participants with stronger $GABA_a$ activity in M1 also showed faster and stronger activations of the fronto-central P3.

These results indicate that there is a direct relationship between the inhibitory activity of $GABA_a$ neurons in primary motor cortex and the cortical processes that purportedly index inhibitory control during action stopping. Notably, correlation does not imply causation, and indeed, our interpretation of this finding does not purport the existence of a direct causal (or physiological) relationship between both signals. Instead, we surmise that both stronger local GABA activity in M1 (reflected by SICI), as well as more efficient inhibitory control-related fronto-central cortical processing after stop signals (reflected in a faster and larger P3 ERP) indicate a superior functioning of an interconnected network of regions underlying inhibitory control of action, which includes cortical regions, inhibitory neurons in the motor system, and the subcortical basal ganglia (1, 3, 60, 61). In other words, we propose that this correlation is explained by a third variable—the overall integrity or functioning of the brain's inhibitory control system. We believe that our results suggest that subjects who generally show a faster/stronger response to the cortical systems purportedly underlying the triggering of inhibitory control processes after signals to stop an action also show stronger inhibitory signaling in motor cortex [i.e., the activity of inhibitory tone measured by resting SIC (62, 63)]. This would indicate a superior functioning of the distributed inhibitory motor control network in these subjects, either as a result of practice, due to genetic factors, or as a result of both. Indeed, previous research has

shown that the ability to exert motor inhibition can both be improved through repeated practice (64) and is partially attributable to genetic variables (65, 66). As it is broadly agreed upon that the precise timing of inhibitory control is paramount to action stopping, especially in tasks such as the stop-signal task, which reflect a race between response preparation and inhibitory control, it is likely that the individual components of the neural network underlying inhibitory control (cortical, subcortical, and motor system level) work in tight accord with one another, resulting in subjects with superior stopping abilities showing indicators of better neural functioning on several levels of measurement. Hence, humans with superior abilities to implement inhibitory control likely do so through a concerted effort that results in a tight relationship between cortical, subcortical, and motor system signatures of inhibition, thereby explaining the correlation we find in this study. However, the magnitude of the observed correlation also suggests that there is ample amount of variance that is not accounted for, suggesting that there is also variability in the functioning of the individual regions and mechanisms that work in concert to effect action stopping. Indeed, despite the correlation observed here, some subjects may rely more on stronger inhibitory GABA networks in M1, whereas others may rely more on the frontal cortical mechanisms that ostensibly trigger the cascade of processing that ultimately results in successful action- topping (as well as subcortical aspects that are not captured here).

Crucially, the current findings directly link the fronto-central P3 to a physiological marker of motor system inhibition in M1. Recent studies have suggested that the fronto-central P3 is related to the inhibitory demand of individual trials in which actions were successfully stopped, indicated by the activity found in (pre)motor cortex (25), as well as to reductions of the force with which responses were made on unsuccessful trials (26). Although these studies suggested a direct correspondence between motor system activity during stopping and the fronto-central stop-signal P3, they had to rely on an indirect inference to conclude that the processes reflected in the fronto-central P3 relate to the "true" inhibition of motor activity. The current investigation goes beyond these studies, but corroborates their interpretation: here, the process(es) reflected in the fronto-central P3 were shown to be directly related to the physiological inhibition of the motor system.

However, a key question regarding the role of the process reflected in the P3 remains unanswered: more and more studies are showing that functional signatures of motor inhibition (including at the level of the motor system and primary motor cortex itself) occur with much faster latency after stop signals than would be indicated by, for example, SSRT. Indeed, EMG and MEP recordings show that the first signs of motor-system inhibition in these measures emerge as early as ~150 ms after the onset of a stop signal (67, 68). In line with this, recent studies have shown that cortical signals that are related to stopping success can also be found in similar time ranges (20, 21, 67, 69). Just like the aforementioned EMG and MEP measurements of functional motor inhibition, these cortical signatures often precede both SSRT, as well as the typical onset latency of the fronto-central P3, by several dozens of milliseconds. This begs the question of the role of the P3, which likely emerges too late to be causally underlying the implementation of the reported reductions of MEP and EMG at the 150 ms mark. This aspect is particularly important in the context of the current set of results. This is because the GABAergic neurons whose activity is captured by SICI are purportedly underlying the early signatures of motor system inhibition in the MEP and EMG. Given the recency of these findings, theoretical developments and empirical studies are still ongoing in this domain. However, it is notable that low-latency reductions of cortico-spinal excitability, such as the MEP suppression at 150 ms following the stimulus, are found not just after stop signals, but indeed after any sort of surprising (70–73) or even merely infrequent events (74). This could suggest that instead of a single, monolithic mechanism, stopping is implemented by a multistep sequence of inhibitory processes, similar to what was proposed in the "pause-then-cancel" model by Schmidt et al. (8, 14). According to this model, action stopping includes two processes: an initial, rapid, broad "pause" process, which temporarily halts all ongoing actions with the lowest latency possible, followed by a more measured, selective "cancel" process, which entirely shuts off the currently invigorated motor program. Along those lines, we tentatively propose that the initial "pause" process occurs after any meaningful infrequent, salient, or surprising event, resulting in the low-latency reductions of the MEP (and EMG) that have recently been reported both inside and outside of the stop-signal paradigm. During outright action stopping in the stop-signal task, the "pause" is then followed (or accompanied) by the slower "cancel" process, which is more specific to stimuli that explicitly instruct the outright cancellation of ongoing action (such as a stop signal). Although a translation of this theoretical framework in humans is still pending, we here tentatively propose that the fronto-central P3, which likely originates from medial frontal regions involved in motor planning, such as the pre-SMA (75), may reflect the second, "cancel" stage (which could more broadly be understood as a reconfiguration of the active motor program). Although the current study was not designed to test this interpretation, the results do suggest that both the inhibition of movement at the level of the motor system and the frontal cortical activity reflected in the fronto-central P3 are closely related, in line with the proposal that both underlying processes contribute to successful action stopping.

Although the SICI-EEG relationship in the current study confirmed the primary hypothesis, our results notably did not confirm a secondary hypothesis and failed to replicate some prior work. Specifically regarding the latter, Chowdhury et al. (49) had reported a positive relationship between SSRT and SICI measured at baseline, representing the main finding that motivated the hypothesis of the current study. Although we did find a positive correlation between SSRT and P3 onset [replicating previous work on the EEG-behavior relationship; cf., Huster et al. (20) and Wessel and Aron (9)], and P3 onset was in turn correlated with SSRT as well (the main result of the current study), SICI and SSRT were not themselves correlated in our data set. There are several potential reasons for this. First, as mentioned in the INTRODUCTION, SSRT has several weaknesses as a variable. In addition to the conceptual criticisms that have recently been levied against SSRT, there is also substantial variability in the algorithmic imple-

mentation of SSRT calculations. Indeed, while Chowdhury et al. used the mean method to calculate SSRT, our study implemented a newly suggested integration procedure in which missing go-trial reaction times due to absent responses (or responses made after the response deadline) were replaced by the slowest validly counted reaction time for that same subject. This technique has been suggested in a recent paper that was not available at the time of the Chowdhury et al.'s study (12). However, it has to be noted that even using Chowdhury et al.'s SSRT calculation method, no correlation between SSRT and SICI was found in the current data set ($r = 0.01$, $P = 0.95$). Second, there were two notable ways in which our SICI measurement deviated from Chowdhury et al.'s work as well. First, our SICI estimates were collected before the performance of the task, whereas Chowdhury et al. measured SICI after the task. In the current data set, we found that MEPs collected before and after the task differed significantly, which is in line with the purported effects that both fatigue (55, 56) and inhibitory control training (57) have on motor excitability. We chose to omit the posttask TMS measurements for this reason, as the pretask measurements should be unaffected by these variables (though we note that an exploratory post hoc analysis of the posttask TMS measurements, i.e., a closer replication of Chowdhury et al.'s procedure, also revealed no significant correlation to SSRT; $r = -0.04$, $P = 0.78$). Perhaps more importantly, our SICI measurement procedure itself differed from the exact implementation of Chowdhury et al. Specifically, while Chowdhury et al. (49) used an interstimulus interval of 3 ms between the conditioning pulse and the test pulse, we here used an interval of 2 ms. This interval was chosen because it has been shown to reliably evoke SICI (28), while temporally avoiding unwanted I-wave facilitation (40, 54, 76, 77). It is entirely possible that the two procedures capture subtly different parts of the underlying $GABA_a$ activity (54, 78), leading to the difference in findings regarding the SICI-SSRT correlation. Finally, our implementation of the stop-signal task itself also differed from Chowdhury et al. While Chowdhury et al. used the classic SST implementation as programmed in the STOP-IT toolbox (79), we collected SST blocks in alternation with pure-go blocks, in which no stop-signals were presented. This was done to test a secondary hypothesis about the potential role of LICI in the implementation of proactive inhibitory control (see the RESULTS). This could have, in principle, affected behavior in the SST blocks in a way that influenced SSRT. Either way, our study was designed to explicitly exclude SSRT as a meaningfully variable from our comparisons, given that we aimed to directly use signatures of physiological inhibition of the motor system to evaluate the relationship of the fronto-central P3 to motor inhibition. Therefore, our study was not optimized to directly replicate the purported SICI-SSRT association demonstrated by Chowdhury et al. (49), and we believe that our nonreplication does not bear on the validity of those results (which the authors have since conceptually replicated using an event-related SICI protocol, cf., Chowdhury et al. (80)).

In regards to the current study's secondary hypothesis, we also did not find a positive association between LICI at baseline and the degree to which participants slowed down their responding when anticipating potential stop-signals (in the SST blocks) compared with when they respond without restraint (in the pure go blocks). This analysis was originally included for reasons of convenience (i.e., because of the ease of implementation of this secondary hypothesis into the primary investigation). However, it is notable that the measurement of LICI at baseline and its comparison to the response delay effect is a substantial deviation from the original study that had purported that $GABA_b$ neurotransmission in M1 may be related to the implementation of proactive control. Indeed, the proposition comes from a study by Cowie et al., (81) in which they measured LICI during a bimanual response inhibition task, demonstrating larger inhibitory effects during blocks with stop trials (compared with only go-trial blocks) and which were positively correlated with the response delay of the left hand, following response cancellation in the right hand (47). This suggests that LICI could reflect the tone of inhibitory circuits in M1, which is increased during tasks that may require rapid action cancellation; although this is not always the case (82). Although the current study shows that LICI at baseline does not relate to the specific behavioral phenomenon of the response delay effect, other studies (especially those that measure LICI during event-related task periods in which proactive control is exerted, rather than at baseline) may well find different results.

CONCLUSIONS

In summary, we here used a unique and novel combination of paired-pulse TMS and scalp EEG to directly investigate the relationship between inhibitory neuronal activity in primary motor cortex and control signals purportedly underlying the inhibitory control of action in frontal cortex. In line with our predictions, we found that local $GABA_a$ activity in primary motor cortex was directly related to both the latency and amplitude of the fronto-central P3 ERP. This suggests that there is a direct correspondence between the properties of this frontal control signal, which has been purported to reflect a process related to the "horse-race" underlying action stopping in the stop-signal task, and the ability of subjects to physiologically inhibit motor signals. Although these results do not, on their own, provide conclusive evidence for the P3-inhibition hypothesis, they do represent further evidence toward the relationship between the fronto-central P3 and motor inhibition, though recent questions about the relative timing of processes remain, and will have to be addressed through sustained theoretical and empirical work.

ACKNOWLEDGMENTS

The authors would like to thank Nathan Chalkley and Brynne Dochterman for help with data collection.

GRANTS

This work was supported by the National Institutes of Health (Grant NIH R01 NS117753), the National Science Foundation (CAREER 1752355), the Iowa Center for Research by Undergraduates, and the Iowa Neuroscience Institute Summer Scholars' program.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.S. and J.R.W. conceived and designed research; M.H. and B.O.R. performed experiments; M.H., C.S., and B.O.R. analyzed data; C.S., B.O.R., and J.R.W. interpreted results of experiments; M.H., C.S., and B.O.R. prepared figures; J.R.W. drafted manuscript; M.H., C.S., and B.O.R. edited and revised manuscript; M.H., C.S., and J.R.W. approved final version of manuscript.

ENDNOTE

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REFERENCES

1. **Aron AR**, **Poldrack RA.** Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci* 26: 2424–2433, 2006. doi:10.1523/JNEUROSCI.4682-05.2006.
2. **Chevrier AD**, **Noseworthy MD**, **Schachar R.** Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. *Hum Brain Mapp* 28: 1347–1358, 2007. doi:10.1002/hbm.20355.
3. **Aron AR**, **Robbins TW**, **Poldrack RA.** Inhibition and the right inferior frontal cortex: one decade on. *Trends Cogn Sci* 18: 177–185, 2014. doi:10.1016/j.tics.2013.12.003.
4. **Levy BJ**, **Wagner AD.** Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. *Ann NY Acad Sci* 1224: 40–62, 2011. doi:10.1111/j.1749-6632.2011.05958.x.
5. **Chambers CD**, **Garavan H**, **Bellgrove MA.** Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* 33: 631–646, 2009. doi:10.1016/j.neubiorev.2008.08.016.
6. **Wager TD**, **Sylvester CYC**, **Lacey SC**, **Nee DE**, **Franklin M**, **Jonides J.** Common and unique components of response inhibition revealed by fMRI. *NeuroImage* 27: 323–340, 2005. doi:10.1016/j.neuroimage.2005.01.054.
7. **Chen W**, **Hemptinne C de**, **Miller AM**, **Leibbrand M**, **Little SJ**, **Lim DA**, **Larson PS**, **Starr PA.** Prefrontal-subthalamic hyperdirect pathway modulates movement inhibition in humans. *Neuron* 106: 579–588.e3, 2020. doi:10.1016/j.neuron.2020.02.012.
8. **Schmidt R**, **Leventhal DK**, **Mallet N**, **Chen F**, **Berke JD.** Canceling actions involves a race between basal ganglia pathways. *Nat Neurosci* 16: 1118–1124, 2013. doi:10.1038/nn.3456.
9. **Wessel JR**, **Aron AR.** It's not too late: the onset of the frontocentral P3 indexes successful response inhibition in the stop-signal paradigm. *Psychophysiology* 52: 472–480, 2015. doi:10.1111/psyp.12374.
10. **Logan GD**, **Cowan WB**, **Davis KA.** On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform* 10: 276–291, 1984. doi:10.1037/0096-1523.10.2.276.
11. **Verbruggen F**, **Logan GD.** Proactive adjustments of response strategies in the stop-signal paradigm. *J Exp Psychol Hum Percept Perform* 35: 835–854, 2009. doi:10.1037/a0012726.
12. **Verbruggen F**, **Aron AR**, **Band GP**, **Beste C**, **Bissett PG**, **Brockett AT**, et al. A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. *eLife* 8: e46323, 2019. doi:10.7554/eLife.46323.
13. **Boucher L**, **Palmeri TJ**, **Logan GD**, **Schall JD.** Inhibitory control in mind and brain: an interactive race model of countermanding saccades. *Psychol Rev* 114: 376–397, 2007. doi:10.1037/0033-295X.114.2.376.
14. **Schmidt R**, **Berke JD.** A pause-then-cancel model of stopping: evidence from basal ganglia neurophysiology. *Philos Trans R Soc B Biol Sci* 372: 20160202, 2017. doi:10.1098/rstb.2016.0202.
15. **Jong RD**, **Coles MGH**, **Logan GD**, **Gratton G.** In search of the point of no return: the control of response processes. *J Exp Psychol Hum Percept Perform* 16: 164–182, 1990. doi:10.1037/0096-1523.16.1.164.
16. **Kok A**, **Ramautar JR**, **Ruiter MBD**, **Band GPH**, **Ridderinkhof KR.** ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology* 41: 9–20, 2004. doi:10.1046/j.1469-8986.2003.00127.x.
17. **Dimoska A**, **Johnstone SJ**, **Barry RJ**, **Clarke AR.** Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biol Psychiatry* 54: 1345–1354, 2003. doi:10.1016/S0006-3223(03)00703-0.
18. **Huster RJ**, **Enriquez-Geppert S**, **Lavallee CF**, **Falkenstein M**, **Herrmann CS.** Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. *Int J Psychophysiol* 87: 217–233, 2013. doi:10.1016/j.ijpsycho.2012.08.001.
19. **Naito E**, **Matsumura M.** Movement-related potentials associated with motor inhibition under different preparatory states during performance of two visual stop signal paradigms in humans. *Neuropsychologia* 34: 565–573, 1996. doi:10.1016/0028-3932(95)00140-9.
20. **Huster RJ**, **Messel MS**, **Thunberg C**, **Raud L.** The P300 as marker of inhibitory control—fact or fiction? *Cortex* 132: 334–348, 2020. doi:10.1016/j.cortex.2020.05.021.
21. **Skippen P**, **Fulham WR**, **Michie PT**, **Matzke D**, **Heathcote A**, **Karayanidis F.** Reconsidering electrophysiological markers of response inhibition in light of trigger failures in the stop-signal task. *Psychophysiology* 57: e13619, 2020. doi:10.1111/psyp.13619.
22. **Matzke D**, **Curley S**, **Gong CQ**, **Heathcote A.** Inhibiting responses to difficult choices. *J Exp Psychol Gen* 148: 124–142, 2019. doi:10.1037/xge0000525.
23. **Skippen P**, **Matzke D**, **Heathcote A**, **Fulham WR**, **Michie P**, **Karayanidis F.** Reliability of triggering inhibitory process is a better predictor of impulsivity than SSRT. *Acta Psychol (Amst)* 192: 104–117, 2019. doi:10.1016/j.actpsy.2018.10.016.
24. **Corcos DM**, **Gottlieb GL**, **Latash ML**, **Almeida GL**, **Agarwal GC.** Electromechanical delay: an experimental artifact. *J Electromyogr Kinesiol* 2: 59–68, 1992. doi:10.1016/1050-6411(92)90017-D.
25. **Wessel JR.** Prepotent motor activity and inhibitory control demands in different variants of the go/no-go paradigm. *Psychophysiol* 55: e12871, 2018. doi:10.1111/psyp.12871.
26. **Nguyen AT**, **Albrecht MA**, **Lipp OV**, **Marinovic W.** Motor output matters: Evidence of a continuous relationship between Stop/No-go P300 amplitude and peak force on failed inhibitions at the trial-level. *Psychophysiology* 57: e13558, 2020. doi:10.1111/psyp.13558.
27. **Rossini PM**, **Barker AT**, **Berardelli A**, **Caramia MD**, **Caruso G**, **Cracco RQ**, **Dimitrijević MR**, **Hallett M**, **Katayama Y**, **Lücking CH**, **Noordhout ALM**, **de Marsden CD**, **Murray NMF**, **Rothwell JC**, **Swash M**, **Tomberg C.** Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 91: 79–92, 1994. doi:10.1016/0013-4694(94)90029-9.
28. **Kujirai T**, **Caramia MD**, **Rothwell JC**, **Day BL**, **Thompson PD**, **Ferbert A**, **Wroe S**, **Asselman P**, **Marsden CD.** Corticocortical inhibition in human motor cortex. *J Physiol* 471: 501–519, 1993. doi:10.1113/jphysiol.1993.sp019912.
29. **Sanger TD**, **Garg RR**, **Chen R.** Interactions between two different inhibitory systems in the human motor cortex. *J Physiol* 530: 307–317, 2001. doi:10.1111/j.1469-7793.2001.0307l.x.
30. **Hall SD**, **Stanford IM**, **Yamawaki N**, **McAllister CJ**, **Rönnqvist KC**, **Woodhall GL**, **Furlong PL.** The role of GABAergic modulation in motor function related neuronal network activity. *NeuroImage* 56: 1506–1510, 2011. doi:10.1016/j.neuroimage.2011.02.025.
31. **Stagg CJ**, **Bestmann S**, **Constantinescu AO**, **Moreno LM**, **Allman C**, **Mekle R**, **Woolrich M**, **Near J**, **Johansen-Berg H**, **Rothwell JC.** Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. *J Physiol* 589: 5845–5855, 2011. doi:10.1113/jphysiol.2011.216978.
32.. **Quetscher C**, **Yildiz A**, **Dharmadhikari S**, **Glaubitz B**, **Schmidt-Wilcke T**, **Dydak U**, **Beste C.** Striatal GABA-MRS predicts

response inhibition performance and its cortical electrophysiological correlates. *Brain Struct Funct* 220: 3555–3564, 2015. doi:10.1007/s00429-014-0873-y.
33. **Lazzaro VD**, **Pilato F**, **Dileone M**, **Ranieri F**, **Ricci V**, **Profice P**, **Bria P**, **Tonali PA**, **Ziemann U.** GABAA receptor subtype specific enhancement of inhibition in human motor cortex. *J Physiol* 575: 721–726, 2006. doi:10.1113/jphysiol.2006.114694.
34. **Valls-Solé J**, **Pascual-Leone A**, **Wassermann EM**, **Hallett M.** Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr Clin Neurophysiol* 85: 355–364, 1992. doi:10.1016/0168-5597(92)90048-G.
35. **Chu J**, **Gunraj C**, **Chen R.** Possible differences between the time courses of presynaptic and postsynaptic GABAB mediated inhibition in the human motor cortex. *Exp Brain Res* 184: 571–577, 2008. doi:10.1007/s00221-007-1125-7.
36. **McCormick DA.** GABA as an inhibitory neurotransmitter in human cerebral cortex. *J Neurophysiol* 62: 1018–1027, 1989. doi:10.1152/jn.1989.62.5.1018.
37. **Lazzaro VD**, **Oliviero A**, **Meglio M**, **Cioni B**, **Tamburrini G**, **Tonali P**, **Rothwell JC.** Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clin Neurophysiol* 111: 794–799, 2000. doi:10.1016/S1388-2457(99)00314-4.
38. **Ziemann U**, **Lönnecker S**, **Steinhoff BJ**, **Paulus W.** Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann Neurol* 40: 367–378, 1996. doi:10.1002/ana.410400306.
39. **McDonnell MN**, **Orekhov Y**, **Ziemann U.** Suppression of LTP-like plasticity in human motor cortex by the GABAB receptor agonist baclofen. *Exp Brain Res* 180: 181–186, 2007. doi:10.1007/s00221-006-0849-0.
40. **Chen R.** Interactions between inhibitory and excitatory circuits in the human motor cortex. *Exp Brain Res* 154: 1–10, 2004. doi:10.1007/s00221-003-1684-1.
41. **Hammond G**, **Vallence A-M.** Modulation of long-interval intracortical inhibition and the silent period by voluntary contraction. *Brain Res* 1158: 63–70, 2007. doi:10.1016/j.brainres.2007.05.014.
42. **Reynolds C**, **Ashby P.** Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology* 53: 730–735, 1999. doi:10.1212/WNL.53.4.730.
43. **Ridding MC**, **Taylor JL**, **Rothwell JC.** The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. *J Physiology* 487: 541–548, 1995. doi:10.1113/jphysiol.1995.sp020898.
44. **Kouchtir-Devanne N**, **Capaday C**, **Cassim F**, **Derambure P**, **Devanne H.** Task-dependent changes of motor cortical network excitability during precision grip compared to isolated finger contraction. *J Neurophysiol* 107: 1522–1529, 2012. doi:10.1152/jn.00786.2011.
45. **Opie GM**, **Ridding MC**, **Semmler JG.** Age-related differences in pre- and post-synaptic motor cortex inhibition are task dependent. *Brain Stimul* 8: 926–936, 2015. doi:10.1016/j.brs.2015.04.001.
46. **Coxon JP**, **Stinear CM**, **Byblow WD.** Intracortical inhibition during volitional inhibition of prepared action. *J Neurophysiol* 95: 3371–3383, 2006. doi:10.1152/jn.01334.2005.
47. **Cowie MJ**, **MacDonald HJ**, **Cirillo J**, **Byblow WD.** Proactive modulation of long-interval intracortical inhibition during response inhibition. *J Neurophysiol* 116: 859–867, 2016. doi:10.1152/jn.00144.2016.
48. **Sohn YH**, **Wiltz K**, **Hallett M.** Effect of volitional inhibition on cortical inhibitory mechanisms. *J Neurophysiol* 88: 333–338, 2002. doi:10.1152/jn.2002.88.1.333.
49. **Chowdhury NS**, **Livesey EJ**, **Blaszczynski A**, **Harris JA.** Variations in response control within at-risk gamblers and non-gambling controls explained by GABAergic inhibition in the motor cortex. *Cortex* 103: 153–163, 2018. doi:10.1016/j.cortex.2018.03.004.
50. **Rossi S**, **Hallett M**, **Rossini PM**, **Pascual-Leone A**; **Safety of TMS Consensus Group.** Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 120: 2008–2039, 2009. doi:10.1016/j.clinph.2009.08.016.
51. **Brainard DH.** The psychophysics toolbox. *Spat Vis* 10: 433–436, 1997. doi:10.1163/156856897X00357.
52. **Chikazoe J**, **Jimura K**, **Hirose S**, **Yamashita K**, **Miyashita Y**, **Konishi S.** Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. *J Neurosci* 29: 15870–15877, 2009. doi:10.1523/JNEUROSCI.3645-09.2009.
53. **Jahfari S**, **Stinear CM**, **Claffey M**, **Verbruggen F**, **Aron AR.** Responding with restraint: what are the neurocognitive mechanisms? *J Cogn Neurosci* 22: 1479–1492, 2010. doi:10.1162/jocn.2009.21307.
54. **Peurala SH**, **Müller-Dahlhaus JFM**, **Arai N**, **Ziemann U.** Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF). *Clin Neurophysiol* 119: 2291–2297, 2008. doi:10.1016/j.clinph.2008.05.031.
55. **Gennaro LD**, **Marzano C**, **Veniero D**, **Moroni F**, **Fratello F**, **Curcio G**, **Ferrara M**, **Ferlazzo F**, **Novelli L**, **Pellicciari MC**, **Bertini M**, **Rossini PM.** Neurophysiological correlates of sleepiness: a combined TMS and EEG study. *NeuroImage* 36: 1277–1287, 2007. doi:10.1016/j.neuroimage.2007.04.013.
56. **Noreika V**, **Kamke MR**, **Canales-Johnson A**, **Chennu S**, **Bekinschtein TA**, **Mattingley JB.** Alertness fluctuations when performing a task modulate cortical evoked responses to transcranial magnetic stimulation. *NeuroImage* 223: 117305, 2020. doi:10.1016/j.neuroimage.2020.117305.
57. **Majid DSA**, **Lewis C**, **Aron AR.** Training voluntary motor suppression with real-time feedback of motor evoked potentials. *J Neurophysiol* 113: 3446–3452, 2015. doi:10.1152/jn.00992.2014.
58. **Bell AJ**, **Sejnowski TJ.** An information-maximization approach to blind separation and blind deconvolution. *Neural Comput* 7: 1129–1159, 1995. doi:10.1162/neco.1995.7.6.1129.
59. **Benjamini Y**, **Krieger AM**, **Yekutieli D.** Adaptive linear step-up procedures that control the false discovery rate. *Biometrika* 93: 491–507, 2006. doi:10.1093/biomet/93.3.491.
60. **Verbruggen F**, **Logan GD.** Response inhibition in the stop-signal paradigm. *Trends Cogn Sci* 12: 418–424, 2008. doi:10.1016/j.tics.2008.07.005.
61. **Wiecki TV**, **Frank MJ.** A computational model of inhibitory control in frontal cortex and basal ganglia. *Psychol Rev* 120: 329–355, 2013. doi:10.1037/a0031542.
62. **Hummel FC**, **Steven B**, **Hoppe J**, **Heise K**, **Thomalla G**, **Cohen LG**, **Gerloff C.** Deficient intracortical inhibition (SICI) during movement preparation after chronic stroke. *Neurology*, 72: 1766–1772, 2009. doi:10.1212/WNL.0b013e3181a609c5.
63. **Zimerman M**, **Wessel M**, **Timmermann JE**, **Granström S**, **Gerloff C**, **Mautner VF**, **Hummel FC.** Impairment of procedural learning and motor intracortical inhibition in neurofibromatosis type 1 patients. *EBioMedicine* 2: 1430–1437, 2015. doi:10.1016/j.ebiom.2015.08.036.
64. **Manuel AL**, **Bernasconi F**, **Spierer L.** Plastic modifications within inhibitory control networks induced by practicing a stop-signal task: an electrical neuroimaging study. *Cortex* 49: 1141–1147, 2013. doi:10.1016/j.cortex.2012.12.009.
65. **Colzato LS**, **Wildenberg WVD**, **Does AD**, **Hommel B.** Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience* 170: 782–788, 2010. doi:10.1016/j.neuroscience.2010.07.050.
66. **Weafer J**, **Gray JC**, **Hernandez K**, **Palmer AA**, **MacKillop J**, **Wit H de.** Hierarchical investigation of genetic influences on response inhibition in healthy young adults. *Exp Clin Psychopharmacol* 25: 512–520, 2017. doi:10.1037/pha0000156.
67. **Jana S**, **Hannah R**, **Muralidharan V**, **Aron AR.** Temporal cascade of frontal, motor and muscle processes underlying human action-stopping. *eLife* 9: e50371, 2020. doi:10.7554/eLife.50371.
68. **Raud L**, **Huster RJ.** The temporal dynamics of response inhibition and their modulation by cognitive control. *Brain Topogr* 30: 486–501, 2017. doi:10.1007/s10548-017-0566-y.
69. **Wessel JR.** β-Bursts reveal the trial-to-trial dynamics of movement initiation and cancellation. *J Neurosci* 40: 411–423, 2020. doi:10.1523/JNEUROSCI.1887-19.2019.
70. **Dutra IC**, **Waller DA**, **Wessel JR.** Perceptual surprise improves action stopping by nonselectively suppressing motor activity via a neural mechanism for motor inhibition. *J Neurosci* 38: 1482–1492, 2018. doi:10.1523/JNEUROSCI.3091-17.2017.
71. **Novembre G**, **Pawar V**, **Bufacchi R**, **Kilintari M**, **Srinivasan M**, **Rothwell J**, **Haggard P**, **Iannetti G.** Saliency detection as a reactive process: unexpected sensory events evoke corticomuscular coupling. *J Neurosci* 38: 2385–2397, 2018. doi:10.1523/JNEUROSCI.2474-17.2017.
72. **Novembre G**, **Pawar VM**, **Kilintari M**, **Bufacchi RJ**, **Guo Y**, **Rothwell JC**, **Iannetti GD.** The effect of salient stimuli on neural oscillations, isometric force, and their coupling. *NeuroImage* 198: 221–230, 2019. doi:10.1016/j.neuroimage.2019.05.032.

73. **Wessel JR**, **Aron AR.** Unexpected events induce motor slowing via a brain mechanism for action-stopping with global suppressive effects. *J Neurosci* 33: 18481–18491, 2013. doi:10.1523/JNEUROSCI.3456-13.2013.
74. **Iacullo C**, **Diesburg DA**, **Wessel JR.** Non-selective inhibition of the motor system following unexpected and expected infrequent events. *Exp Brain Res* 238: 1–10, 2020. doi:10.1007/s00221-020-05919-3.
75. **Enriquez-Geppert S**, **Konrad C**, **Pantev C**, **Huster RJ.** Conflict and inhibition differentially affect the N200/P300 complex in a combined go/nogo and stop-signal task. *NeuroImage* 51: 877–887, 2010. doi:10.1016/j.neuroimage.2010.02.043.
76. **Chen R**, **Garg R.** Facilitatory I wave interaction in proximal arm and lower limb muscle representations of the human motor cortex. *J Neurophysiol* 83: 1426–1434, 2000. doi:10.1152/jn.2000.83.3.1426.
77. **Hanajima R**, **Ugawa Y**, **Terao Y**, **Enomoto H**, **Shiio Y**, **Mochizuki H**, **Furubayashi T**, **Uesugi H**, **Iwata NK**, **Kanazawa I.** Mechanisms of intracortical I-wave facilitation elicited with paired-pulse magnetic stimulation in humans. *J Physiol* 538: 253–261, 2002. doi:10.1113/jphysiol.2001.013094.
78. **Fisher RJ**, **Nakamura Y**, **Bestmann S**, **Rothwell JC**, **Bostock H.** Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. *Exp Brain Res* 143: 240–248, 2002. doi:10.1007/s00221-001-0988-2.
79. **Verbruggen F**, **Logan GD**, **Stevens MA.** STOP-IT: windows executable software for the stop-signal paradigm. *Behav Res Methods* 40: 479–483, 2008. doi:10.3758/BRM.40.2.479.
80. **Chowdhury NS**, **Livesey EJ**, **Harris JA.** Individual differences in intracortical inhibition during behavioural inhibition. *Neuropsychologia* 124: 55–65, 2019. doi:10.1016/j.neuropsychologia.2019.01.008.
81. **Coxon JP**, **Stinear CM**, **Byblow WD.** Selective inhibition of movement. *J Neurophysiol* 97: 2480–2489, 2007. doi:10.1152/jn.01284.2006.
82. **Cirillo J**, **Cowie MJ**, **MacDonald HJ**, **Byblow WD.** Response inhibition activates distinct motor cortical inhibitory processes. *J Neurophysiol* 119: 877–886, 2018. doi:10.1152/jn.00784.2017.