EMG MARKERS OF GLOBAL INHIBITION WHILE STOPPING

by

ISAIAH J MILLS

A THESIS

Presented to the Department of Human Physiology
and the Robert D. Clark Honors College
in partial fulfillment of the requirements for the degree of
Bachelor of Arts

May 2022

An Abstract of the Thesis of

Isaiah Mills for the degree of Bachelor of Arts
in the Department of Human Physiology to be taken June 2022

Title: EMG Markers of Global Inhibition While Stopping

Approved: *Dr. Ian Greenhouse*
Primary Thesis Advisor

Selectively stopping parts of complex movement plans is a critical part of reacting correctly to stimuli. For example, when driving a car one may have to stop one arm from reaching toward the gearshift while pressing the brakes to avoid a crossing deer. While humans can coordinate movements effectively, our brains limit our ability to selectively stop. Canceling one action can delay the execution of other simultaneous actions, especially when these actions are bimanual and symmetrical. This type of interference is hypothesized to reflect the activation of a specific neural pathway that non-selectively (globally) inhibits the motor system during stopping before continuing actions can be reinitiated. Here, we hypothesized that electromyography (EMG) can provide a marker of global inhibition in the motor system during stopping behavior. To examine this hypothesis, we tested twenty subjects using a novel version of the bimanual anticipatory response inhibition (ARI) task with their index fingers while maintaining a constant force (tonic) muscle contraction as measured by EMG. Contrary to our hypothesis, we found no evidence of nonselective inhibition in the tonic EMG during successful stopping compared to going. Future directions include examining particular time points of interest during the stopping process in order to determine if the hypothesized inhibition may be limited to a transient period.

Acknowledgements

I would like to thank Dr. Ian Greenhouse for the guidance and incredible support that he has given me over the course of the past years that I have been a part of the Action Control lab and during this thesis project. Thank you, Mitchell Fisher, for being so generous with your time and being a wonderful mentor and a great friend. Thank you to Dr. Lisa Munger for serving as my CHC committee representative and for teaching me so much about the wonderful world of marine mammals. Thank you, Carey Mills, for turning me into the person I am today and being my biggest cheerleader. Thank you, McGwire Smith, for helping me realize that I can do good work without burning myself out, and for keeping me focused on what is important. Thank you, Eli Serrao, for encouraging me from day one, for showing up when I needed to see a friendly face, and for motivating me all the way through the finish line. Finally, thank you to the Knight Campus, and the Knight Campus Undergraduate Scholars program for generously supporting me throughout this project.

Table of Contents

List of Figures

List of Tables

Introduction

Stopping of individual and interrelated movements is an integral part of moving in a coordinated and safe manner. Stopping is generally studied using a task paradigm known as a stop signal task. In a simple stop task, subjects complete many trials in which they receive a computer-generated go stimulus and must react by completing an action such as pressing a button as fast as they can. A small percentage of trials, generally 25-33%, are stop trials in which a stop signal is given soon after the go stimulus, and the subject must attempt to stop or cancel their action, i.e. not pressing the button. In this paradigm, the subject's behavior can be described as an independent horse race in which a stopping process is initiated in response to the stop signal and races against an already initiated go process associated with the completion of an action. If the stopping process finishes first, the action is inhibited, but if the go process finishes first the action is executed (Logan & Cowan, 1984).

Studying the organization and function of these specific neural pathways is important for understanding the mechanisms of movement disorders and the specific roles of physiological inhibition. Many disease mechanisms have been studied using a stop signal task in which patient populations show performance deficits, such as Parkinson's disease. A variety of movement disorders arise from dysfunctional basal ganglia, a group of nuclei in the center of the brain, supporting the long-held interpretation that this organizational network plays an important role in shaping motor activity. Patients who suffer from dystonia, chorea, and tics all display patterns of basal ganglia activity that result in a lack of inhibition of competing motor patterns as

compared to healthy patients, while those who suffer from diseases like Parkinson's exhibit excessive inhibition (Mink, 2003). When investigating the human motor system, specific changes in inhibition and resulting motor outputs can be compared to the outputs of healthy patients to discover more about the causes and potential avenues of treatment for these diseases.

The role of the basal ganglia in movement inhibition suggests that their inhibitory output on the motor system is suited to play a role in action cancellation as well. One influential model suggests action cancellation is accomplished by a cortico-basal ganglia pathway known as the hyperdirect pathway which bypasses the striatum via monosynaptic projections to the subthalamic nucleus (STN). This pathway culminates in divergent excitatory projections onto motor areas of the thalamus which allow for rapid nonspecific suppression of ongoing actions (Nambu et al., 2002).

STN activity during stopping was investigated in an fMRI study in which participants performed a reactive choice stop task (Aron & Poldrack, 2006). In this variation of the stop task, the go signal presented during all trials was an arrow that pointed either to the left or to the right, indicating that the subject should respond by pressing a button with the index or middle finger of the right hand, respectively. During stop trials a stop signal indicated that the subject should cancel the initiated action. The experiment showed that a pathway involving the pre-supplementary motor area (pre-SMA), the right inferior frontal cortex (rIFC), and the STN, which receives direct projections from the rIFC, is activated during stopping. Additionally, subjects who exhibited faster stopping times during a stop signal task had greater activation of both

the rIFC and the STN. Because experimental evidence suggests that this network bypasses the striatum, it is hypothesized that the hyperdirect pathway is recruited during rapid action cancellation, meaning that areas of the frontal cortex directly communicate with the STN to influence motor output.

The global inhibitory effect of this network has been studied using stop signal tasks in which the excitability of task-irrelevant muscles during stopping was measured using transcranial magnetic stimulation (TMS). This technique allows researchers to elicit involuntary muscle contractions known as motor evoked potentials (MEPs) using electromagnetic stimulation of the motor cortex on the brain. The MEP amplitude provides an index of the excitability of the corticospinal tract between the motor cortex and muscles of the body. Relative increases or decreases in MEP amplitude are indicative of increases or decreases in corticospinal tract excitability respectively and can be used to describe the inhibitory output of the brain on a given muscle. In a previous study, subjects received TMS stimulation during the stopping process of the task. During successful stop trials, resulting MEP amplitudes were reduced compared to baseline (Badry et al., 2009). This effect was present in contralateral muscles homologous to the muscles that were recruited by the task, as well as in leg muscles that were completely unrelated to the task. This suggests that the stopping process is an active process mediated by a motor suppression system that is separate from the excitatory motor system and highlights the nonselective character of suppression.

The results of this experiment were corroborated and the scope was expanded by others who used a verbal response instead of a button press in their novel stop signal

task (Cai and Aron, 2012). Furthermore, Wessel et al. had participants execute a rapid eye movement between two fixation points (a saccade) which had to be canceled during stop trials (2013). Following successful inhibition of speech or eye saccades during these tasks, there was a measurable decrease in the excitability of task-irrelevant hand muscles compared to trials in which the response was executed. This was shown by a decrease in the amplitude of resulting MEPs, indicating global suppression of the motor system potentially via the hyperdirect pathway.

Evidence from multiple experiments suggests that this same mechanism is employed during stopping in a variety of circumstances and task designs, including when the stop signal is manipulated across multiple stimulus dimensions. One study in particular investigated whether the use of a complex stopping template requiring integration across stimulus dimensions would activate a different neural stopping mechanism than a simple standard stop signal as measured via EEG. Before each block of trials, subjects memorized a specific template which told them the number of arrows and the arrow position, print, style, and color that would serve as the stop signal for each block. If the signal they received was different in any of these categories they were expected to execute the button press. They found that even in this unique paradigm, action stopping activated the same important nuclei, namely the pre-SMA, rIFC, and STN. Importantly, this circuit was also activated during trials in which the stimuli only partially matched the stopping template where it acted as a braking system and led to motor slowing (Wessel and Aron, 2014). This shows that the mechanism can be activated to suppress and delay movements without completely canceling them.

Finally, the hyperdirect pathway may also be specifically involved in the stopping of unitary actions, those composed of multiple individual and related movements which are executed together. In one experiment a bimanual anticipatory response inhibition task (ARI) was used instead of a reactive stop task, in which an anticipated finger lift had to be executed simultaneously at a target lift time with both hands. During stop trials, subjects had to cancel one or both of these anticipated lifts after receiving a stop signal. Here, the subjects either used both index fingers, both thumbs, or one of each to hold a pair of buttons down. When one finger lift was canceled, the other lift was delayed past its target. This phenomenon is known as the interference effect, and it occurs as a result of the limitations in the brain's selective stopping ability (Aron & Verbruggen, 2008). The delays were longer when two index fingers or two thumbs were used compared to one of each. This experiment indicates that there are limits to the selectivity of rapid action suppression, and the more highly coupled an action is, the more this effect interferes with continued activity as described by a larger increase in reaction time (MacDonald et al, 2012).

Another experiment conducted by Wadsley et al. produced similar results (2019). In this study, the two bars cuing the lift time either rose synchronously or asynchronously corresponding to finger lifts that would occur simultaneously or one finger and then the other. By cueing the two fingers to lift together at the same time, it was predicted that there would be greater interference to the continued response when one of the fingers needed to stop, a consequence of great bimanual coupling. Here, asynchronous movement between the two hands was hypothesized to result in more selective stopping. Indeed, it was shown that partial cancellation during synchronous lift

trials when the target lift time was the same between fingers led to greater lift delays than during asynchronous lift trials in which the target time was different between fingers, a pattern consistent with global inhibition when the two hands are coupled and more selective inhibition when they are not.

While much of the previous research on this topic has focused on combining TMS with stop signal paradigms to determine corticospinal excitability of individual muscles, our approach incorporates a tonic EMG measure from muscles not involved in the primary task as a means of assessing changes in excitability throughout the process of stopping. A decrease in the amplitude of the tonic EMG signal during stopping would be evidence of decreased excitability, which in this context would be consistent with global motor inhibition via the STN. The use of tonic EMG recording has several potential advantages over the use of TMS to evaluate inhibition of specific muscles during stopping. First, tonic EMG provides a continuous recording of muscle activation during the entirety of the stopping process as opposed to only the individual time points at which TMS occurs. This allowed us to search for evidence of important information about the stopping process such as the onset and duration of global inhibition at the muscular level. Surface EMG is also a noninvasive benign technique that has exceedingly few contraindications and is suitable for use even in patient populations.

A previous experiment within the Action Control Lab has not been successful in finding evidence of global suppression in this tonic EMG signal which may be because the chosen experimental setup required subjects to decouple their hands to complete all aspects of the task. To address this problem, we have shifted our focus to a stopping

paradigm which allows subjects to perform tonic contractions and task relevant movements symmetrically and simultaneously across the hands. To this end, subjects performed a modified ARI task during which they tonically contracted the left and right adductor digiti minimi of the little finger while EMG was recorded. We hypothesize that there will be a decrease in tonic EMG amplitude relative to the stop signal in this task as a result of the activation of the hyperdirect pathway during the stopping process.

Methods

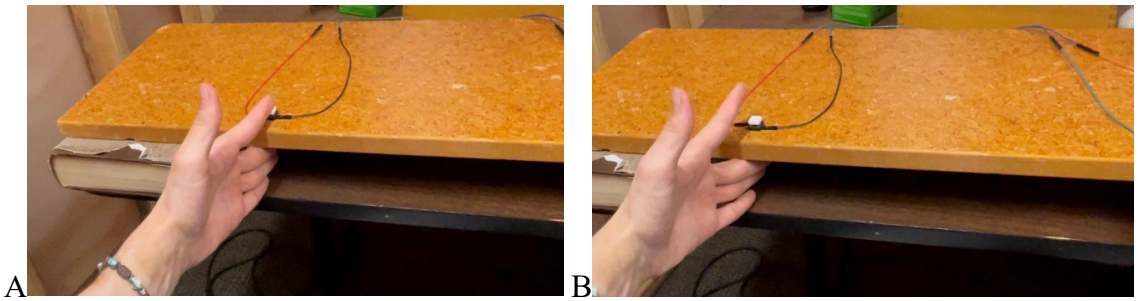
Participants

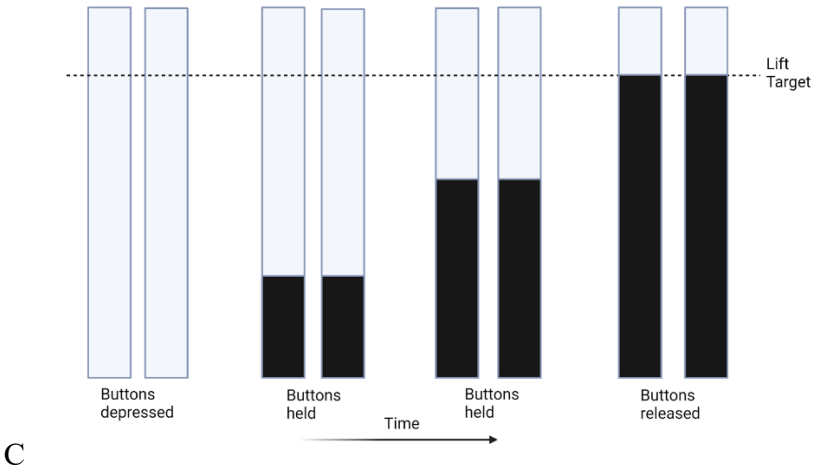
20 right-handed subjects (self-reported) participated in this study (9 male, age = 21.4 ± 0.92). However, after data collection 2 subjects were excluded for failure to complete the task correctly, leaving 18 usable datasets for analysis. Subjects were recruited through word of mouth and written advertisements in University of Oregon Human Physiology classrooms. Potential subjects with a history of specific movement disorders were excluded from the study. All subjects gave informed consent in accordance with the University of Oregon IRB.

Behavioral Anticipatory Response Inhibition Task

We investigated neural stopping networks in humans using a bimanual anticipatory response inhibition (ARI) task coded in MATLAB 2019b. This code was adapted from an ARI task created by Mike Claffey. Subjects were seated in front of a computer screen with their arms supported on armrests, hands extended, and palms facing inward. The third, fourth, and fifth digits of each hand were placed in the space between the surface of the table and a raised wooden board of adjustable height (Figure 1A). The left and right index fingers rested above the board on individual buttons. Subjects began a tonic contraction of their little fingers against the table by moving the digit directly downwards, perpendicular to the midline of the palm. Each individual trial started when the subject pressed both index finger buttons simultaneously. This triggered two parallel bars to begin filling up on the screen in front of them. In the

majority of trials, the left and right bars filled for as long as their corresponding button was depressed, and stopped filling only when their corresponding button was released, i.e. the index fingers were lifted off the buttons (Figure 1B, 1C). These bars filled completely to the top if the buttons were held for one full second. During two-thirds of all trials subjects were instructed to lift their fingers off of the buttons to stop the bars at the target mark 80% of the way up the bar, referred to as a go trial (Figure 1C).





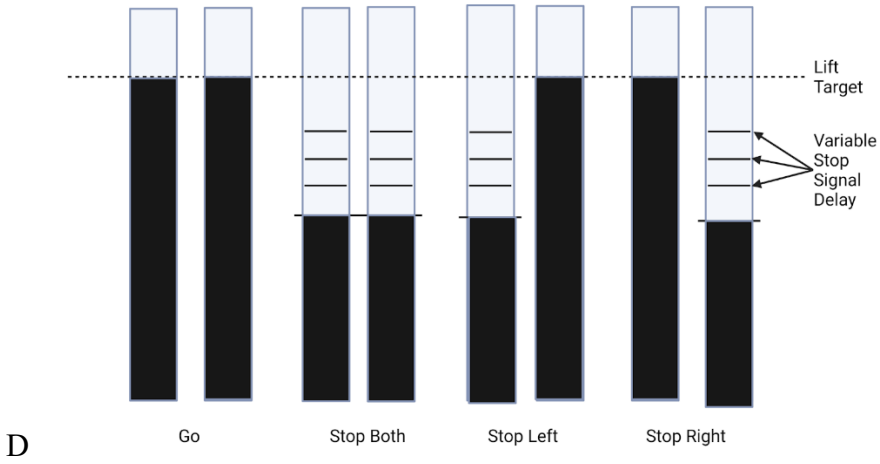


Figure 1. Task descriptions. (A) Left hand performing a tonic contraction with the pinky against the table surface and depressing the left button with the medial aspect of the index finger as the left bar fills. (B) Left hand maintaining a constant contraction with the pinky as the left index finger is lifted in order to stop the bars at the target mark. (C) Representation of task stimuli during a go trial. The bars fill for as long as the corresponding buttons are depressed and the subject lifts at the appropriate time to stop the bars at the target mark. (D) Representations of the 4 types of trials including go, stop both, and selective stop conditions

The remaining ⅓ of trials was an equal mixture of stop both, stop left, and stop right trials. During stop both trials, the bars stopped filling after a predetermined stop signal delay (SSD), and the subjects were instructed to cancel their planned index finger lifts while maintaining the contraction with their little fingers. During selective stop trials, one bar stopped filling while the other continued filling to the target mark. On these trials, subjects were instructed to cancel the lift of the finger which corresponded to the stopped bar while lifting the other finger when the other bar reached the target mark. SSDs started at 600, 550, and 550 ms after the trial start, as indicated by the start of the bar rising, for the stop both, stop left, and stop right conditions, respectively. SSDs were adjusted individually for each stopping type using a staircase procedure (Figure 1D). The SSD decreased by 50 ms after a failed stop trial (when subjects lifted their fingers despite the bar stopping) and increased by 50 ms after a successful stop trial. This dynamic procedure achieved a stopping success rate of approximately 50% in all subjects. The SSD was calculated differently for this task as compared to other versions of stop signal tasks because the subject anticipated a timed go response instead of reacting to a go signal as fast as possible. This means that the SSDs presented in this experiment represent the length of time after the trial starts when the stop signal is presented, and as such are reported as much larger values than is typical of a stop signal task.

Subjects completed 9 blocks of 32 trials (288 trials total), and trial types were randomized for each subject. After each block subjects received feedback about their performance in that block, including their average lift time relative to the target mark.

Electromyography

We recorded surface EMG using bipolar electrodes adhered to the skin above the first dorsal interosseus muscle (FDI) and the adductor digiti minimi (ADM) of both hands. A ground electrode was attached above the styloid process of the left ulna. EMG was recorded at 5,000 Hz, amplified by a factor of 1000, and bandpass filtered (50–450 Hz; Delsys). Prior to beginning data collection, subjects performed a maximum voluntary contraction of each ADM to assess their maximum contractile output. This was done by taking the maximum peak EMG amplitude measured during four consecutive 1 second contractions with both little fingers. Each subject was instructed to maintain a contraction at 10% of their maximum voluntary contraction during the task. EMG data was recorded for the duration of each individual trial as well as for 1 second after each trial concluded. One subject was rejected due to failure to maintain tonic contractions during a large proportion of trials. Subjects completed a small set of practice trials with EMG recording prior to starting the experimental block to ensure that there was good contact with the skin, and that electrical interference in the recording was minimized. The practice session also allowed subjects to become familiar with the various trial types on a nonrandom schedule.

Data Analysis

Behavioral Analyses

Behavioral data was gathered using MATLAB and a Makey Makey ® to integrate button presses into our computer-based paradigm. Mean Go lift time was

calculated for go trials by determining the difference between the actual lift time relative to the start of each trial and the fixed target lift time (0.8s). The staircase method of adjusting the SSD based on stopping performance allowed the subject to settle on an SSD where they succeed on approximately 50% of the stop trials, which is critical for the validity of estimates of the duration of the stopping process. One additional subject who attained a probability of stopping that was calculated below 25% was excluded from analysis. Stop signal reaction time (SSRT), an estimate of the duration of the stopping process, was calculated using the integration method with the replacement of go omissions in order to minimize the slowing effect of go trial reaction time distribution skew (Verbruggen et al., 2019). In this context, go reaction times were defined relative to the start of the trial. Lift times for go omissions, go trials in which subjects failed to respond, were replaced with the maximum reaction time of positive 100 ms. Go trial accuracy refers to the proportion of trials in which the subjects responded within 100 milliseconds of the target lift time.

EMG analysis

The data that we gathered from EMG recordings were rectified and averaged across trials for each trial type to determine the average activation of the ADM during tonic contraction. These average values were then z-scored to determine their variation from baseline during periods of interest. We compared EMG during successful stop both trials and failed stop both trials with analogous epochs from go trials. This was done by locking to the stop stimulus onset for the left and right hands during stop trials and the average SSD on go trials. Specifically, the stopping epoch started at each individual trial SSD and continued through to the end of the calculated stop both SSRT.

The go epoch contained EMG values from the average Stop Both SSD through to the end of the calculated stop both SSRT. These EMG data were analyzed using a 2 x 3 repeated measures ANOVA to determine if there was a significant effect of hand (left vs right) side or trial type (successful stop, failed stop, go). EMG data were z-scored within each epoch to account for between-subject differences in the raw EMG amplitudes. The EMG data from selective stop trials were not analyzed for this report.

Results

Behavioral Measures

Trial Type	Go Left	Go Right	Stop Both	Stop Left	Stop Right
Average Lift Time (ms)	25 ± 11	14 ± 5		111 ± 29	106 ± 32
SSRTs (ms)			305 ± 52	311 ± 46	333 ± 57
Average SSD (ms)			563 ± 45	542 ± 38.0	511 ± 55
Accuracy (%)	78 ± 8.1	83 ± 6.4	48.0 ± 2.4	49.5 ± 2.4	48.8 ± 2.9
Interference effect (ms)				80 ± 34	97 ± 27

Table 1. Behavioral metrics

Behavioral metrics (mean ± std) determined from button lift times

Behavioral metrics of interests are presented in Table 1. A one way repeated measures ANOVA revealed a significant effect of SSRT across the stop both, stop right, and stop left conditions $F(2,17) = 6.87$, $p < 0.05$. Post-hoc t-tests showed stop right SSRT values were significantly longer than stop both SSRTs and stop left SSRTs ($p < 0.01$), and there was no significant difference in SSRT between stop both and stop left conditions ($p = 0.287$). Stop right SSD values were shorter than stop both SSD values $F(2,17) = 24.6$, $p = < 0.001$ and stop left SSD values $F(2,17) = 24.6$, $p = < 0.01$, and stop left SSD values were shorter than stop both SSDs $F(2,17) = 24.6$, $p < 0.01$. Stop right lift times (left index lift responses) were significantly longer than go trial left hand lift times ($p < 0.001$), and stop left lift times (right index lift responses) were significantly longer than go trial right hand lift times ($p < 0.001$). Additionally, the magnitude of this response slowing, i.e. the interference effect, was larger for stop right

lift times than stop left lift times as compared to their go trial equivalents ($p < 0.001$). Stopping accuracy was not significantly different across trial types, ($p > 0.14$).

EMG Results

During data collection several patterns were noted from the visible EMG traces. During some go trials and selective stop trials ADM activation was increased during the lift of the index finger of the same hand, likely due to unintentional spreading of the fingers as the index finger was lifted. Alternatively, this facilitation may be related to observed increases in corticomotor excitability in task relevant muscles preceding movement initiation (Macdonald 2014). Additionally, FDI bursts associated with index finger lifts were delayed in the responding hand during selective stop trials relative to go trials, consistent with previous interference effect observations.

There was no observed main effect of hand (left vs right) or trial type (Go, successful stop both, failed stop both) on tonic EMG output of the ADM muscles and no significant interaction between factors $F(2,17) = 1.12$, all $p > 0.304$. Although no statistical tests were performed, we visually identified a decrease in the z-scored EMG trace for failed stop trials from approximately 140 ms to 200 ms following the stop signal. This pattern was not present for go trials or apparent during successful stop trials.

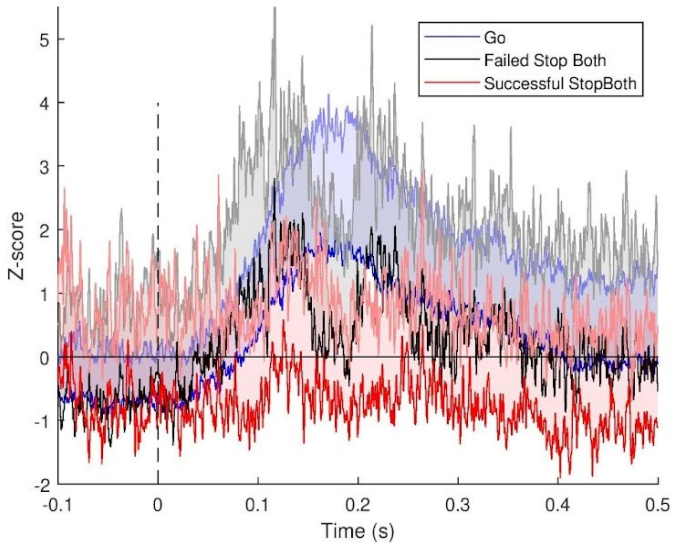


Fig 2. Z scored mean, rectified tonic EMG data

Z-scored mean, rectified tonic EMG data for stop both and go trials. EMG data was gathered from left and right ADM and averaged between hands The zero time point corresponds to the onset of the stop stimulus on stop both trials and corresponds to the average stop both SSD for go trials. In theory, the duration of the stopping process is represented by the epoch from 0 to 0 + stop both ssrt (~0.3)

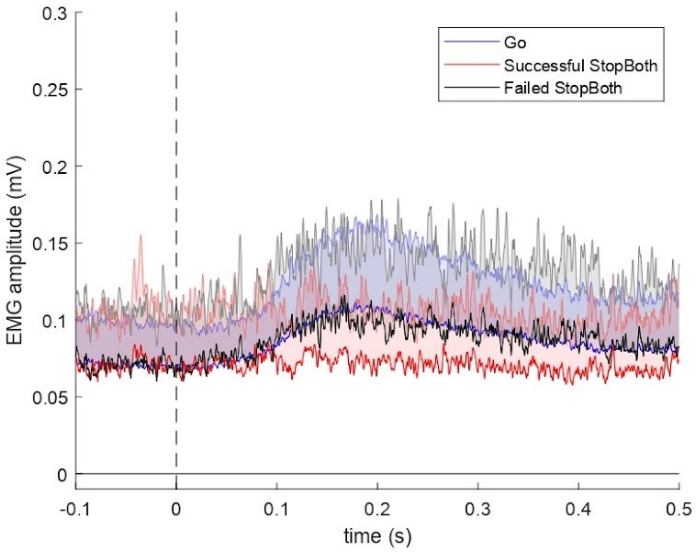


Fig 3 Mean, rectified raw tonic EMG data

As in Figure 2, the mean, rectified raw tonic EMG data are locked to the stop stimulus (zero time point) for successful and failed stop both trials. The average stop both SSD is the zero time point for go trial data. The pattern of failed stop both trials and Go trials are visually similar.

Discussion

Our analyses did not support our hypothesis that there would be a decrease in tonic EMG amplitude of the ADM during stopping. However, we did find SSRT values were longer in the selective Stop Right condition compared to our other two stop conditions. This pattern was supported by the differences in SSDs across task conditions. Lift times were significantly delayed during selective stop trials as compared to go trials, and this interference effect was more pronounced in the Stop Right condition than Stop Left. Visual analysis of raw EMG data shows that during go trials and failed Stop Both trials there is an increase in EMG amplitude near the target lift time, but there is no increase in Stop Both trials. Additionally, visual analysis of the baseline corrected zscored data indicates that there is a transient decrease in tonic EMG amplitude during failed stop trials from approximately 140 ms to 200 ms after the stop signal as compared to a matched interval in go trials.

We hypothesized that there would be a significant decrease in tonic EMG amplitude during the stopping process as compared to an analogous epoch of tonic EMG during go trials. However, our analyses did not support this hypothesis. This hypothesis was based on a large body of evidence which indicates that nonselective suppression of movements via the hyperdirect pathway of the basal ganglia is required for successful response inhibition in a wide variety of tasks (Alegre et al., 2013; Aron and Poldrack, 2006; Wessel and Aron, 2014). This phenomenon has been primarily investigated using TMS which can be used to index the excitability of muscles during stopping by comparing MEP values evoked during periods of interest to measurements taken at rest (Barker et al., 1985).

Because maintaining a tonic contraction as measured by EMG requires a constant level of electrical activation of the muscle, we expected that the engagement of an inhibitory neural network such as the hyperdirect pathway would decrease the amplitude of tonic EMG during these known periods of widespread reduced corticomotor excitability. When considering the entirety of the stopping epoch, differences in EMG amplitude between trial types did not reach significance, although additional ongoing analyses may identify narrower time ranges of interest during Stop Both trials in which markers of suppression may exist. The visually different tonic EMG profiles of the successful stop trials as compared to go and failed stop trials suggest that successful stopping may precede the onset of EMG activity in the context of this stopping task.

Additionally, the pattern of transient inhibition in the z-scored EMG traces for the failed stop both trials may be indicative of a global inhibitory mechanism based on the timing and magnitude of the change in the EMG amplitude. This pattern is consistent with what we hypothesized would be present for successful stopping. However, tonic EMG activity at the level we chose for our experiment may be below that required to detect such a marker in the EMG, and fortuitously, the level of activation during responding may have provided greater sensitivity to this pattern. This pattern of transient suppression is consistent with when the stopping process should be active, towards the tail end of the duration of calculated Stop Both SSRT and may be indicative of activation of a global suppressive mechanism. In this graphical representation of the data, each subject's tonic EMG trace was z scored against their own baseline tonic EMG amplitude to account for differences in EMG amplitude

between subjects. Further, analyses are needed to determine whether this marker is present within individual trials and across participants equally.

Our findings related to behavioral measures are largely consistent with previous experiments. SSRT values for selective stop trials were significantly longer than the same measures in Stop Both trials as has been observed in multiple previous studies that employed an ARI task (Macdonald et al., 2012; Wadsley et al., 2019). Our observed difference in SSRT between Stop Left and Stop Right conditions is unique to the current experiment, but speculation about differences between hands may not be appropriate in our sample since it was limited to right handed participants. There are however several outcomes related to hand dominance that are explicitly different between trial types.

Average lift time was significantly delayed during selective stop as compared to go trials which is a manifestation of the well defined interference effect (Mcdonald et al., 2012, Wadsley et al., 2019). This effect is thought to occur as a result of the limitations of the brain's selective stopping ability. Results from past experiments support the idea that our brains functionally couple the various components of bimanual responses together which reduces the processing costs of executing those movements (Wenderoth et al., 2009). A side effect of this coupling is that it results in delays of continuing responses after canceling one part of the integrated response. We also found that response times were delayed more during Stop Right trials as compared to Stop Left trials which corroborates data from previous experiments (Coxon et al., 2007; Mcdonald et al., 2012). This interaction is potentially a manifestation of stronger coupling of the non-dominant hand to the dominant hand during bimanual tasks

resulting in larger interference when the response needs to be decoupled and reinitiated (Byblow et al., 2000).

The overall goal of this experiment was to find evidence of a biomarker of global response inhibition using noninvasive surface EMG. Such a marker could potentially be compared between healthy subjects and patients with motor disorders to investigate differences in their motor system physiology. Because nonselective inhibition during stopping is understood to be mediated by the hyperdirect pathway, this type of biomarker would be most helpful for studying diseases which are known to be associated with basal ganglia dysfunction such as Parkinson's, dystonia, chorea, etc (Mink, 2003).

Basal ganglia circuits are involved in the control of movement via multiple net excitatory and net inhibitory networks. During movement initiation, the striatum receives input from widespread areas of the brain and in turn releases inhibition of the internal globus pallidus (GPi) and substantia nigra pars reticulata (SNr) via a polysynaptic pathway involving the STN and external globus pallidus. The GPi/SNr in turn increase their inhibitory output onto selected and competing cortical motor representations via tonically active thalamocortical projections. Concurrently, the striatum receives input from the cerebral cortex and selectively inhibits regions of the GPi/SNr in a context-dependent manner, releasing inhibition of the selected movement (Nambu et al., 2002, Mink, 1996). This organization allows for inhibitory input from the striatum on the GPi to selectively release inhibition of the appropriate motor representations while widespread inhibition of unrelated and competing representations prevents involuntary movement. When we need to cancel actions, the cerebral cortex

and premotor areas directly excite the STN via the hyperdirect pathway, which in turn sends excitatory projections to the GPi/SNr, leading to widespread inhibition of movement. The mono-synaptic cortico-STN projection is referred to as the hyperdirect pathway and is hypothesized to rapidly halt ongoing movements.

Parkinsonian patients are known to have particular trouble executing movements, but they have been found to exhibit deficits in inhibitory control, or stopping ability as well. When a group of Parkinsonian subjects completed a stop signal task, their calculated SSRTs were significantly longer than those of age matched controls. This indicated that it took them a longer amount of time to inhibit an ongoing response, indexing decreased inhibitory control and potential dysfunction or impairment of the hyperdirect pathway (Gauggel et al., 2004).

Specific patterns of output from the STN have been shown to be required for successful and timely action stopping in another cohort of Parkinsonian patients. In this study, a high frequency gamma signal ((55–75 Hz) from the STN, was isolated during completion of task related actions. The signal strength and coherence increased during go trials, while it decreased during successful stop trials, suggesting that the STN takes an active role in action stopping, and providing a mechanism by which it may do so (Alegre et al., 2013). In a similar study of Parkinsonian patients, deep brain stimulation (DBS) via implanted electrodes electrically stimulated the STN during a stop task. Stimulation resulted in faster stop signal reaction times (SSRTs) and greater inhibitory control, supporting the idea that output from the STN plays an integral role in action cancellation (van den Wildenberg et al., 2006). These results also indicate that it may be possible to alleviate the stopping deficits associated with Parkinsons by targeting nuclei

that make up the hyperdirect pathway for stimulation. Finding an easily measured biomarker of global inhibition, and by extension the hyperdirect pathway, would be particularly helpful in understanding differences between the brains of Parkinsonian patients and the general population because of the well characterized nature of dysfunction associated with the disease.

This same brain network which is activated during outright action stopping has also been shown to activate in response to novel or unexpected events during a verbal reaction time task (Wessel & Aron, 2013; Wessel & Aron, 2017). It has further been proposed that this pathway is recruited in response to unexpected or surprising events such as a car running a red light as one is crossing the street because, in the context of avoiding the danger they may pose, our brains do not have time to selectively sort and stop individual movements. The whole motor system is instead rapidly suppressed to make way for new input geared towards reacting to the surprise.

These last studies highlight the importance of the hyperdirect pathway in bodily control and response inhibition in contexts where not being able to stop quickly may have serious consequences. Deficits in the functionality of this pathway are not only associated with disease states and poorer quality of life, but can potentially lead to genuine injury. The potential applications of an easily measurable marker of function or dysfunction of these networks would therefore be useful in early diagnosis and further study of the mechanisms of disease for people who are currently and will later deal with these problems. While we have not isolated a marker of global inhibition using tonic EMG in this experiment, further analyses are warranted.

Our task design was relatively novel due to the requirement of incorporating a tonic EMG measure, so while comparisons to previous studies are not always straightforward, there remains potential to find meaningful results.

References

Alegre, M., Lopez-Azcarate, J., Obeso, I., Wilkinson, L., Rodriguez-Oroz, M. C., Valencia, M., Garcia-Garcia, D., Guridi, J., Artieda, J., Jahanshahi, M., & Obeso, J. A. (2013). The subthalamic nucleus is involved in successful inhibition in the stop-signal task: A local field potential study in Parkinson's disease. Experimental Neurology, 239(1), 1–12. https://doi.org/10.1016/j.expneurol.2012.08.027

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: Role of the subthalamic nucleus. Journal of Neuroscience, 26(9), 2424–2433. https://doi.org/10.1523/JNEUROSCI.4682-05.2006

Aron, A. R., & Verbruggen, F. (2008). Stop the Presses: Dissociating a Selective From a Global Mechanism for Stopping. Psychological Science, 19(11), 1146–1153. https://doi.org/10.1111/j.1467-9280.2008.02216.x

Badry, R., Mima, T., Aso, T., Nakatsuka, M., Abe, M., Fathi, D., Foly, N., Nagiub, N., Nagamine, T., Fukuyama, H., (2009). Suppression of Human Cortico-Motoneuronal Excitability during the Stop-Signal Task. Clinical Neurophysiology 120 (9), 1717–1723. https://doi.org/10.1016/j.clinph.2009.06.027

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. Lancet (London, England), 1(8437), 1106–1107. https://doi.org/10.1016/s0140-6736(85)92413-4

Cai, W., Oldenkamp, C. L., & Aron, A. R. (2012). Stopping speech suppresses the task-irrelevant hand. Brain and Language, 120(3), 412–415. https://doi.org/10.1016/j.bandl.2011.11.006

Byblow, W., Lewis, G., Stinear, J., Austin, N. J., Lynch, M.. The subdominant hand increases the efficacy of voluntary alterations in bimanual coordination. Exp Brain Res 131, 366–374 (2000). https://doi.org/10.1007/s002219900271

Coxon, J. P., Stinear, M. C., & Byblow, W. D. (2007). Selective Inhibition of Movement. Journal of Neurophysiology, 97(3), 2480-2489. https://doi-org.libproxy.uoregon.edu/10.1152/jn.01284.2006

Gauggel, S., Rieger, M., & Feghoff T. (2004) Inhibition of ongoing responses in patients with Parkinson's disease Journal of Neurology, Neurosurgery & Psychiatry, 75(4), 539-544.

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), 295–327. https://doi.org/10.1037/0033-295X.91.3.295

MacDonald, H. J., Stinear, C. M., & Byblow, W. D. (2012). Uncoupling response inhibition. Journal of Neurophysiology, 108(5), 1492–1500. https://doi.org/10.1152/jn.01184.2011

Mink, J. W. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. Pergamorr Progress in Neurobiology, 50, 26. https://learn.bu.edu/bbcswebdav/pid-6634749-dt-content-rid-25380329_1/courses/19sprgcasps504_a1/Mink_1996.pdf

Mink, J. W. (2003). The basal ganglia and involuntary movements. Archives of Neurology, 60(10), 1365. https://doi.org/10.1001/archneur.60.10.1365

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neuroscience Research, 43(2), 1–7. papers2://publication/uuid/84A4B9C7-C039-48B6-9E84-A9E2597729F5

Van Den Wildenberg, W. P. M., Van Boxtel, G. J. M., Van Der Molen, M. W., Bosch, D. A., Speelman, J. D., & Brunia, C. H. M. (2006). Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. Journal of Cognitive Neuroscience, 18(4), 626–636. https://doi.org/10.1162/jocn.2006.18.4.626

Verbruggen F, Aron AR, Band GP, Beste C, Bissett PG, Brockett AT, Brown JW, Chamberlain SR, Chambers CD, Colonius H, Colzato LS, Corneil BD, Coxon JP, Dupuis A, Eagle DM, Garavan H, Greenhouse I, Heathcote A, Huster RJ, Jahfari S, Kenemans JL, Leunissen I, Li CR, Logan GD, Matzke D, Morein-Zamir S, Murthy A, Paré M, Poldrack RA, Ridderinkhof KR, Robbins TW, Roesch M, Rubia K, Schachar RJ, Schall JD, Stock AK, Swann NC, Thakkar KN, van der Molen MW, Vermeylen L, Vink M, Wessel JR, Whelan R, Zandbelt BB, Boehler CN. (2019). A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. eLife, 8, e46323. https://doi.org/10.7554/eLife.46323

Wadsley, C. G., Cirillo, J., & Byblow, W. D. (2019). Between-hand coupling during response inhibition. Journal of Neurophysiology, 122(4), 1357–1366. https://doi.org/10.1152/jn.00310.2019

Wessel, J. R., & Aron, A. R. (2014). Inhibitory motor control based on complex stopping goals relies on the same brain network as simple stopping. NeuroImage, 103, 225–234. https://doi.org/10.1016/j.neuroimage.2014.09.048

Wessel, J. R., & Aron, A. R. (2013). Unexpected events induce motor slowing via a brain mechanism for action-stopping with global suppressive effects. Journal of Neuroscience, 33(47), 18481–18491. https://doi.org/10.1523/JNEUROSCI.3456-13.2013

Wessel, J. R., & Aron, A. R. (2017). On the globality of motor suppression: unexpected events and their influence on behavior and cognition. Neuron, 93(2), 259–280. https://doi.org/10.1016/j.neuron.2016.12.013

Wessel, J. R., Reynoso, H. S., & Aron, A. R. (2013). Saccade suppression exerts global effects on the motor system. Journal of Neurophysiology, 110(4), 883–890. https://doi.org/10.1152/jn.00229.2013