Saccade suppression exerts global effects on the motor system

Jan R. Wessel*1, H. Sequoyah Reynoso2, Adam R. Aron1,2

1 Psychology Department, University of California San Diego, La Jolla, USA
2 Neuroscience Graduate Program, University of California San Diego, La Jolla, USA

*Corresponding Author:
Jan R. Wessel, PhD
Psychology Department, University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92103
Email: jwessel@ucsd.edu

Running head: Stopping eyes has global motor effect
Abstract
Stopping inappropriate eye-movements is a cognitive control function that allows humans to perform well in situations that demand attentional focus. The stop-signal task (SST) is an experimental model for this behavior. Participants initiate a saccade towards a target and occasionally have to try to stop the impending saccade if a stop signal occurs. Prior research using a version of this paradigm for limb-movements (hand, leg), as well as for speech, has shown that rapidly stopping action leads to apparently global suppression of the motor system, as indexed by the Corticospinal Excitability (CSE) of task-unrelated effectors in studies with Transcranial Magnetic Stimulation (TMS) of M1. Here, we measured CSE from the hand with high temporal precision while participants made saccades, and while they successfully and unsuccessfully stopped these saccades in response to a stop signal. We show that 50 ms before the estimated time at which a saccade is successfully stopped there is reduced CSE for the hand, which was task irrelevant. This shows that rapidly stopping eye movements also has global motor effects. We speculate that this arises because rapidly stopping eye movements, like skeleto-motor movements, is possibly achieved via input to the subthalamic nucleus of the basal ganglia, with a putatively broad suppressive effect on thalamocortical drive. Since recent studies suggest that this suppressive effect could also impact non-motor representations, the current finding points to a possible mechanistic basis for some kinds of distractibility: abrupt onset stimuli will interrupt ongoing processing by generating global motor and non-motor effects.

Keywords: Inhibitory Control, Stop signal task, Motor-evoked potential, Eye-movements, Saccade countermanding
Introduction

Stopping an inappropriate action before execution is an important cognitive control function for limb-movements (e.g. stopping one’s step into the street when a car approaches) and eye-movements (e.g. avoiding gaze-shifts towards irrelevant stimuli in situations demanding sustained attention). A better understanding of how eye-movements are stopped is important as everyday life affords many situations that call for control of eye-movements towards distracting stimuli.

Recent evidence shows that rapid stopping of (skeleto-motor) actions is achieved via a non-selective, global signal, leading to reduced excitability across the entire motor system, rather than a specific effector (Badry et al. 2009; Cai et al. 2012; Majid et al. 2012). At the behavioral level, many studies have shown that when one response is stopped, the execution of another is delayed (Coxon et al. 2007; MacDonald et al. 2012; Bissett and Logan, in press). At the physiological level, evidence for global stopping comes from using TMS of primary motor cortex (M1). When a TMS stimulus is delivered over the hand area, corticospinal excitability (CSE) can be indexed via the amplitude of the motor evoked potential (MEP) that is measured using electromyography from the muscles of the hand. In this way, one can index the excitability of the hand representation in the brain with high temporal resolution. Using this method several studies have now shown that stopping the hand reduces CSE of the leg, when the leg is task-irrelevant (Badry et al. 2009; Majid et al. 2012), and stopping speech reduces CSE of the hand, when the hand is also task-irrelevant (Cai et al. 2012). Here, we test whether stopping eye-movements, which are not part of the skeleto-motor system, engages the same global stopping system.
The execution of eye- and limb-movements involves dramatically different neural circuitry (e.g. Wurtz and Hikosaka 1986). In particular, eye-movements do not involve M1; they are initiated via circuitry including the frontal eye fields and superior colliculi. Regarding stopping of eye-movements, some studies emphasize frontal cortical regions (Schall et al. 2002; Curtis et al. 2005; Nachev et al. 2005; Stuphorn and Schall 2006; Boucher et al. 2007) that differ from those critical for stopping limb movements (Chambers et al. 2009; Aron et al. 2007). However, others do point to overlap, particularly in right inferior frontal cortex and presupplementary motor area (Heinen et al. 2006; Michael et al. 2006; Leung and Cai 2007; Isoda and Hikosaka 2007; Hwang et al. 2012), and also, notably in the subthalamic nucleus (STN) of the basal ganglia. For example, a neurophysiological study in monkeys showed increased STN-activity for saccade-countermanding and NoGo trials (Isoda and Hikosaka 2008). Hence, a rapid, stopping-generated, cortical input into the oculomotor region of the STN (Matsumara et al. 1992; Nambu et al. 2002) could have broad effects on basal ganglia motor output.

We measured CSE from the hand during an oculomotor stop-signal task (Logan 1983; similar to a saccade-countermanding task, Hanes et al. 1998). Based on previous research (Majid et al. 2012; Cai et al. 2012), we predicted that if rapidly stopping eye-movements involves a global stop, stopping saccades leads to hand-suppression on successful stop-trials compared to go-trials and failed stop-trials.

**Materials and Methods**

**Participants**
Fourteen (three female) right-handed healthy UCSD undergrads participated in the study (aged 18 – 30y, mean 22.7, SEM: .81). Subjects had normal or corrected to normal vision, no history of neurological or psychiatric illness and were not taking any medication at the time of the study. They underwent TMS safety screening, signed written informed consent, and were paid $15/hr.

Task

Stimuli were presented on a 21-inch (51 cm horizontal width) CRT monitor using Psychtoolbox 3 (Brainard 1997) and MATLAB 2010a, running on an IBM-compatible PC. Each trial began with a centrally placed fixation cross and two yellow boxes on either side of the screen (~30° of visual angle from the centre) (Figure 1). After one second of fixation, the fixation cross was replaced by a white arrow (go stimulus) pointing to the right or left, with the participants being instructed to direct their gaze into the square on the respective side of the screen as fast and accurately as possible. However, on 33% of trials, the arrow turned red shortly after its appearance, requiring the participants to try to stop the impending saccade. The stop-signal delay (SSD) was initially set to 100ms and was then updated after each stop trial depending on the participants’ performance on the trial using an adaptive staircase algorithm: it was prolonged by 50ms following a successful stop trial, and shortened by 50ms following a failed stop trial, thereby eventually converging on a 50% probability of successful stopping. Participants had 1000ms to respond to each arrow. Each trial was 3200ms long, with the remaining time after the response window being the inter-trial interval.

Participants performed a training phase of 100 trials, during which accuracy and RT feedback were displayed after each response. No TMS was performed during this phase. Then, they
performed 600 trials of actual experiment divided into 6 blocks. During this phase, they only received trial-by-trial feedback if they failed to respond on a go trial (reminding them to respond within the response window), and TMS data were collected.

Eye-tracking

Eye-movement data was collected using an SMI RED USB (SensoMotoric Instruments, Teltow, Germany) infrared eye-tracking system with a sampling rate of 120 Hz. Participants rested their chin on a table-mounted chin- and forehead-rest 45 cm away from the screen-mounted eye-tracker. Gaze coordinates were imported into MATLAB in real-time. Saccades were detected whenever horizontal gaze-shifts occurred with a peak velocity that corresponded to two degrees of visual angle in saccadic amplitude (according to the saccadic main sequence; Bahill et al. 1975). This was done by initially displaying ten stimuli that were offset by two degrees of visual angle from the screen center at the beginning of the experiment. Participants were prompted to make saccades towards these stimuli. These gauging trials were then plotted as raw data traces as well as angular velocity (first derivative of the raw data). A velocity detection threshold was then adjusted so that each of these gauging saccades would have been detected. During the experiment, eye-tracking data were read out by MATLAB on each trial and converted to velocity (by calculating the first derivative). The first sample on which the velocity threshold was exceeded (if any) marked the response onset. The system was re-calibrated during every break between blocks to ensure steady data fidelity. Trials on which the first saccade was preceded by an eye-blink were discarded. Trials with RT < 80ms were treated as anticipations (Fischer et al. 1993) and also discarded.

EMG recording
Surface EMG was recorded from the first dorsal interosseous (FDI) muscle of the right hand via Ag–AgCl hydrogel electrodes (Lead-Lok, Sandpoint, ID). A ground electrode was placed over the distal end of the ulna. The signal was amplified using a Grass QP511 Quad AC Amplifier (Grass Products, West Warwick, RI), with a recording band-pass filter between 30Hz and 1000Hz (60Hz notch). The amplified data were sampled using a CED Micro 1401 MK-II acquisition system (sampling rate: 2000Hz) and recorded using CED Signal software (Version 4, Cambridge Electronic Design, Cambridge, UK).

**TMS procedure**

CSE was measured using motor evoked potentials (MEPs) elicited by TMS. TMS stimulation was performed using a MagStim 200-2 system (MagStim, Whitland, UK) with a 70-mm figure-of-eight coil. Hotspotting was performed to identify the hand stimulation locus and correct intensity. The coil was first placed 5 cm lateral and 2 cm anterior to the vertex and repositioned to where the largest MEPs were observed consistently. Resting motor threshold (RMT) was then defined as the minimum intensity required to induce MEPs of amplitudes exceeding .1mV peak-to-peak in 5 out of 10 consecutive probes (Rossini et al. 1994). TMS intensity for the experimental stimulation was then adjusted to 110-120% of RMT (mean intensity = 47.3% of maximum output; min = 36%, max = 60%).

An EMG sweep was started 150ms before every TMS pulse to obtain an estimate of baseline EMG activity for later artifact correction. TMS stimulation was timed to correspond with the point in time when the stopping-related influence on the motor system should be maximal. To maximize our chances of identifying this time-point, we adopted three different
approaches based on earlier studies of stopping-related changes in CSE.

Approach 1: Earlier studies (e.g. Majid et al. 2012) showed that global stopping effects can be of high temporal specificity: While in their study, stopping the hand lead to a significant suppression of leg-CSE at 200 and 220ms after SSD, they found no such effect at SSD+240ms (SSRT in their experiment was 246ms. This means that stimulation in their experiment occurred on average at SSD+SSRT-46ms, SSD+SSRT-26ms, or SSD+SSRT-6ms, with the latter time-point showing no global stopping induced CSE changes). Hence, we decided to time stimulation to SSD+SSRT-50ms, which roughly corresponds to the SSD+200ms time-point in Majid et al. (2012).

Approach 2: Despite the results presented by Majid and colleagues (2012), other studies do suggest that the motor impact of stopping is indeed to be expected towards the end of estimated SSRT, perhaps even in the last 10ms (Boucher et al. 2007), which for our this approach motivated stimulation at SSRT itself.

Approach 3: Other recent TMS studies used a stimulation time of mean GoRT – 100ms to good effect (Badry et al. 2009, Cai et al. 2012). This approach relies on the idea that if the probability of stopping is 50%, the stop process will, on average, finish at the mean GoRT; and therefore stimulating at mean GoRT – 100 ms will mostly fall within the time at which the stop process is active.

Hence, on go and stop trials, TMS was delivered either at 1) the current SSD plus the current estimate of SSRT minus 50 ms (Approach 1), 2) the current SSD plus the current estimate of SSRT (Approach 2), or 3) the current average GoRT – 100ms (Approach 3).

GoRT and SSRT projections were derived on a trial-by-trial basis. Initial estimates were derived from the training block (in which no TMS was performed). SSRT was estimated using the mean method, i.e. subtracting the SSD that gives approximately p(stop) = .5 from mean GoRT
(Verbruggen and Logan 2009). Estimates of mean GoRT and SSRT were then updated on a trial-by-trial basis in the actual experiment (using all trials until that point). Stimulation on go trials was yoked to the current stimulation time point on stop trials. Stimulation time points (derived according to approaches 1, 2, and 3) were alternated in a fixed sequence for each trial type (go and stop) individually, i.e. for go trials, the first stimulation time-point was derived using approach 1, then 2, then 3, then 1 etc (same for stop trials).

**TMS analysis**

Post-hoc, average stimulation timepoints (relative to stimulus onset) for the three approaches were:

- Approach 1: 327ms (go trials, SEM: 20ms), 325ms (successful stop trials, SEM: 20ms),
  332ms (failed stop trials, SEM: 20ms)
- Approach 2: 373ms (go, SEM: 20ms), 367 (successful stop, SEM: 22ms), 383ms (failed stop, SEM: 22ms)
- Approach 3: 301ms (go, SEM: 15ms), 299ms (successful stop, SEM: 15ms), 301ms (failed stop, SEM: 15ms).

In a first step, we ensured that there were no systematic differences in stimulation time between the three trial types for any of the approaches. Hence, we tested the above stimulation times for significant differences for each approach individually using a repeated measures-ANOVA with the repeated factor TRIALTYPE (go, successful stop, failed stop). Indeed, there was a marginally significant difference in stimulation time between the three trial types in Approach 2 (SSD+SSRT, main effect of TRIALTYPE: $F(2,26) = 2.4$, $p = .1$). The other two approaches did not
have significant differences (Approach 1: $F(2,26) = .35, p = .7$; Approach 3: $F(2,26) = 1.46, p = .25$). Hence, we excluded Approach 2 from further analyses.

Further examination of the stimulation times revealed that the remaining two Approaches (1 and 3) had partially overlapping stimulation times, meaning that estimates of the MEP were not statistically independent between the two approaches (and therefore could not be coded as an independent variable in a combined ANOVA). Therefore, we had to make a decision as to which Approach to select. We decided to select Approach 1, because:

a) Approach 1 gave a tighter timing of the stopping process compared to Approach 3, which was time-locked to the go-process (GoRT-100ms), and it was the effect of the stopping process that was of interest in this study.

b) Approach 1 produced the smallest post-hoc differences in stimulation time between trial types, ($p = .7$; Approach 3: $p = .25$, see above), meaning that comparisons between the trial types would be least affected by differences in stimulation times between trial types.

c) Post-hoc, Approach 3 produced average stimulation times at around GoRT-120ms instead of the intended GoRT-100ms (GoRT: 420ms, compare with the stimulation times above). This was due to the stochastic nature of the RT forecast. Approach 1, on the other hand, (incidentally) turned out to produce values closer to the GoRT-100ms time-point that was targeted by Approach 3. Since global suppression as indexed by CSE of task-irrelevant effectors can be sensitive to very small timing differences, differences in stimulation times of 20 ms can have significant effects (Majid et al., 2012 showed significant differences for 200 and 220 ms post SSD, but not for 240 ms). As we did not
have a hypothesis regarding stimulation at GoRT-120ms (as Approach 3 turned out to produce), we focus on Approach 1 in the presentation of results.

Regardless of these considerations, however, it should be noted that both Approach 1 (SSD+SSRT-50ms) and Approach 3 (GoRT-100ms) produced qualitatively similar MEP results (as did Approach 2). See results section for further details.

EMG analysis

MEPs were identified from EMG using in-house software developed in Matlab (Mathworks, Natick, MA). Trials were excluded if the root mean square power of the EMG trace 100ms before the TMS pulse exceeded .01 mV (since such pre-stimulus noise can contaminate the MEP measurement), if the MEP amplitude on a given trial exceeded +/- 1mV (which is beyond the resolution of the amplifier and leads to saturation), or if the MEP amplitude did not exceed .01 mV (trials in which no MEP was elicited, mostly due to coil misplacement or missing stimulation due to e.g. coil overheating).

MEP amplitude was quantified using a peak-to-peak rationale, measuring the difference between maximum and minimum amplitude within a time period of 10 to 50ms following the pulse. Both automated artifact rejection and MEP quantification were visually checked for accuracy on each individual trial for every dataset by a rater who was blind to the respective trial type (go, successful stop, failed stop). MEP amplitudes were then averaged for each condition individually.

Results
Behavioral

Misses on go trials were rare (probability = .02, SEM: .007). Direction error probabilities were .05 (SEM: .009) and .088 (SEM: .014) for go and stop trials, respectively. The average number of valid trials per participant was 385 (SEM: 9.2) for correct go trials, 76 (3.6) for successful stop trials, and 78.5 (2.6) for failed stop trials. The overall probability of stopping was .47 (SEM: .01, Table 1), meaning that the SSD-staircase procedure was effective at reaching a p(stop) of .5 (a Wilcoxon signed-rank test revealed no significant group-level differences of p(stop) from .5). In order to ensure that all individual participants met the requirement of p(stop) ≈ .5, we also tested the individual stopping success probabilities across the experimental blocks within each dataset against a median of .5 using the same Wilcoxon test. One participant revealed significant deviations of stopping success rate from .5 (mean p(stop) for this participant: .443, p = .03). In order to ensure that this participant’s data did not bias the results in any way, we ran all TMS analyses twice, once on the full sample and once in a limited sample that excluded that participant. TMS results did not differ between both samples in terms of significance, but will still be reported separately (see below).

In order for the assumptions of the race model (and hence, SSRT estimates) to be valid, failed stop RTs need to be faster than correct GoRTs. This was the case in our sample on the group level (median GoRT = 412ms (SEM: 14.4); median failed-stop RT: 363ms (SEM: 11.4); t(13) = 3.0, p = .01, d = .75; testing the mean RTs instead of the median also yields significant differences: 420 (17) vs. 398 (10) ms, p = .03, one-sided). Individual RT distributions can be seen in Figure 2. As can be seen, data from two participants did not fulfill the requirements of the race model (marked with black Xs in Figure 2), as their median GoRT were numerically faster than their
median failed-stop RT. As with the above analysis, in order to ensure that these participants’
data did not bias the results in any way, we ran all TMS analyses twice, once on the full sample
and once in a limited sample that excluded those two participants (one of which was the same
participant whose p(stop) deviated from .5). As above, TMS results between both samples did
not differ, but will be reported separately (see next section).

TMS

Full sample. Based on previous reports of global stopping (Cai et al. 2012; Majid et al. 2012;
Badry et al. 2009) we hypothesized that hand MEP amplitudes would be reduced in the
successful stopping trials compared to go- and failed stop trials. Descriptively, 12 out of the 14
participants showed a reduction of CSE on successful stop trials compared to go trials (Figure
3a); 11 out of 14 show a reduction of CSE on successful compared to failed stop trials, and 8 out
of 14 show a reduction of CSE on failed stop trials compared to go trials (Figure 3b). On average,
MEP amplitude was .51mV (SEM: .048) for correct go trials, .46mV (SEM: .046) for successful
stop trials, and .50mV (SEM: .057) for failed stop trials (Figure 4a). An ANOVA with the factor
TRIALTYPE revealed significant differences between the three types of trials (F(2,26) = 4.67, p =
.019). Importantly, as predicted, MEP amplitude for successful stop trials was significantly
reduced compared to both go trials (t(13) = 3.43, p = .0045, d = .26) and failed stop trials (t(13) =
2.5, p = .027, d = .21). Both effects remain significant after Bonferroni-correction for multiple
comparisons (the comparison between failed and successful stop trials survives this strict
correction if it is tested in a one-sided fashion. This is justified, as this was our exact hypothesis
based on prior studies). This pattern very clearly replicates our two earlier studies.
Another way to quantify these results is to normalize the stop trial MEPs by the participants’ go trial MEP amplitudes, resulting in a measure that is equal to 1 in case there are no differences between go trial amplitude and the respective stop trial amplitude. Reduced stop trial MEP amplitudes lead to numbers smaller than 1. Importantly, this measure accounts for differences in overall MEP amplitude and variability between subjects. T-tests of these values against 1 confirmed the findings from the raw MEP analysis above: Successful stop trials showed ratios significantly smaller than 1 (mean = .9, SEM: .03; t(13) = 3.0, p = .01), whereas failed stop trials showed no such effects (mean = .97, SEM: .04; t(13) = .81, p = .43, Figure 4b).

Notably, exploratory analyses revealed that the two critical findings of a) reduced CSE of the hand on successful stopping compared to go trials and b) absence of such an effect on failed trials compared to go trials, could also been observed in both other stimulation time-point conditions. This is true for both the raw trial analysis (Approach 2: successful stop vs. go: t(13) = 2.72, p = .017; failed stop vs. go: t(13) = .83, p = .42; Approach 3: successful stop vs. go: t(13) = 1.97, p = .07; failed stop vs. go: t(13) = .79, p = .44, all p-values two-sided), as well as the normalized MEP analysis (Approach 2: successful stop vs. go: t(13) = 2.6, p = .022; failed stop vs. go: t(13) = 1.18, p = .26; Approach 3: successful stop vs. go: t(13) = 2, p = .065; failed stop vs. go: t(13) = .87, p = .25, all p-values two-sided).

Limited sample. In the subset of 12 participants whose data fulfilled all requirements of the race model (see above), mean MEP amplitude was .50mV (SEM: .055) for correct go trials, .46mV (SEM: .054) for successful stop trials, and .50mV (SEM: .067) for failed stop trials. An ANOVA with the factor TRIALTYPE again revealed significant differences between the three types of
trials ($F(2,22) = 3.62, p < .05$). Again, MEP amplitude for successful stop trials was significantly reduced compared to both go trials ($t(11) = 3.11, p < .01, d = .24$), and marginally reduced compared to failed stop trials ($t(11) = 2.13, p = .057, d = .2$). As in the full sample, t-tests of the ratios between both types of stop trials and go trials against 1 confirmed the findings from the raw MEP analysis above: Successful stop trials showed ratios significantly smaller than 1 (mean = .9, SEM: .036; $t(11) = 2.7, p = .02$), whereas failed stop trials showed no such effects (mean = .96, SEM: .044; $t(11) = .84, p = .42$).

**Discussion**

Stopping action has global consequences on the motor system: Stopping the hand reduces CSE in the leg (Badry et al. 2009; Greenhouse et al. 2012; Majid et al. 2012); stopping speech reduces CSE of the hand (Cai et al. 2012). Here, we establish that this effect extends beyond the skeleto-motor system. We studied human participants performing an oculomotor stopping task in a head-restrained setup with a TMS coil placed over the hand area of left M1. Using a dynamic estimate of behavior, we delivered TMS stimulation at a point in time that was estimated to correspond the process of stopping the eyes (i.e. SSRT minus 50 ms). We measured CSE for the hand representation, which was task-irrelevant, via the amplitude of the motor evoked potential recorded from electromyography. We show that when participants successfully stopped eye-movements, there was reduced CSE from the hand, relative to Go trials, and relative to failed-stop trials, replicating the exact pattern of results of our earlier

This finding is of special importance for several reasons. First, while eye-movements are initiated via a dramatically different pathway compared to the hand-, leg-, and vocal movements of earlier studies, which are all wired via M1, clearly there is some commonality in how eye and non-eye movements are stopped (c.f. Curtis and D’Esposito 2009). In particular, we suppose that the rapid stopping of eye-movements is achieved by fast input from potentially specialized areas within the frontal cortex to the STN, and we suppose that neurons in that territory have a very broad (massive) effect on the motor pallidum (GPi), including on the hand area, and perhaps on all skeleto-motor representations. The STN is implicated in stopping (Kühn et al. 2004; Aron and Poldrack 2006; van den Wildenberg et al. 2006; Isoda and Hikosaka 2008; Mirabella et al. 2012; Ray et al. 2012; Alegre et al. 2013), and potentially exerts a broad influence on basal-ganglia output (Hazrati and Parent 1992; see also: Mink 1996; Gillies and Willshaw 1998; Nambu et al. 2002). The STN has been found to be active during successful manual stopping in both LFP and fMRI studies (e.g. Aron and Poldrack 2006; Kuhn et al. 2004; Ray et al. 2012), and at least one other study also implicates the STN in oculomotor countermanding, apparently via a hyperdirect input from the presupplementary motor area (Isoda and Hikosaka 2007 2008). We hypothesize that successful rapid stopping via the broad STN-GPi projection temporarily disrupts broad thalamocortical drive, thereby non-selectively suppressing all motor activity.

Secondly, of high relevance to this study is the fact that motor stopping appears to also affect non-motor representations. In a recent study, we have demonstrated that rapid stopping disrupts ongoing working memory maintenance (Wessel et al. 2012). One explanation for this is
that the STN has a very broad effect (Parent and Hazrati 1992), even on non-motor parts of pallidum; another explanation is that activation of one part of STN spreads to other parts of STN, thus affecting on-motor basal-ganglia circuitry (Haber 2003; Temel et al. 2005). Taking together our current result (rapidly stopping eye-movements has a global motor effect) with the finding that rapid stopping affects working memory (Wessel et al. 2012) raises an intriguing possibility, namely that the basis for one kind of distractibility (loss of working memory contents) is a globally-induced effect of a cancelled (eye-)movement. Future research will need to fully explore this possibility, and especially to establish the boundary conditions of which kinds of abrupt onset distractors (Yantis 1993), and which kinds of saccade cancelation (e.g. stop signal, antisaccade, and other kinds of countermanding tasks, Hasegawa et al. 2004) could generate the effect.

One mentionable difference between the current study and numerous previous reports of saccade countermanding in humans is the comparatively slow SSRT (236ms) in our current study. Most studies using the saccade-countermanding task (Hanes et al. 1998) report much faster SSRTs (e.g. Hanes and Carpenter 1999; Cabel et al. 2000; Corneil and Elsley 2005; Curtis et al. 2005). However, a decisive difference between these tasks and our current study is that in those studies, pro-saccades towards extra-foveally presented target stimuli had to be inhibited when a stop signal occurred. In contrast, here we presented go stimuli which were centrally presented arrows pointing either to the left or right hand side of the screen, meaning that an additional perceptual decision process had to be made before emitting a response (as opposed to the unambiguous stimuli in the saccade-countermanding paradigm), which significantly prolongs GoRT (and, very possibly, SSRT estimates). Indeed, a study contrasting both versions of the oculomotor stop-signal task (Logan and Irwin 2000) did report both prolonged GoRT and
SSRT measurements for the version of the task that we used compared to the pro-saccade countermanding version. The SSRT estimate for the type of task similar to ours was 195ms, which was closer to our estimate.

An alternative interpretation of CSE reduction on stop trials is that it relates to a brain arousal signal (e.g. a fast dopamine signal, Redgrave et al. 1999, which would have effects on M1, Huda et al. 2001; Awenowicz and Porter 2002) rather than being the sign of motor suppression per se. As we argued previously (Cai et al. 2012) this interpretation is highly unlikely to explain our results, since one would also predict brain arousal on failed stop trials just as there is on successful stop trials. Yet in all three studies, the MEP for failed stop trials was no different from Go trials, and in both Cai et al. (2012) and Majid et al. (2012), the MEP on Go trials was no different from the MEP in the inter-trial interval. Moreover, evidence from error processing studies would predict even higher arousal for failed stop trials compared to successful stop trials (O’Connell et al. 2007; Wessel et al. 2011); yet again, all studies unanimously report motor suppression specifically for successful stop trials, whereas failed stopping did not show an effect on CSE. This speaks against a mere arousal explanation.

To our knowledge, obtaining MEPs of task-unrelated effectors is the most effective non-invasive method to quantify global stopping in healthy volunteers. However, other approaches are possible. For example, successfully stopping actions leads to decreases in heart rate (Jennings et al. 1992), i.e. to ‘cardio-muscular suppression’, which could be a marker of the global nature of motor stopping, even in a non-voluntarily controlled muscle. However, heart rate activity is influenced by a multitude of factors, many of which are not (directly) related to motor processing, e.g. increased effort (Lehle et al. 2009) or infrequent stimuli (Rockstroh et al. 1987). Accordingly, if successfully stopping an impeding action is an effortful process or an
orienting-like situation, changes in heart-rate could merely be a by-product of these processes rather than a direct manifestation of a global motor stopping process affecting the heart muscle. Also, it is of note that failed pro-saccade inhibitions in anti-saccade experiments have also been shown to induce heart-rate deceleration (Wessel et al. 2011), whereas such effects have yet to be reported for CSE on failed stop trials. While slowing of heart rate as a potential indicator of the global nature of motor stopping processes is thus an interesting avenue for future study, TMS measured CSE is a cleaner operationalization, which shows specific effects for successful motor stops and is directly related to motor activity.

In conclusion, we show that eye-movements, despite not being part of the skeleto-motor system, are stopped in a global manner, reducing the excitability of an unrelated effector when stopping is fast and reactive. This finding sheds light on the mechanism underlying global stopping (showing that it is not constrained to the stopping of the skeleto-motor system or of movements that are controlled via M1). It also has potentially important implications for better understanding the relation between stopping of eye-movements and the distractibility that is putatively generated by global effects on non-motor representations.

Acknowledgements

The authors thank John Serences for the loan of the eye-tracker.

Grants

This research was funded by NIH Grant DA026452.
References


Figure / Table legends

Figure 1: Experimental paradigm. In these examples, the TMS pulse is delivered at the estimated stop signal reaction time (SSRT) minus 50ms – a point in time that putatively corresponds to the maximum impact of the stopping process on the motor system. Note that in the actual version of the task, the stop-signal consisted of the arrow turning red (instead of gray as depicted here).

Figure 2: Validity of the race model in individual participants. Depicted are histograms of individual go trial RT distributions (light grey) and failed-stop RT distributions (dark grey). Median RT for each condition is denoted by vertical lines (solid for go trials, dashed for failed-stop trials). Participants whose data do not fulfill the requirements of the race model are marked with a black X. Excluding the data from those participants had no influence on the TMS results.

Figure 3: A) Scatter plot of go trial amplitudes plotted against successful stop trial amplitudes per subject. Length of the lines represents SEM on each measure. MEP suppression on stop- compared to go-trials is indicated by values in the lower right half of the plot, below the diagonal line. B) Scatter plot of go trial amplitudes plotted against failed stop trial amplitudes per subject.

Figure 4: A) MEP results in the current study (raw mean amplitude). B) Mean normalized MEP amplitudes for both types of stop trials (stop trial MEP amplitudes divided by go trial MEP amplitudes within each subject). The line at value 1 delineates go trial MEP amplitude. Error bars represent the standard error of the mean.

Table 1: Behavioral results. SSD: Stop-signal delay. SSRT: Stop-signal reaction time, p(stop): Probability of successful stopping on stop trials. Results are displayed for the full sample (upper table), as well as the reduced sample of N=12 participants whose data fulfilled all requirements of the race model.
<table>
<thead>
<tr>
<th></th>
<th>Correct Go RT (ms)</th>
<th>Incorrect Go RT (ms)</th>
<th>Failed Stop RT (ms)</th>
<th>p(inhibit) %</th>
<th>SSD (ms)</th>
<th>SSRT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Sample (N = 14)</td>
<td>420</td>
<td>280</td>
<td>398</td>
<td>47</td>
<td>184</td>
<td>236</td>
</tr>
<tr>
<td>Reduced Sample (N = 12)</td>
<td>426</td>
<td>283</td>
<td>404</td>
<td>48</td>
<td>191</td>
<td>235</td>
</tr>
<tr>
<td>SEM</td>
<td>17</td>
<td>17</td>
<td>10</td>
<td>1</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>
Go trial
Fixation ➔ Go Stimulus ➔ Response
SSD+SSRT-50ms ➔ Reaction time

Stop trial (successful)
Fixation ➔ Go Stimulus ➔ Stop Signal ➔ Response
SSD ➔ SSRT-50ms

Stop trial (failed)
Fixation ➔ Go Stimulus ➔ Stop Signal ➔ Response
SSD ➔ SSRT-50ms

Eyes moving
Eyes not moving
TMS stimulation
go trials
failed stop trials
median go RT
median failed stop RT
race model violated
A) SUCCESSFUL STOP MEP BY GO TRIAL MEP

B) FAILED STOP MEP BY GO TRIAL MEP
A) MEP AMPLITUDES

- Correct go
- Successful stop
- Failed stop

B) STOP TRIAL MEP (NORMALIZED)

- Go trial MEP
- Successful stop
- Failed stop