The Inhibition of Unwanted Actions

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ABSTRACT
Inhibitory control is one of many high-level cognitive processes that fall under the rubric of "executive" or "cognitive" control. Successfully withholding an over-learned, prepotent, or planned motor response is a critical demonstration of inhibitory control. Here, we briefly review key studies of inhibitory control with a special emphasis on cognitive neuroscience studies. We aim to provide some insights into the potential neural mechanisms that may underlie our ability to inhibit unwanted action. Leveraged with these findings, we argue that inhibitory control, like voluntary control more generally, is best modeled as the process by which we select the best response among the competing responses, including not responding at all. One implication of this model is that no single area of the brain is specialized for inhibiting all unwanted actions.

INTRODUCTION

All animals are endowed with the capability of motor behavior. With that endowment they are faced with the continuous responsibility of selecting certain courses of action over others in order to ascertain their goals. A distinguishing feature of the higher animal species, like primates, is their exceptional ability to voluntarily control their actions. Voluntary control is necessary when an optimal motor response is uncertain or when a competing motor response must be overcome. A special case of voluntary control, or the more general term "executive" or "cognitive" control, is the ability to inhibit an unwanted action. Successfully withholding an over-learned, prepotent, or planned motor response is a critical demonstration of inhibitory control. Indeed, the ecological validity of such a construct is high and we can all think of a multitude of instances when we have had to inhibit our behavior. In social situations, our gaze at any given instant communicates to others information about our internal thoughts. For example, you might find it prudent to inhibit your

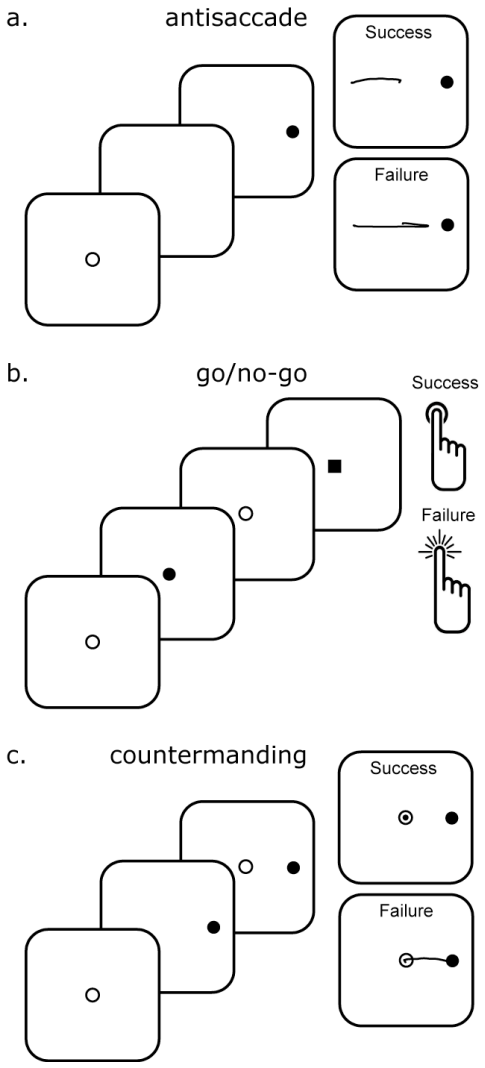


Figure 1. Tasks that require inhibitory control. a. Antisaccade task. The subject maintains central fixation until a visual target appears. On prosaccade trials, the subject makes a saccade to the target. On antisaccade trials, the reflex-like prosaccade must be inhibited so that an antisaccade can be generated to the target's mirror image location. Inhibitory failures take on the prototypical form of small prosaccades followed rapidly by corrective antisaccades. b. Go/ No-go task. The subject makes a speeded button press whenever a "GO" stimulus is presented, in this example, a black circle. On rare occasions, a "No-go" stimulus, a black square in this example, is presented and the subject must inhibit responding. c. Stop-signal task. On frequent "GO" trials, the subject maintains central fixation and makes speeded saccades to the appearance of a peripheral target to the left or right of fixation. On rare "STOP" trials, a visual cue, in this case the reappearance of the fixation point, is emitted after a period of time known as the stop signal delay. This signals to the subject to cancel or inhibit the planned movement. Sometimes the subject is successful at withholding the saccade, but sometimes fails canceling the planned saccade.

glances towards an attractive person sitting at an adjacent table especially if you are dining with your partner. Here, we briefly review key cognitive neuroscience studies that have investigated the neural responses of monkeys and humans performing tasks that are laboratory analogs of everyday response inhibition. We aim to provide some insights into the potential neural mechanisms that may underlie our ability to inhibit unwanted action.

LABORATORY TESTS OF INHIBITION

A variety of tasks are used to study inhibitory control in some form or another pitting an over-learned, stereotyped, prepotent, or naturally compatible response against a response contingent upon a novel or unnatural mapping. For example, the Stroop task (Stroop, 1935) requires subjects to say aloud the font color of a word instead of reading the word itself (e.g., say "blue" if presented with the word "RED" printed in a blue font). Vocal response times and errors increase when subjects have to say the font color compared to when they have to read the word. The Eriksen flanker task (Eriksen & Eriksen, 1974) requires subjects to press a left or right button if a centrally presented arrow stimulus is pointed to the left or right, respectively. If the central target arrow stimulus is flanked by arrows that are incongruent in direction with the target (e.g., "<<<<><<<<" indicates respond right), response times and errors increase. The Simon task (Simon, 1969) requires subjects to press a left or right button depending on the color of a stimulus cue. Response times and errors increase when

the stimulus is presented to the side that is opposite to the button with which the stimulus is associated (e.g., if ●=left button and O=right button, response times will be slower when ● compared to O is presented on the right side of the display). The Stroop task requires inhibition of the over-learned behavior of reading text. The Eriksen flanker task requires inhibiting the incompatible and competing response indicated by the flanking distracters. The Simon task requires inhibiting the button press that is congruent with the spatial position of the stimulus cue.

Although these classic tasks have a long prominent history in cognitive psychology studies of inhibitory control, for a variety of reasons and with a few notable exceptions they have not been used as regularly in cognitive neuroscience studies. Here we will focus on three tasks that have strong response inhibition demands and have been widely and successfully used to study the neural correlates of response inhibition, antisaccade tasks, go/no-go tasks, and stop-signal tasks (Figure 1).

We will first describe each task, including the similarities and differences, and then we will delve into the basic research into the neural mechanisms supporting inhibition in each of these tasks, and finally will draw some conclusions across the studies using the various tasks.

ANTISACCADE TASK

In an antisaccade task (Hallett, 1978), subjects make a saccade (i.e., shift their gaze with a rapid ballistic eye movement) to the opposite hemifield, away from a visually-cued location (Figure 1a). Correct performance requires that the subject first, inhibit the "reflex-like" prepotent tendency to shift their gaze to the visual cue and second, generate a saccade to the mirror imaged location of the cue. Prosaccade trials, where gaze is simply shifted to the visual cue, are commonly performed in separate blocks or randomly intermixed with antisaccade trials. Compared to prosaccades, antisaccades are slower due to the extra time required to inhibit the automatic saccade plus the time to program the antisaccade. Errors on antisaccade trials are characterized by small amplitude saccades generated towards the visual cue and are thought to reflect inhibitory failures. The power of the antisaccade task stems from the fact that one must suppress a response with high stimulus-response (SR) spatial compatibility (i.e., shift gaze to a location that matches the location of the visual cue.)

GO/NO-GO TASK

In a go/no-go task, subjects make a speeded manual response, typically a button press, as soon as a go cue, typically a visual stimulus, is detected (Figure 1b). On rare trials, the go cue is replaced with a stimulus that instructs the subject to withhold the response, the no-go cue. Responding gains potency because speeded responses are generated so frequently and are often erroneously generated following the no-go cue. The power of the go/no-go task stems from the fact that the difficulty of suppressing the response increases as the response is habitualized through the relative infrequency of no-go trials.

STOP-SIGNAL TASK

Stop-signal or countermanding tasks (Logan, 1994), as they are called, require the voluntary control over the production of movements because an imperative stop signal is infrequently presented instructing the subject that the planned movements should be withheld. In a stop-signal task,

subjects make a speeded response, typically a manual button press or an eye movement, upon the presentation of a visual go cue (Figure 1c). On rare trials, just after the presentation of the go cue, an imperative stop signal is presented instructing the subject to withhold the planned movement. Intuitively, as the stop signal is delayed, the motor plan has more time to evolve toward execution, and the probability that the subject will be able to inhibit the response decreases. Similar to the go/no-go task, the power of the stop-signal task relies on the difficulty of suppressing the speeded habitualized response.

Although each task similarly requires withholding a prepotent response, they differ in terms of when in the perception-action cycle inhibition is thought to begin. During a stop-signal task, inhibition begins late, after the go cue has been presented and therefore during the planning of the motor response. During a go/no-go task, inhibition begins earlier, simultaneous with the no-go cue. During an antisaccade task, before a block or before a trial the subject must be instructed whether the trial is an antisaccade or prosaccade trial. Therefore, inhibition can begin even earlier, as soon as the subject is cued that the trial is an antisaccade trial.

NEURAL MECHANISMS OF INHIBITION

Here, we describe human and non-human primate research that has provided insights into the potential neural mechanisms of response inhibition. Although the construct of inhibition can be operationalized at many levels, from the molecular to psychological level, we will limit our scope of analysis to the systems level (i.e., populations or networks of neurons).

Eye movements are used as the response modality most often in studies of monkeys chiefly because we know more about the oculomotor system than any other motor system (Figure 2) (Carpenter, 2000; Glimcher, 2003). The use of eye movements as a dependent variable has several advantages specifically for investigations into inhibition. Since the cost of making unwanted reaches, for example, is often greater than the cost of making unwanted glances (i.e., touching someone or something maybe more costly than just looking), the neural mechanisms for the executive control over eye movements may be simpler. In addition, since eye movements can be generated with very fast response latencies (e.g., typically less than 200ms in humans and 150ms in monkeys) control processes such as inhibition must act quickly or errors are likely to be made. Increased frequency of errors can be advantageous for experimentation because if we want to really understand inhibition we need to investigate the causes of failures of

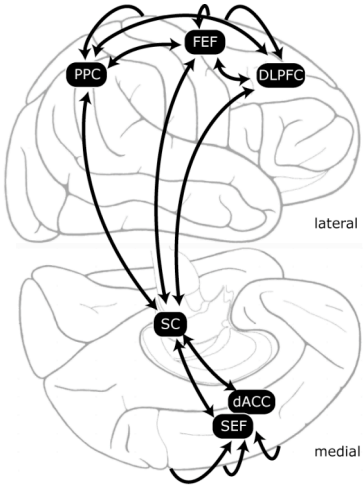


Figure 2. Key connections between nodes of the oculomotor network in the human brain. This network, with the superior colliculus (SC) serving as the final common pathway, is thought to govern the generation of saccades. Together, these areas are also thought to play important roles in visuospatial and visuomotor behavior, such as that required for the production and inhibition of saccades. Abbreviations: PPC = posterior parietal cortex; FEF = frontal eye fields; DLPFC = dorsal lateral prefrontal cortex; SEF = supplementary eye fields; dACC = dorsal anterior cingulate cortex.

inhibition. Finally, another advantage of using the oculomotor system is that the position of gaze is experimentally controlled at all times. This is important because much of the work on inhibition deals explicitly or implicitly with the spatial compatibility of visual cues and motor responses, and the position of a visual stimulus on the retina changes with regard to the position of gaze.

Electrophysiological studies of the monkey frontal eye field (FEF) have yielded promising clues to the neural mechanisms of response inhibition. FEF neurons are traditionally thought to play a critical role in transforming visual information into saccade commands (Bruce *et al.*, 2004).

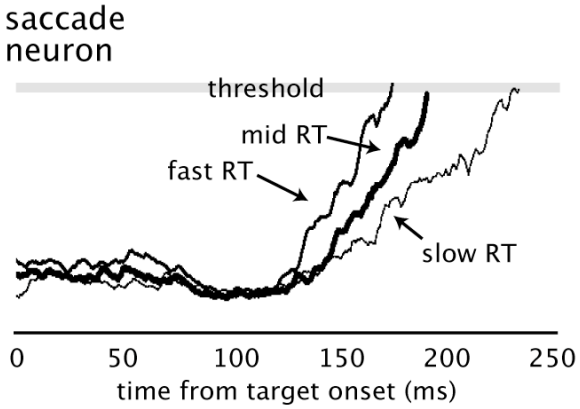


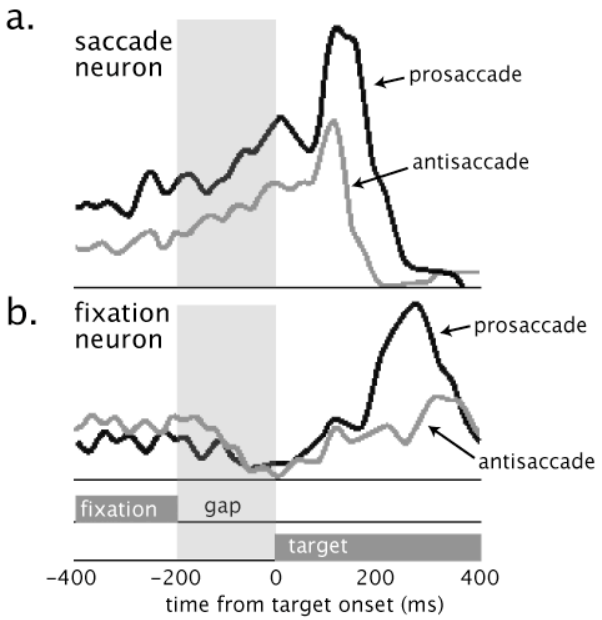
Figure 3. The stochastic variability in the time it takes to initiate a saccade to a flashed visual target is directly related to the time it takes for the firing rate of motor FEF neurons to reach a fixed threshold. The rate of growth in firing rate in the same FEF neuron during numerous trials in which the response time tended to be fast, medium, or slow. Note that the variability in response time is a function of the time needed to reach the threshold. Modified from (Thompson et al., 1997).

Indeed, several types of neurons exist in the FEF. Visual FEF neurons respond when a visual stimulus falls within the neuron's response field (i.e., a spatially localized portion of the visual field). Motor FEF neurons respond just prior to the execution of a saccade into the neuron's response field. Visuomotor FEF neurons are hybridizations; they show both visually-evoked and saccade-evoked activity. Saccades (i.e., fast ballistic eye movements) with specific vectors can be elicited by electrical microstimulation of FEF motor neurons. These motor neurons possess all of the characteristics of a cell that controls the production of movement (Schall, 2002). For example, the stochastic variability in the time it takes to initiate a saccade to a flashed visual target is directly related to the time it takes for the firing rate of motor FEF neurons to reach a fixed threshold (Thompson *et al.*, 1997). Figure 3 illustrates this relationship by showing the rate of growth in firing rate in the same neuron during numerous trials in which the response time tended to be fast, medium, or slow. Note that the variability in response time is a function of the time needed to reach the threshold. Therefore, FEF motor neurons control the production of saccades. In direct opposition to these saccade neurons are another class of neurons in the FEF that are active when the monkey is actively fixating gaze on a stationary position. If fixation neurons are microstimulated during the course of smooth pursuit or saccadic eye movements, oculomotion is immediately halted (Burman & Bruce, 1997). Overall, saccades are produced when activity in FEF motor neurons that drive the eyes to a stimulus increases and activity in FEF fixation neurons that lock gaze in place decreases (Everling & Munoz, 2000; Hanes & Schall, 1996).

With these two different types of FEF neurons in mind, now let us consider the behavior of FEF saccade and fixation neurons during prosaccade compared to antisaccade trials. Saccade neurons in the monkey FEF exhibit a greater firing rate

during prosaccade compared to antisaccade trials (Figure 4a) (Everling & Munoz, 2000). Moreover, the difference in firing rate can be seen as early as the fixation interval, well before the target even appears. Fixation neurons in the FEF exhibit a greater firing rate just prior to antisaccades compared to prosaccades (Figure 4b), again hundreds of milliseconds before the appearance of the target. Therefore, on antisaccade trials when the animal anticipates that he will need to inhibit the prepotent reflex-like saccade, the firing rate of FEF saccade neurons decreases while the firing rate of fixation neurons increases. These changes are thought to bias the oculomotor system towards a less motile state where the onset of the target and its associated capture of attention is less likely to result in an unwanted saccade (Munoz & Everling, 2004). If activity in saccade neurons can be kept below a critical threshold (e.g., Figure 3) just long enough for the voluntary antisaccade to be programmed and initiated, then the decision to make a correct antisaccade is likely to be achieved. Indeed, activity in FEF saccade neurons is greater on trials in which the animal failed to inhibit the saccade towards the target (Figure 4c) (Everling & Munoz, 2000).

Therefore, with these observations we can posit a simple neuronal mechanism that determines the ability to inhibit an unwanted saccade. At the time when the peripheral visual target stimulus appears, competition between FEF gaze-holding and gaze-shifting mechanisms determines whether a reflexive saccade is triggered or not. Moreover, the difference in firing rate between prosaccade and antisaccade trials, and the difference in firing rate between successful and failed antisaccades trials, can be seen several hundred milliseconds before the visually guided saccade must be inhibited. These competitive interactions may give rise to a psychological preparatory set that primes the oculomotor system towards a gaze



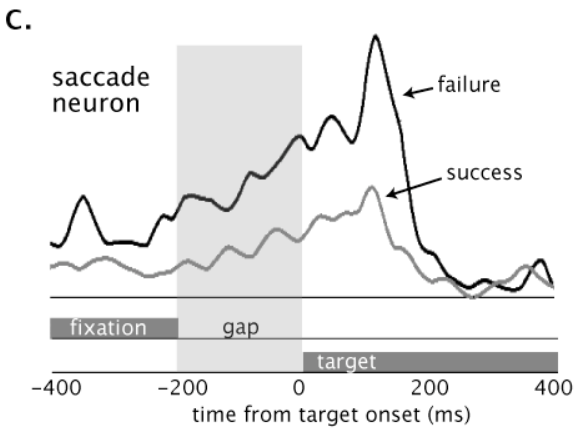


Figure 4. FEF neuronal firing during prosaccade and antisaccade trials. a. The firing rate of saccade neurons is greater prior to prosaccade than antisaccades. b. The firing rate of fixation neurons is greater prior to antisaccade than prosaccades. c. The firing rate of saccade neurons is greater on antisaccade trials where the animal failed to inhibit the prosaccade compared to when the animal was successful. Modified from (Everling & Munoz, 2000).

holding or shifting state. Stochastic fluctuations in the firing rates of FEF neurons may destabilize the preparatory state leading to failures in the ability to inhibit the unwanted prosaccade.

The voluntary control of behavior, of which withholding an action is a critical demonstration, can be exerted at any point along the series of processes that evolve over time from sensation to action. In the context of a stop-signal task, inhibition takes place far downstream in this evolution, after the movement has been planned. Inhibiting or canceling a planned movement following an imperative stop signal can be modeled as a race between independent GO and STOP mechanisms (Hanes & Carpenter, 1999; Logan *et al.*, 1984) (Figure 5). Which process first reaches a critical threshold, or finish line, determines whether the planned response is generated or not. By adjusting the time between the presentation of the stimulus that initiates the GO response processes and the presentation of the stop stimulus, an interval known as the stop signal delay, the probability that either one of the two possible responses will win the race can be adjusted (Logan, 1994). Canceling is easier when the stop signal delay is short because one has more time to cancel the movement. Importantly, using the saccadic response time distribution for GO trials and the probability of successful saccade cancellation at different stop signal delays, one can estimate the time needed to cancel a planned saccade once the stop signal had been given; this time is referred to as the *stop signal reaction time* (SSRT).

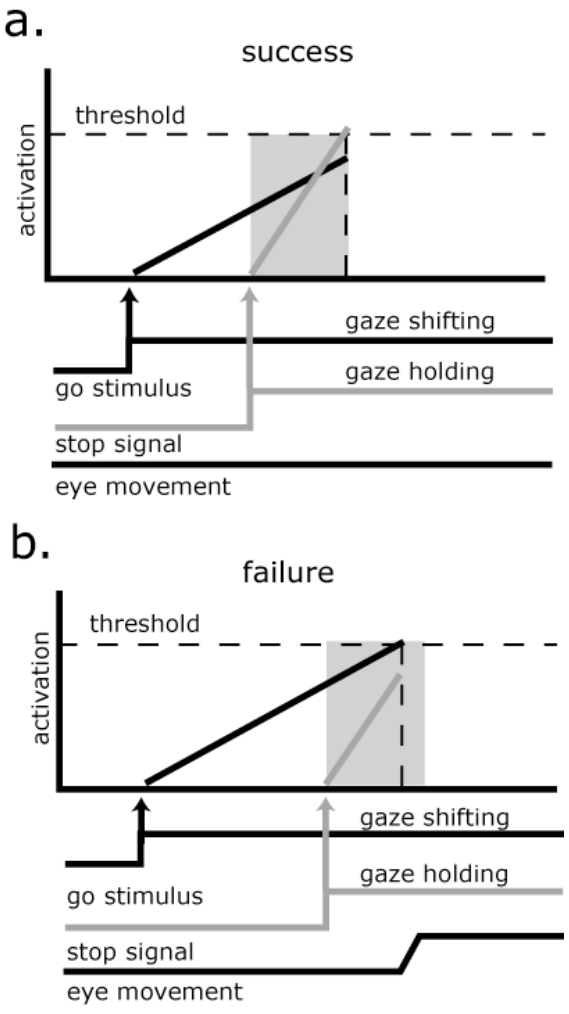
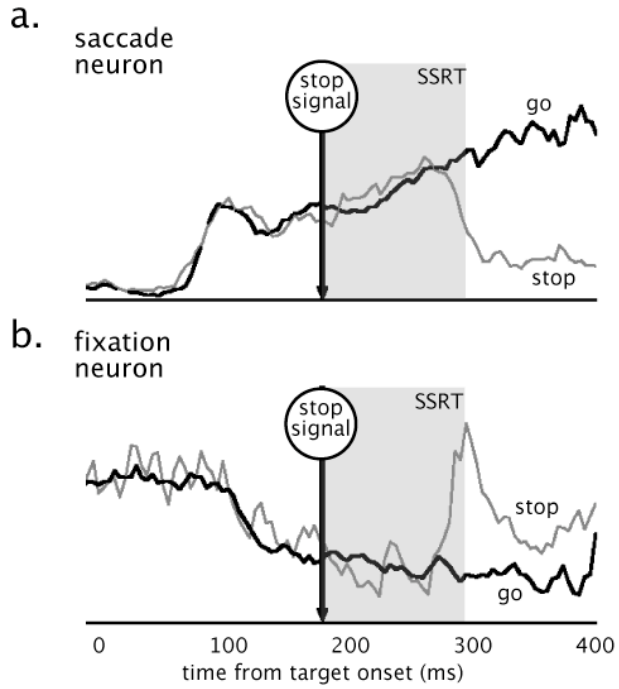


Figure 5. Race model of stop-signal task. Performance on the stop-signal task has been conceptualized to be a race between GO and STOP processes. The activation of neural GO processes related to shifting gaze (black line) race against the activation of neural STOP processes related to holding gaze (gray line) toward a winner-take-all threshold (dashed horizontal line) that determines whether a saccade is trigger or not. The gray bar represents the time needed to cancel a saccade after a stop signal has been emitted, a time known as the stop signal reaction time (SSRT) a. If the processes leading to holding gaze reach a critical threshold before the processes that lead to shifting gaze, then successful saccade cancellation will occur. b. However, if the gaze shifting processes reach threshold first, then a saccade will be triggered. Notice that in b. the stop signal delay was longer, which resulted in less time for the processes leading to holding gaze to grow to threshold. Manipulating this delay can reliably affect successful saccade countermanding.

The presaccadic growth of activity in FEF saccade neurons is correlated with saccade production while the growth of activity in FEF fixation neurons is correlated with saccade withholding during the performance of stop-signal tasks (Schall, 2001). FEF saccade neurons show a phasic burst of activity within 100 ms following the appearance of the visual target, while FEF fixation neurons activity declines rapidly (Hanes *et al.*, 1998). These early changes in neuronal firing reflect the planning and preparation of the visually guided saccade. When no stop-signal is emitted (i.e., GO trials) the firing rate of saccade neurons continues to build until the critical threshold is breached and a saccade is finally generated (Figures 6a & 6b). When a stop-signal is emitted (i.e., STOP trials) and the animal is successful at inhibiting the planned saccade, fixation neurons exhibit a burst of firing that coincides with a sharp decrease in the firing rate of saccade neurons (Figures 6a & 6b). However, if these changes in firing invoked by the stop signal do not occur quickly enough, or to be more precise, do not occur within the SSRT, then the animal is not able to withhold the movement and a failure of inhibition occurs (Figure 6c). Overall, the activity pattern of FEF saccade and fixation neurons corresponds very well with the hypothetical GO and STOP processes of the race model where the outcome of a race between saccade and fixation neurons determines whether or not a saccade is generated.

Functional MRI studies have provided critical support in humans for the findings from monkey electrophysiology. For example, the generation of antisaccades compared to prosaccades causes greater activation in the human FEF (Connolly *et al.*, 2002; Curtis & D'Esposito, 2003). The increase is presumably due to the co-activation of saccade and fixation neurons



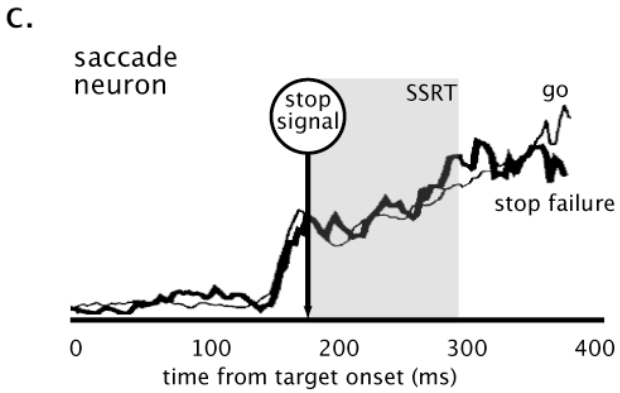


Figure 6. FEF neuronal firing during a stop-signal task. a. The firing rate of a saccade neuron during a GO and a STOP trial. Following the initial visually evoked response, the firing rate increases presumably towards a threshold that when breached results in a saccade. On STOP trials the firing rate declines rapidly following the presentation of the stop signal. Importantly, this decline occurs within the SSRT. b. The firing rate of a fixation neuron on GO and STOP trials. c. The firing rate of a saccade neuron on trials in which the no stop signal was given (GO) and when a stop signal was given but the animal did not cancel the saccade in time. Modified from (Hanes et al., 1998).

in the FEF during antisaccade trials. Similarly, during a stop-signal task, the successful cancellation of a planned saccade (i.e., STOP trial) causes greater human FEF activation than the generation of a saccade on no-stop signal, or GO, trials (Curtis *et al.*, 2005). Again, the increased activation likely reflects the co-activation of saccade and fixation neurons on STOP trials.

An important implication of these data is that the inhibition of an unwanted action emerges or is the consequence of the competition between different potential responses. Therefore, inhibitory control like voluntary control more generally may be best modeled as the process by which we select the best response among all competing responses, including not responding at all. At least at the level of premotor structures, a mechanism specialized for inhibiting actions, *per se*, does not seem necessary for the behavioral expression of inhibiting an unwanted action.

Functional MRI studies consistently activate the inferior frontal gyrus (IFG) in ventral premotor cortex during tasks that require inhibiting a manual button press (Aron *et al.*, 2004). For instance, during Go/No-Go task performance, IFG activity time-locked to No-Go trials is higher than activity time-locked to Go trials in both humans (Garavan *et al.*, 1999; Konishi *et al.*, 1999; Konishi *et al.*, 1998; Liddle *et al.*, 2001) and monkeys (Morita *et al.*, 2004) (Figure 7a & 7c). This activation is thought to reflect some process related to inhibiting the unwanted motor response. In addition, activity in right IFG is greater on STOP trials compared to GO trials during a manual version of the stop-signal task (Figure 7b) (Aron & Poldrack, 2006). This difference is greater in individuals with faster SSRTs, perhaps suggesting that the larger activation difference reflects more efficient inhibitory control. Moreover, damage to the right IFG in humans impairs one's ability to inhibit responding and lengthens the SSRT (i.e., the time needed to inhibit a planned action) (Aron *et al.*, 2003). In summary, it appears that the IFG

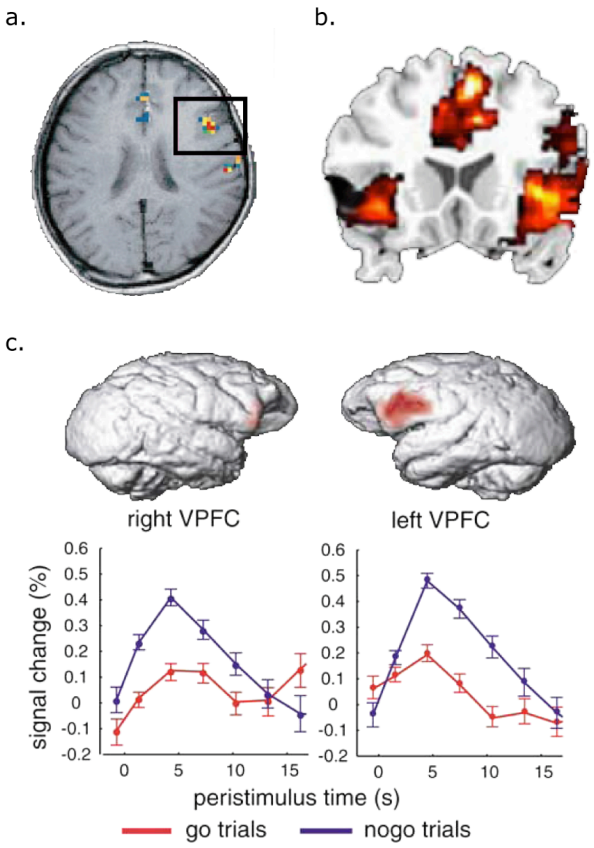


Figure 7. Functional magnetic resonance imaging of Go/No-go task performance. a. Subtracting activation during No-go performance from Go performance yields activation in right inferior frontal gyrus (Konishi et al., 1998). b. Subtracting activation during STOP from GO trials on a stop-signal task yields activation that is greater in right compared to left inferior frontal gyrus (Aron & Poldrack, 2006). c. A homologous frontal cortical area in the monkey has recently been identified with fMRI (Morita et al., 2004). Although a bilateral response is found, it is larger in the left hemisphere, contralateral to the hand used for responding.

is critically involved in the inhibition of unwanted manual motor responses just as the FEF is involved in suppressing eye movements.

However, the precise mechanisms reflected by IFG activity to support inhibitory control over manual motor responses needs several lines of clarification. First, most of the human studies find that IFG activity is right lateralized. Given that ventral premotor cortex, as well as all other motor systems, has a strong contraversive organization (i.e., neurons in one hemisphere largely code for movements towards the opposite side of space or movements made with limbs on the opposite side of the body), one would predict that activation should be greater in the hemisphere contralateral to the hand that is used for the response. With this assumption one would predict that the left IFG should be more active when canceling movements with the right hand, which is the hand that most of the studies have used for responding. Therefore, the right lateralization of the IFG activation does not concur with what we know about the functional organization of the motor system. To date, there is not a clear explanation for why the activations are right lateralized other than the speculation that inhibitory control may be right lateralized just as language is left lateralized. Another intriguing possibility is that that the right lateralization may be related to the lateralized bias of attention. For instance, the clinical syndrome of unilateral spatial neglect (Heilman Neuropsych book) and numerous human functional imaging studies of spatial attention (Corbetta & Shulman, 2002) have found that the right hemisphere is dominant for selective attentional processes. For example, in the neglect syndrome, after right hemisphere lesions, patients fail to attend, look at and respond to stimuli located on the left side of space. Possibly more pertinent for the current discussion, it has been proposed that some neglect patients have a premotor "intentional" deficit (Coslett *et al.*, 1990; Heilman & Valenstein, 1998). In other words, impairment exists within an intentional system, which serves to select among many locations in which to act. These patients have a disinclination to initiate movements or move towards or into contralateral hemispace. Thus, it is possible that the right IFG that is engaged during response inhibition tasks is part of this intentional motor system, and in this way, inhibition of a motor response may be a special form of disengaging attention, or in this case, disengaging *intention*.

Second, it has been proposed that the right IFG is a cortical region that is involved in inhibiting actions irrespective of the response effector (e.g., hand, eye, voice), a general "cognitive brake" of sorts (Aron et al., 2004). It has even been suggested that the right IFG may be involved in inhibiting non-motor responses, such as emotional responses (Lieberman *et al.*, 2005). However, not all inhibition tasks evoke activity in the right (or left) IFG. Inhibiting eye movements, as compared to manual movements, do not typically evoke activity in right IFG (Ford *et al.*, 2005). Additionally, it remains unclear, in terms of neural circuitry, how neurons in the right IFG would exert their influence in the control of all types movements. There is a paucity of electrophysiological recordings of neurons in ventral premotor cortex during motor inhibition tasks, which leaves open the possibility that the activations reported in IFG may not be directly related to inhibition. They could be related to the emotional *sequelae* of inhibiting a prepotent response or the conscious

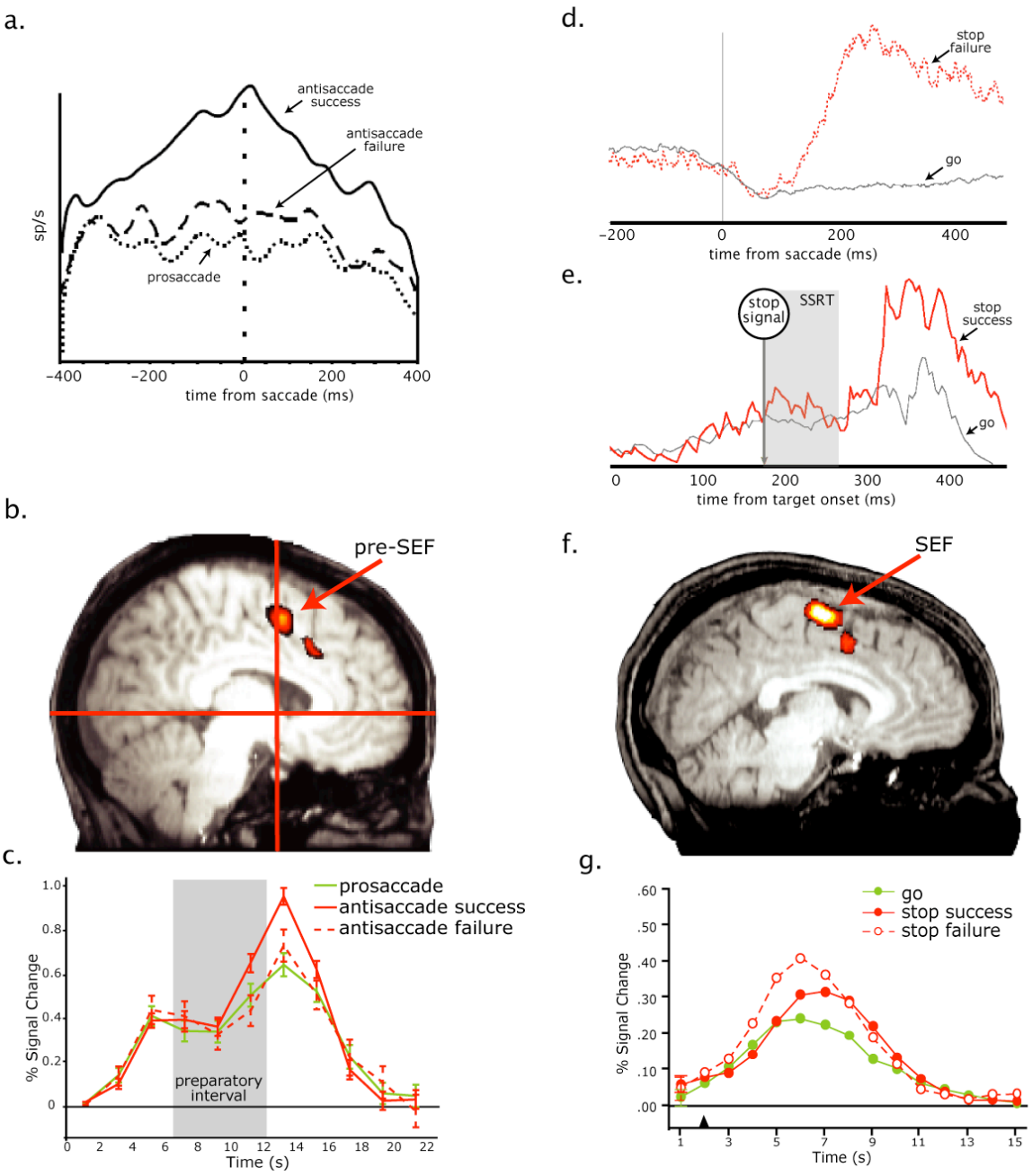


Figure 8. Performance monitoring in the SEF. a. The firing rate of SEF neurons is greater prior to antisaccades than prosaccades and antisaccade failures (Schlag-Rey et al., 1997). a. and b. Activity in an area just anterior to the human SEF shows greater activity just prior to antisaccades compared to prosaccades and antisaccade failures (Curtis & D'Esposito, 2003). d. Some monkey SEF neurons show a burst of activity following errors on STOP trials of a stop-signal task and e. some show a burst of activity following successfully cancelled STOP trials (Stuphorn et al., 2000). f. and g. Similarly in humans, the SEF shows increased activation related to success and failures of inhibition (Curtis et al., 2005).

awareness of the conflicting responses. For example, one might experience an emotional reaction when attempting to inhibit an unwanted response when the chances of task failure are high. Similarly, the simple conscious awareness of conflicting motor plans, even without an emotional reaction, could also invoke

neural activity in the IFG (Nieuwenhuis *et al.*, 2001). In any case, whether or not the hypothesis that the right IFG is an area specialized for general inhibitory control is correct, more research is needed in this area. Specifically, the response effector and types of inhibition tasks should be systematically manipulated.

Two other important components of tasks that require inhibitory control are the need to detect conflicting motor responses and the ability to monitor performance so that strategic adjustments can be implemented to optimize behavior. There is clear evidence that animals adjust their behavior following errors and even after successfully avoiding an error, say on an antisaccade trial (Fecteau & Munoz, 2003; Gratton, 1992; Rabbitt, 1966). In the oculomotor system, motor regions along the medial frontal wall have been associated with both error detection and conflict monitoring (Botvinick *et al.*, 2004; Schall *et al.*, 2002). Thus, neurons in the supplementary eye field (SEF) have an increased rate of firing prior antisaccades compared to prosaccades (Figure 8a) (Schlag-Rey *et al.*, 1997). This difference can be seen several hundreds of milliseconds before the saccade is generated, essentially as soon as the instructional cue is given as the animal prepares for the appearance of the stimulus and contingent response. We have demonstrated an identical pattern in humans, where voxels near the SEF begin to ramp-up during the preparation interval when the subjects know only that the trial is an antisaccade trial (Figures 8b & 8c) (Curtis & D'Esposito, 2003). Moreover, the amount of activity in the preparation interval predicts how successful the subject will be in subsequently inhibiting the reflexive saccade to the visual target. In both monkeys and humans, activity in the SEF was much lower on trials in which the subject failed to inhibit the unwanted glance. In fact, the preparatory activity is on par with the amount of activity during trials in which inhibition is not required (Curtis & D'Esposito, 2003; Schlag-Rey et al., 1997). Therefore, neurons in the SEF may somehow anticipate that conflict between the reflexive response to the visual target's location and the controlled need to maintain fixation until the antisaccade can be computed and generated. An output signal from the SEF may bias other nodes in the oculomotor network making it less likely that the system is reactive to external visual inputs. For example, SEF projections to the FEF may increase the firing rate of fixation neurons or decrease the firing rate of saccade neurons making it less likely that an error will be produced when the target appears.

Additionally, there must be a mechanism or set of mechanisms that allow animals to monitor their performance such that strategic changes can be implemented. Detecting the production of errors is necessary for one to make adaptive changes in future behavior. Neurons in the SEF show a pattern of activity during stop-signal tasks that suggest that they may play an important role in monitoring performance. Some SEF neurons show a burst of activity following errors on STOP trials (Figure 8d) and some show a burst of activity following successfully cancelled STOP trials (Figure 8e) (Stuphorn *et al.*, 2000). Note that the onset of the activity is after the SSRT so these signals are too late to be critically involved in the act of inhibition. Instead, they signal how successful or not the animal is performing the required task. Moreover, activity in the human SEF is greater for both successful and unsuccessful STOP trials compared to GO trials (Figure 8f and 8g) (Curtis et al., 2005) suggesting that the human SEF

contains the requisite signals for monitoring performance that could be used in feedback learning. Presumably, these signals cause changes in the oculomotor system by biasing the activity of saccade and fixation neurons on the upcoming trials. In sum, during oculomotor tasks that require inhibiting unwanted saccades, neurons in frontal areas along the medial wall, like the SEF, may contain signals that can be used to optimize performance. These include increased activity when one anticipates and prepares for conflicting oculomotor responses and activity that signals both successes and failures inhibiting the unwanted responses.

CONCLUSIONS

Goal-directed behavior involves the engagement of a wide array of cognitive processes that allow us to bridge the gap between the processing of incoming sensory input and the execution of actions adaptively suited to the current environment. Achieving our goals requires higher-level influences over sensory input, internal states, and motor output. By exerting influence over these domains, humans have evolved increasingly more sophisticated control over interactions with both the natural world and each other. This control permits the goal-directed override of primitive and inflexible reactions to environmental stimuli as occurs in other animals, what Mesulam refers to as the "default mode" (Mesulam, 2002). In this chapter, we have reviewed the potential neural mechanisms mediating the voluntary control of an action, which is necessary when an optimal motor response is uncertain or when a competing motor response must be overcome. Determining the mechanisms of such control may lead to greater insight regarding more general control mechanisms. The empirical findings we reviewed in this chapter support the notion that the inhibition of actions is best modeled as the process by which we select the best response among the competing responses, including not responding at all.

The empirical evidence we have reviewed derives from both human non-human primate research, using electrophysiological and functional neuroimaging methods. It is important to note the tremendous value of using both approaches for gaining an understanding of brain-behavior relationships. Since both types of research have particular strengths as well as limitations, neither approach is ideal in isolation. Rather, the data derived from each is complimentary, convergent and the sum is greater than its parts. For example, single-unit recording in awake behaving monkeys has the temporal and spatial resolution that cannot be achieved by functional neuroimaging methods in humans. However, human imaging methods provides whole brain recording allowing for investigations of an entire neural circuit and its interactions.

In this chapter, we emphasized studies of the oculomotor system, which serves as an excellent model for studying the neural mechanisms underlying our ability to inhibit unwanted actions. When we intend to move our eyes, there is competition between FEF gaze-holding and gaze-shifting mechanisms that will determine whether an eye movement occurs. Withholding of an action, such as an eye movement, can obviously be exerted at any point along the series of processes that evolve over time from sensation to action. Overall, the activity pattern of FEF saccade and fixation neurons corresponds very well with the hypothetical GO and

STOP processes of the race model derived from behavioral studies. In this model, the outcome of the race between saccade and fixation neurons determines whether or not a saccade is generated. Also, this mechanism seems to be initiated before the actual action, which likely serves as a preparatory set that primes the oculomotor system towards a gaze holding or shifting state. Another node of the oculomotor curcuit, the SEF, appears critically involved in detecting conflicting motor responses and monitoring performance so that strategic adjustments can be implemented to optimize behavior.

There are two important implications of these empirical data. First, inhibition of an unwanted action emerges or is the consequence of the competition between different potential responses, and is not due to an "inhibitory" signal *per se*. This idea is similar to that put forth by other investigators studying other domains of cognition such as language (Thompson-Schill *et al.*, 1997; Thompson-Schill *et al.*, 1998). For example, in a verb-generation task, the need to overcome a prepotent response may occur when choosing one associated verb for a given noun from among competing alternatives. That is, some nouns (e.g. 'cat') have many weakly associated verbs whereas others (e.g. 'scissors') have only a few strongly associated verbs ("cut"). In a human fMRI study, Thompson-Schill and colleagues found that generating verbs to nouns with many possible responses (as in the case of 'cat') was associated with increased left ventral PFC activity. Interestingly, this region is homologous to that activated in the right hemisphere during the response inhibition tasks discussed in this chapter. Furthermore, patients with damage to this region were impaired at retrieving verbs only under conditions of increased competition. These findings were interpreted in the context of the demands for the selection of information among competing alternatives. Kimberg and Farah have put forth a similar idea (Kimberg & Farah, 1993), implemented as a computation model, demonstrating that tasks such as the Stroop tasks can be successfully performed without an "inhibitory" module in their model. Rather, correct response are achieved by a module (presumably in the PFC) that mediates the selection of an action by the weighting of information active in working memory. Thus, at least at the level of premotor structures such as the FEF and SEF, and possibly at the level of the PFC, a mechanism specialized for inhibiting actions, *per se*, does not seem necessary for the behavioral expression of inhibiting an unwanted action.

A second implication that arises from our review is that it is unlikely that there is a single area of the brain is specialized for the computations necessary for *withholding all unwanted actions*. As we have discussed regarding the oculomotor system, selecting an appropriate eye movement for the task at hand requires the interplay between different premotor structures such as the FEF and SEF, and is also likely under the control of higher level regions such as the PFC. Moreover, it is likely that different neural circuitry is required for withholding other type of output modalities such as speech and manual responses.

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