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# Current advances and pressing problems in studies of stopping

## Jeffrey D Schall and David C Godlove

The stop-signal task probes agents' ability to inhibit responding. A well-known race model affords estimation of the duration of the inhibition process. This powerful approach has yielded numerous insights into the neural circuitry underlying response control, the specificity of inhibition across effectors and response strategies, and executive processes such as performance monitoring. Translational research between human and non-human primates has been particularly useful in this venture. Continued progress with the stop-signal paradigm is contingent upon appreciating the dynamics of entire cortical and subcortical neural circuits and obtaining neurophysiological data from each node in the circuit. Progress can also be anticipated on extensions of the race model to account for selective stopping; we expect this will entail embedding behavioral inhibition in the broader context of executive control.

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### Introduction

Response control has been the subject of fruitful investigation using the stop-signal (or countermanding) task (reviewed by [1<sup>••</sup>,2]). Subjects must respond quickly when targets appear but must cancel partially prepared movements when infrequent stop signals occur (Figure 1). This task provides crucial leverage to investigate response control, because performance can be understood as a race between 2 processes that initiate (GO process) or cancel (STOP process) movement [3]. Using this race model, the duration of the covert STOP process can be derived from the proportion of successful stop trials and the distribution of reaction times (RT) on trials without stop signals. This stop-signal reaction time (SSRT) measures the time needed to cancel movements. This paradigm is very general, applying to simple and

choice response tasks accomplished with any effector system.

The stop-signal task enables powerful, translational research because it can be studied with humans, monkeys, and even rats, employing behavioral [4<sup>••</sup>,5,6], neurochemical [7], neurophysiological [8<sup>••</sup>,9<sup>••</sup>], electrophysiological [10,11], magnetic and electrical stimulation [12–14], and functional imaging [15<sup>•</sup>,16<sup>•</sup>,17<sup>••</sup>,18<sup>•</sup>] techniques. Moreover, the task provides traction to understand the nature of clinical disorders of impulse control and response monitoring [19<sup>•</sup>,20<sup>•</sup>,21,22]. From such a large and growing literature, we can focus on only a few salient developments and emerging problems with emphasis on neurophysiological findings.

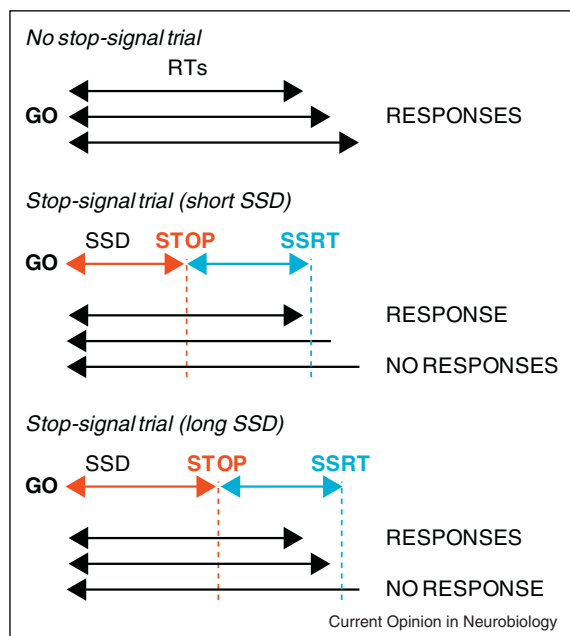
### Neural mechanism of response inhibition

The clearest mechanistic explanations of response inhibition are framed by neurophysiological studies in the frontal eye field (FEF) and superior colliculus (SC) of macaque monkeys performing an eye movement stopping task [23–25]. Two criteria must be met for neurons to participate in controlling movement initiation. First, neurons must discharge differently when movements are initiated or withheld; if neurons still discharge when movements are canceled, their activity was not affected by the stop process. Second, the differential modulation on canceled trials must occur before SSRT; otherwise, the neural modulation happens after the movement has already been canceled. Neurons that initiate or inhibit eye movements in FEF and SC modulate early enough to control movements directly (Figure 2A). These neurons project to brainstem structures that house ocular motor neurons, enabling them to influence response production directly [26,27]. After the target appears, movement-related activity begins to grow toward a threshold that triggers response initiation [28]. If the activity reaches threshold, a response is produced regardless of whether a stop-signal was presented. However, responses are canceled when the movement-related activity is inhibited so that it does not reach the threshold activation level. The source of this inhibition is a signal such as that conveyed by fixation neurons in FEF and SC. Crucially, the pronounced modulation of fixation-related and movement-related activity precedes SSRT.

Single-neuron recordings resolve patterns of modulation within neural microcircuits that are invisible to noninvasive methods such as fMRI and event related potential (ERP). For example, neurons with purely visual responses in FEF do not satisfy the criteria necessary to participate in controlling movements [24], and visuomovement neurons

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Figure 1



The stop-signal task measures response inhibition. Two trial types are randomly interleaved. 'No stop-signal', 'No signal', or simply 'Go' trials do not contain stop signals (top). A GO signal instructs subjects to initiate a response. The times between GO signals and responses are the subject's reaction times (RTs). 'Stop signal', 'Signal', or 'Stop' trials are randomly interleaved (middle and bottom). With some delay after the GO signal (stop-signal delay or SSD), a stop signal is presented. This cues subjects to cancel impending responses, which they are able to do with varying success. Short SSDs increase the probability of cancellation (middle) while long SSDs decrease the probability of cancellation (bottom). If responses are elicited in spite of the stop signal, trials are classified as 'Signal respond', 'Noncanceled', or 'Stop failure' trials. If no response is elicited, trials are classified as 'Signal inhibit', 'Canceled', or 'Stop success' trials. Stop-signal reaction time (SSRT) measures the time necessary for the covert inhibitory process to cancel responses. RTs faster than SSD plus SSRT will result in Signal respond trials, while RTs slower than the stop process will lead to Signal inhibit trials.

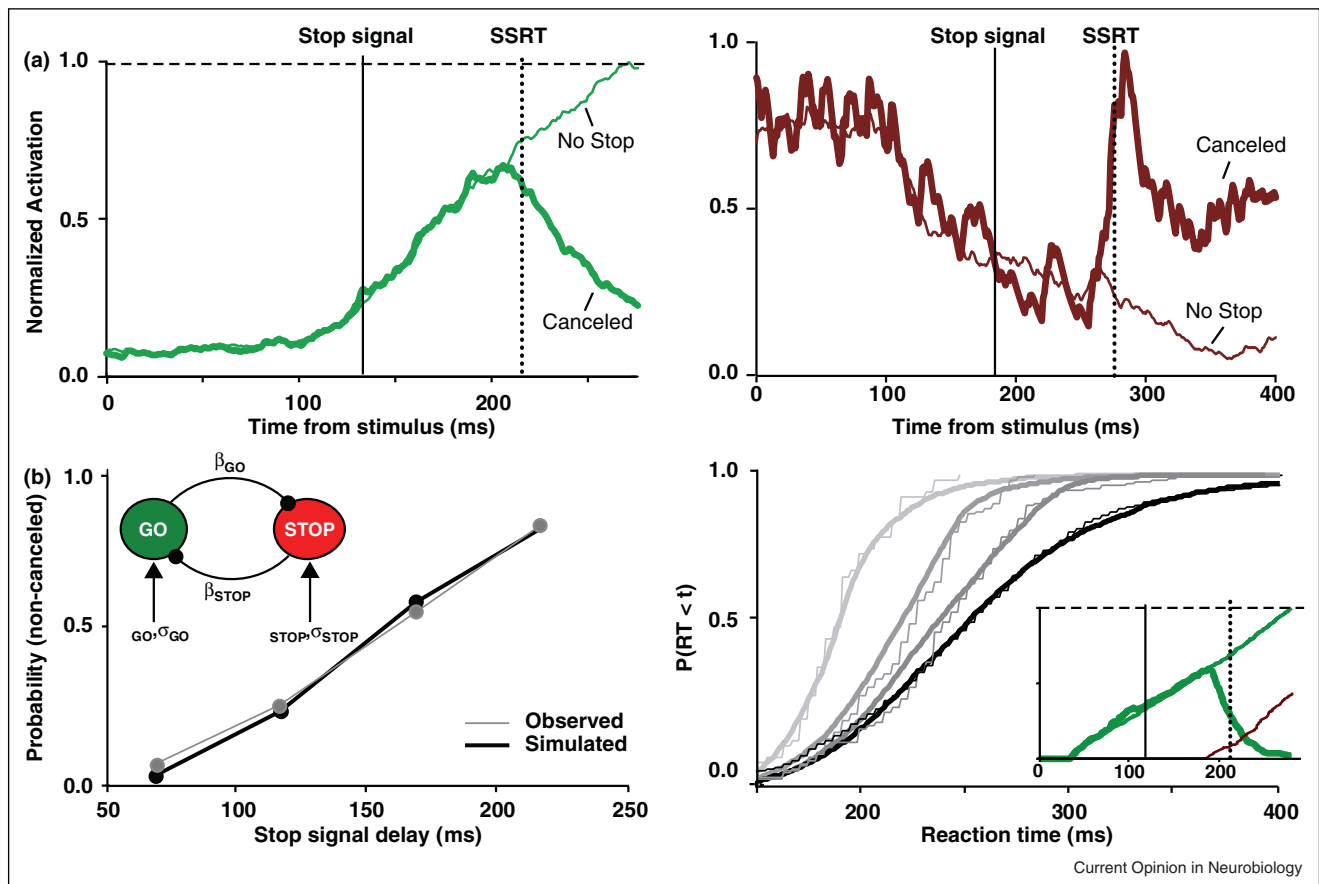
exhibit a pattern of modulation distinct from that of movement neurons [29]. Because noninvasive techniques are unable to resolve such heterogeneous signals in the stop-signal task, associated claims framing mechanisms in terms of one gross anatomical structure influencing another must be interpreted cautiously (e.g. [30]).

The straightforward criteria laid forth by the race model identify neurons that produce signals sufficient to control movement initiation. The results from FEF have been replicated and extended in a task requiring changing instead of just stopping saccades [31]. Meanwhile, neurons in other cortical areas, such as the supplementary eye field (SEF) and lateral intraparietal area (LIP), have also been described as movement-related. However, tests with the stop-signal paradigm have produced unambiguous results; vanishingly few neurons modulate before

SSRT in SEF [9••] or LIP [32]. Thus, SEF and LIP do not satisfy the logical criteria necessary to contribute directly to movement control. Similarly, neurons in supplementary motor area (SMA) do not modulate early enough to control limb movements [33•]. Results from preSMA are mixed. One laboratory has recorded from preSMA [34] and subthalamic nucleus (STN) [35] during a 'saccade overriding' and a go/no-go task. The latter task resembles a stop-signal task with SSD = 0 but lacks a measure like SSRT. These researchers identified some neurons in both structures with increased activity on successful no-go trials, similar to those modulating on canceled trials in SEF [9••,36] and SMA [33•]. However, whereas activity in SEF and SMA was too late to contribute to response inhibition in the stop signal task, the modulation of neurons in preSMA and STN did occur within the transition between error and correct response times. Another laboratory has described neural activity in preSMA during the stop-signal task. Similar to findings in SMA, the majority of these neurons modulate after SSRT [33•]. Further research is needed to resolve this question in preSMA, and data must be recorded from STN while monkeys perform the stop-signal task to test for modulation before SSRT.

It is tempting to hypothesize that movement and fixation neurons instantiate the race model. But the central assumption that finish times of the GO and STOP processes must be independent complicates this interpretation [3]. If circuits that instantiate the race model consist of interacting neurons, how can they produce behavior that appears to result from independent processes? This paradox has been resolved through a model network of interacting GO and STOP units with randomly accumulating activation ([37••] see also [38]). The model fits performance data and replicates neural data if and only if the STOP unit inhibits the GO unit in a delayed and potent fashion (Figure 2B). Thus, a neurally plausible mechanism of interaction is the only way that the model naturally fits behavior. This interactive race model has since been extended to a network of biophysically realistic spiking neurons [39•]. Others have modeled behavioral inhibition in Bayesian terms [40], but the utility of this approach for elucidating neural mechanisms is uncertain. Only the race model has afforded precise description at multiple levels, both neural and behavioral, during the stop-signal task. This rare coordination between psychophysics, formal mathematical modeling, and neurophysiology establishes a clear linking proposition between the GO and STOP processes of the race model and gaze-shifting and gaze-holding neurons in the ocular motor circuit. We are curious to know if this interactive race framework will extend gracefully to explain manual stopping, and we expect that this framework will be necessary to understand the diversity of selective stopping findings across stimulus conditions and effectors.

Figure 2



Neural and computational mechanisms of movement inhibition. **(A)** Normalized activity of FEF gaze-shifting (left) and gaze-holding (right) neurons. Activity on trials in which movements were produced but would have been canceled if the stop signal had been presented (thin line) are compared with activity on trials when the planned saccade was canceled because the stop signal appeared (thick line). Presentation of the stop signal is indicated by the solid vertical line. The time needed to cancel the planned movement – stop signal reaction time (SSRT) – is indicated by the dashed vertical line. When the movement was canceled, gaze-holding activity increased and gaze-shifting activity decreased abruptly immediately before SSRT. The timing of this modulation demonstrates that FEF neurons convey signals sufficient to control the initiation of the movement. **(B)** The interactive race model elucidates how a network of mutually inhibitory GO and STOP units (left inset) can produce behavior consistent with the Logan race model. With proper parameters, the network produces error rates (left) and RT distributions (right) that are indistinguishable from observed values. Moreover, using the same parameters, GO and STOP unit modulation (right inset) correspond quantitatively to the form of actual neural activation. Movement inhibition can be accomplished only by late, potent interruption of the GO process by the STOP process. Adapted from [37\*\*].

Meanwhile, a series of clinical and MRI studies have drawn attention to a specific region of ventral prefrontal cortex as a central focus of response inhibition in conjunction with preSMA and the STN. The evidence began with a correlational study relating frontal lesion location and size to SSRT [41]. Further work showed hemodynamic activation in right inferior frontal cortex (rIFC) and STN during response inhibition [42]. Based on findings that deep brain stimulation (DBS) of STN in Parkinson’s disease (PD) patients improved stopping performance [43], and evidence from diffusion tensor tract tracing for a direct connection between IFC and STN [44], a hypothesis was advanced that rIFC inhibits responses

directly and immediately through the hyperdirect pathway by increasing  $\beta$  synchronization.  $\beta$  synchronization has been reported to decrease in primary motor cortex (M1) and STN locally during manual response initiation in patients [11,45,46]. Another study reported that DBS of STN in PD patients improved response inhibition and was associated with increased  $\beta$  power in surface EEG [10].

Confidence that rIFC is the seat of inhibition must be tempered, however, because key aspects of the data are uncertain and alternate hypotheses explain more observations.

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- (1) The evidence for potent anatomical connectivity between rIFC and STN is uncertain. In monkeys, prefrontal inputs to STN arise from FEF and dorsal medial frontal areas but not from ventral PFC [47]. Moreover, the prefrontal inputs terminate in a ventral sector of STN that does not overlap with the M1 and SMA terminals [47,48]. In humans, a recent comprehensive survey of STN connectivity shows that fibers connecting IFC to STN are vanishingly weak in comparison to those connecting STN to caudate, putamen, globus pallidus, and thalamus [49]. Although some have hypothesized that a common inhibitory mechanism operates in humans and rats [50\*\*], comparison across species must be made with caution because STN connectivity differs between rodents and primates [51].
- (2) Numerous studies identify rIFC with functions other than response inhibition [52]. In particular during the stop-signal task, activation of rIFC may be caused by cognitive functions such as attentional capture [16\*,53] (although these effects are difficult to parse from increased RTs in these studies) or violations of event expectations [17\*\*]. Outside of the stop-signal task, IFC is consistently implicated in stimulus driven attentional capture [54,55] and this activation scales with the degree of stimulus unexpectedness [56,57]. In general, rIFC is often implicated as part of a network involved in orienting attention toward salient stimuli (reviewed by [58]). While the specific homologue of IFC has not been identified in nonhuman primates, it is probably located ventral to the principal sulcus and rostral to or in the arcuate sulcus. This region has not been explored extensively neurophysiologically, but an fMRI study in macaques identifies its activation with cognitive set shifting [59]. Thus, plausible alternative hypotheses about the role of IFC abound.
- (3) Confidence in the claim that  $\beta$  oscillations serve to synchronize rIFC and STN to interrupt movement preparation must also be tempered. One study reporting increased intracranial  $\beta$  power over rIFC when responses were canceled was clear in just one of four patients [11]. In monkeys, increased  $\beta$  power has been observed in cortical areas in which no neurons modulate early enough to contribute directly to response inhibition, and such elevation is dissociated from increased  $\gamma$  power that is most commonly associated with spike rate modulation [60\*\*]. Another study reporting that DBS of STN in PD patients improved response inhibition with increased  $\beta$  power in surface EEG [10] has an inconsistent behavioral effect [61]. In fact, several studies have noted that DBS of STN *reduces* or *reverses* response inhibition in PD patients under conditions of decision conflict [62,63]. And others have recorded *increased* impulsivity measures in PD patients undergoing DBS ([64] but see [65] for a possible reconciliation). Causal links

between  $\beta$  power, STN, and behavioral inhibition are therefore far from established.

- (4) Other cortical areas and basal ganglia pathways are known to contribute to response inhibition [18\*,66]. Of these, the SMA and preSMA have received considerable attention (e.g. [15\*]). But recent work suggests that medial frontal areas may play a more nuanced role in behavioral inhibition that will be discussed below. Meanwhile, as reviewed above, FEF and SC contain neurons with the connectivity and patterns of modulation sufficient to explain response inhibition and execution. Neurons in premotor cortex likewise modulate before SSRT [8], and parallel results are obtained in M1 (Stuphorn personal communication). Studies using paired pulse transcranial magnetic stimulation show that inhibition in M1 is recruited in humans carrying out the stop-signal task [12]. Ultimately, an effective model of response control cannot emphasize one node or pathway in a complex system at the exclusion of other, more powerful pathways; it must include the dynamics of the entire network.

#### General vs. specific inhibition mechanisms

Most stop-signal experiments with humans test manual responses. As detailed above, our laboratory has used this task to investigate gaze control [67]. To investigate the generality of stopping mechanisms across effectors, we tested whether human subjects could stop eye and hand movements independently [6]. SSRTs were longer for hand movements than for eye movements, and advanced knowledge of which effector to stop did not confer any stopping advantage. We concluded that there must be some independence between the processes that stop eye and hand movements. Additional evidence for differences between effectors comes from studies examining the fine dynamics of movements on stop trials. Several groups have reported partial muscle activation when overt manual responses are canceled [33\*] and one group has reported reduced response force on noncanceled trials [68]. Similarly, when combined eye and head gaze shifts are canceled, neck muscles are often active [69,70\*\*]. However, partial muscle activation is not observed when eye movements are canceled in isolation, and eye-movement dynamics are indistinguishable on no-stop and noncanceled trials [71]. This ballistic ‘all or nothing’ property of saccadic eye movements highlights a difference between the control of eyes and hands in typical testing conditions.

In addition to generality across effectors, how general is inhibition across strategies? And what is the relationship between slowing and stopping outright? These ethologically appealing issues have recently received attention under the headings of (1) global versus selective stopping, and (2) proactive versus reactive inhibition. Much work



has focused on a role for the SMA and preSMA in proactive and selective inhibition in humans [10,17<sup>••</sup>,72] and nonhuman primates [9<sup>••</sup>,14,60<sup>••</sup>,73]. These medial frontal areas exhibit single neuron and hemodynamic modulation that anticipates presentation of stop signals and relates to the quality of performance of the task. The contributions of other brain regions remain uncertain, though. Moving forward, we see issues needing clarification:

- (1) Many tasks confound proactive versus reactive stopping with selective versus global stopping (e.g. [74]). It is often implicitly assumed that proactive inhibition strategies are selective, whereas reactive inhibition is global (e.g. [1<sup>••</sup>]). At least one study suggests that, under certain conditions, exerting proactive control leads to more selective inhibition [13], but care should be taken to manipulate one or the other of these variables until more data have been collected.
- (2) Logan's original race model must be extended to understand selective stopping. For example, when different movements or effectors are used, multiple GO processes and possibly multiple STOP processes will be required [75]. In addition, many selective stopping studies have reported violations of race-model assumptions, with noncanceled RTs equal to or exceeding no-stop RTs (e.g. [76,77]). Such data invalidate the face-validity of SSRT calculated using Logan's original race model. Therefore, caution should guide interpretation of results until the underlying processes are understood through the next generation of race models. We believe that the interactive race model provides a foundation for models of selective stopping with different stimuli, rules and effectors. Like any RT, SSRT is comprised of successive stages, an initial encoding stage followed by an interactive stage during which the GO process is interrupted [37]. Encoding duration will vary based on stop-signal modality, task rules, history, or context. However, the interactive stage must be brief to produce noncanceled RTs faster than no-stop-signal RTs. Under selective stopping conditions, delayed noncanceled RTs can arise when the influence of the STOP process is weaker and prolonged. Thus, the interactive race model may extend naturally to selective stopping conditions. By whatever means the interaction between the GO and STOP processes is adjusted, an executive control circuit is necessary to register the need for these adjustments.

### Executive control of stopping

An extensive body of work has associated areas of human medial frontal cortex with executive control. Consistent with this framework, SEF and anterior cingulate cortex (ACC) of monkeys both contain distinct populations of neurons active after errors or in association with

reinforcement [36,73,78] (Figure 3). SEF also contains a population of neurons active after successful withholding of a partially prepared eye movement and proportional in their activation to the momentary co-activation of gaze-shifting and gaze-holding neurons. These neurons are hypothesized to signal response conflict. Several theories dealing with the precise functions carried out by medial frontal cortex have been advanced, ranging from error detection or prediction, to reinforcement learning to conflict monitoring. The existence of distinct populations of neurons signaling error, reinforcement, and putative response conflict indicates that each hypothesis has merit. But no neurons or LFPs have been recorded in monkey ACC that could signal conflict [78,79<sup>•</sup>,80]. Some have proposed that macaque monkeys do not have the neural substrates necessary to generate performance monitoring ERPs similar to those observed in humans [81,82]. However, the presence of monitoring signals in both single units and LFPs as well as a monkey homologue of the error-related negativity (see below) call into question the merits of this proposal.

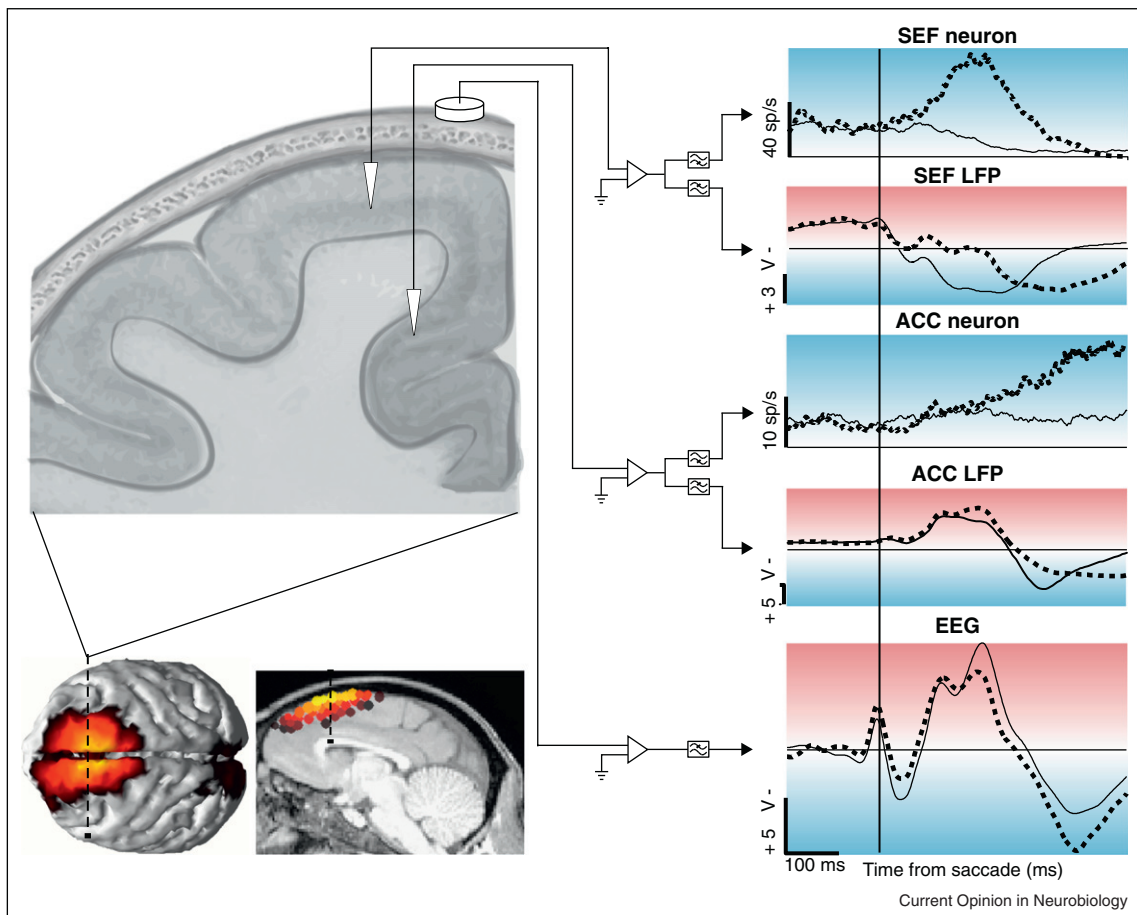
Error-related activity in SEF and ACC may contribute to an ERP recorded over medial frontal cortex known as the error-related negativity (ERN) [83<sup>•</sup>]. This ERP was the first physiological signature of a supervisory control system. A bridge between the monkey single-neuron results and the human ERN began with a series of studies showing that LFPs in ACC and SEF exhibit polarization corresponding precisely to the ERN [79,84]. This was followed by the keystone finding that macaque monkeys exhibit an ERN recorded from the cranial surface consistent with a current source in medial frontal cortex [85<sup>••</sup>] (Figure 3), and nearly identical in form and distribution to that recorded from humans performing the same task [86<sup>•</sup>]. The neural origins and cognitive correlates of the ERN have been subjects of intense research, and an animal model of the ERN will certainly provide effective leverage on elucidating mechanisms.

As soon as performance monitoring signals were discovered, their relationship to performance adjustment was explored [83<sup>•</sup>]. After mastering the stop-signal task, fine adjustments of performance continue [4<sup>••</sup>,87,88]. For example, RT is delayed as more stop-signal trials are encountered or expected [4<sup>••</sup>,89<sup>•</sup>]. The role of medial frontal cortex in performance monitoring has been tested through intracortical microstimulation of SEF while monkeys performed the stop-signal task [14]. Stimulation was delivered simultaneous with stop-signal presentation, at current levels well below threshold for eliciting eye movements. Microstimulation of sites in SEF improve performance by reducing the fraction of non-canceled responses.

A reanalysis of data from FEF and SC shows how this behavioral slowing is accomplished [90<sup>••</sup>]. RTs are presumably adapted to minimize errors and maximize

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Figure 3



Performance monitoring signals in and over medial frontal cortex of macaque monkeys during the stop-signal task. Schematized coronal section on top left illustrates location of intracranial recordings from SEF, ACC, and cranial surface recordings. Intracranial signals from microelectrodes were amplified and filtered to provide spikes or LFP, and cranial signal was processed as typical EEG (right panels). Solid lines plot activity on no-stop (correct) trials, and broken lines plot activity on noncanceled (error) trials. In both SEF and ACC, many neurons show increased activity following noncanceled error responses. Simultaneously, the LFP at some sites in SEF and most sites in ACC exhibit greater polarization after errors. These LFPs contribute to the greater polarization recorded on the surface, corresponding to the ERN, as indicated by the current sources calculated from the surface voltage distribution projected onto dorsal and medial surfaces of structural MRI data (lower left). Adapted from [36,78,79\*,84,85\*].

rewards. Stochastic accumulator models commonly account for this adaptation through changes in response threshold. However, Pouget *et al.* [90\*\*] demonstrated that RT adaptation is accomplished not through a change of threshold, baseline, or accumulation rate, but instead through a change in the time when presaccadic movement activity first begins to accumulate. This result highlights the subtlety of mapping computational models onto neural processes.

Of course, performance adjustments need not be implemented via RT adaptation alone. In the stop-signal task, subjects may also adjust SSRT. The question of how motivational factors may influence SSRT is particularly interesting. To date, only one study has manipulated

motivational state and tested for changes in SSRT [91]. These researchers manipulated reward contingencies to favor either speed or accurate inhibition, and found that SSRTs were lower when subjects were encouraged to value stopping. Unfortunately, SSRT estimates in this study were unreliable since only a single SSD was used. When estimating SSRT from a single SSD, it is important to use the SSD that yields 50% errors. Since the probability of making a noncanceled error was higher in the motivated speed condition, sampling error rates in both conditions at a single SSD means that SSRT was estimated from different tails of the RT distribution. Thus, the observed SSRT differences in this study probably represent well-known confounds in SSRT estimates rather than motivational factors. This study should be

repeated using standard staircasing procedures. Until then, the effect of motivation on SSRT remains an open topic of great interest and importance.

### Conclusions

Investigation of the stop-signal task in humans and animal models will probably accelerate because of the paradigm's powerful utility for elucidating mechanisms of response control from muscles to cognition. Its unique translational leverage is afforded by the race model, which provides a common language linking behavior, models, and neurons. The race model also provides powerful constraints on mechanisms and predictions, encouraging the use of strong inference. We look forward to new insights pinpointing neural circuitry responsible for interrupting responses in multiple effector systems, resolving mechanisms of proactive and reactive inhibition, and placing behavioral inhibition in the broader context of performance monitoring and executive control.

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- of special interest
- of outstanding interest

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This paper contrasts trials containing task relevant stop signals with those containing task irrelevant signals in an effort to obtain pure measures of response inhibition, attentional capture, and error processing in an fMRI paradigm. The authors conclude that pre-SMA, not rIFC is responsible for response inhibition.

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