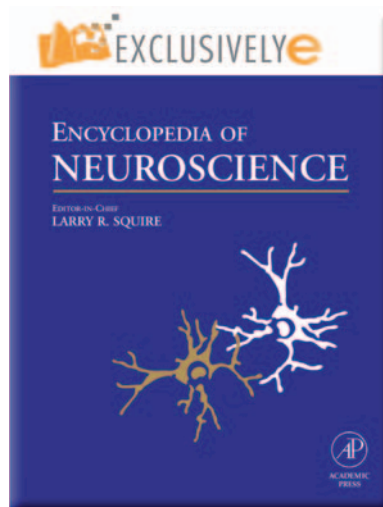


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Inhibitory Control over Action and Memory

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Functions of Inhibitory Control

The ability to suppress strong habitual (prepotent) responses supports at least two broad computational functions necessary for the effective control of behavior: selection and stopping. Selection refers to the act of isolating one representation among competitors vying for the control of behavior or thought. Selection is necessary at all stages of cognitive activity. In memory, selection must occur to retrieve a target memory trace in the face of many competing memories activated by the cues guiding retrieval. In action, a stimulus may initiate multiple compatible physical actions, only one of which should guide behavior. Stopping refers to the need to either preempt or override a mental or physical activity that is inappropriate in a certain context or that, in the course of execution, has become undesirable. For instance, reflexively reaching to catch a falling object might be abruptly stopped when it is realized that the falling object is a hot pan or a potted cactus. The general models of both functions are depicted in [Figures 1\(a\) and 1\(b\)](#).

In both selection and stopping, the ability to limit the influence of unwanted representations is mediated by a top-down control process acting directly or indirectly on this entity, rendering it temporarily less accessible. In this article, we refer to the brain structure originating the top-down control signal as the source of the inhibitory control and the area representing the to-be-controlled representation or process as the site of inhibition. Broadly, research indicates regions in the lateral prefrontal cortex (either the ventrolateral prefrontal cortex (VLPFC), Brodmann's area 44/45, or the dorsolateral prefrontal cortex (DLPFC), Brodmann's area 9/46) as likely candidates for the source of control, whereas differing cortical and subcortical targets constitute control sites, depending on the content to be controlled.

Paradigms Used to Study Inhibitory Control

Behavioral paradigms used in research with human subjects have taken two approaches to measuring inhibitory control. Many studies measure subjects' ability to implement control by quantifying the accuracy or speed with which selection or stopping is achieved. This approach provides a straightforward

measure of behavioral control. Other studies, however, focus on the aftereffects of selection or stopping on the stopped representations. If a response is suppressed, there should be measurable consequences on the ability to subsequently access the representation, reflecting persisting inhibition. For instance, if a motor action is inhibited, people should be slower to emit that same response later, or if a memory has been inhibited, it should become more difficult to retrieve. Methods that measure the inhibitory aftereffects of response override have the advantage of not presupposing inhibition as the mechanism. For example, although inhibition may be engaged to stop a motor action, stopping may instead be achieved by facilitating an antagonistic response that precludes the execution of the to-be-stopped action. Measures based on the first approach cannot conclusively confirm that inhibition is involved in stopping the rejected representation. Examples of both methods are discussed here.

Inhibitory Control of Action

Inhibitory control of actions has been studied in the contexts of selection and stopping, and it is typically measured with functionally oriented tasks. The use of these paradigms, accompanied by various imaging and electrophysiological techniques has established that inhibitory control engages the lateral prefrontal cortex (LPFC). Further, inhibitory control depends on the integrity of this region, as revealed by studies of patients with LPFC damage, studies using transcranial magnetic stimulation (TMS), and lesions in non-human primates.

Inhibitory Control in Selective Responding

A variety of paradigms have focused on the role of inhibitory control in selecting one response in the face of interference from prepotent competitors. One approach used to investigate response selection across a variety of stimulus modalities and response types is to manipulate the compatibility of perceived stimuli and their associated responses. Tasks measuring stimulus–response (S–R) compatibility effects have two conditions: (1) trials in which S–R mappings (i.e., associations) are compatible and exploit innate biases, and (2) trials characterized by incompatible S–R mappings which require that the tendency to make the natural response be overcome and the task-appropriate response selected. For example, subjects might see an arrow in the center of a screen pointing left or right and be required to indicate

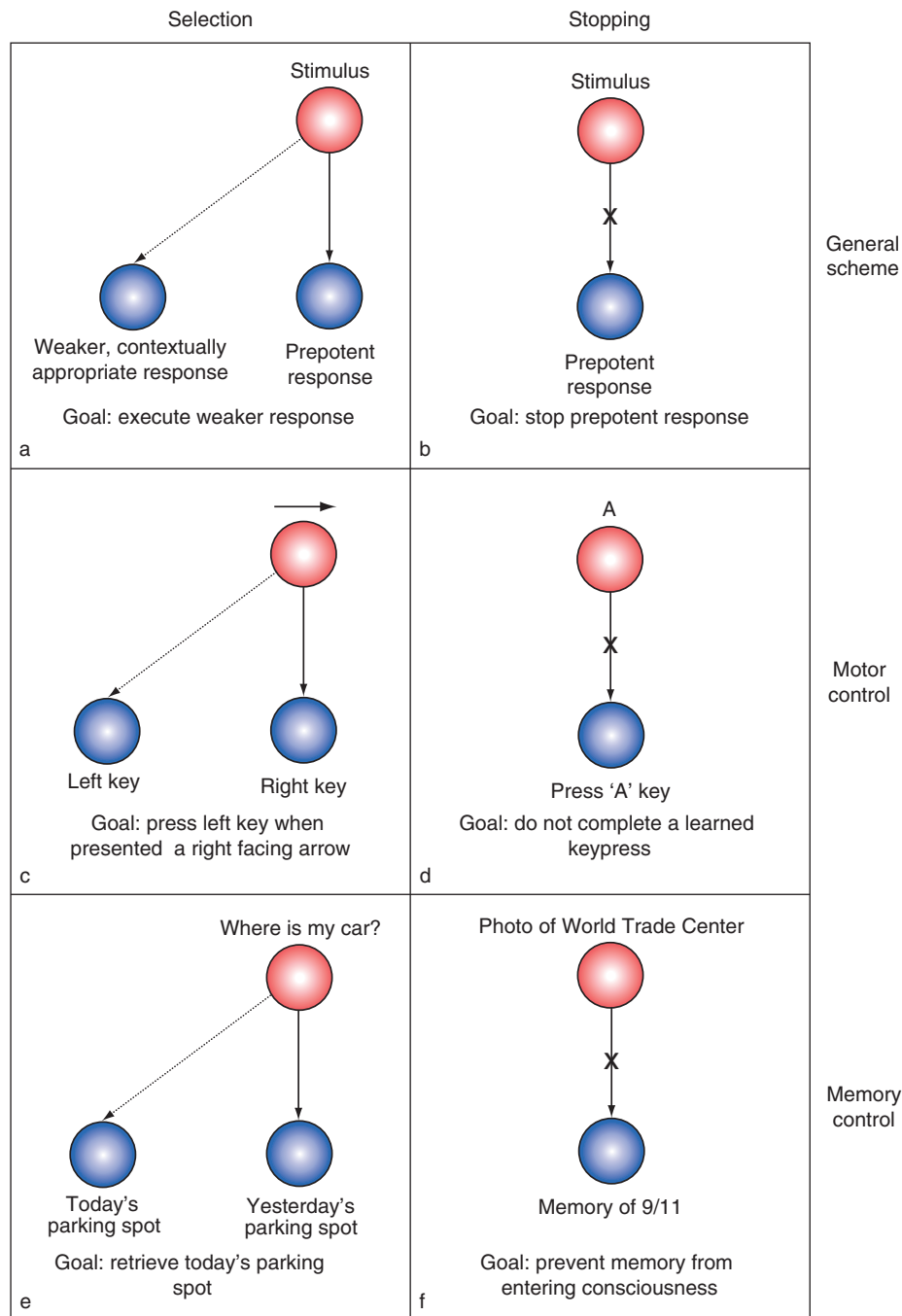


Figure 1 Two situations that require response override in human action and thought and commonly used paradigms: (a) selection; (b) stopping; (c) S–R compatibility paradigm; (d) stop-signal paradigm; (e) selection to inhibit the interference of a memory; (f) stopping the retrieval of a memory. The top row represents a schematization of these two situations. In each instance, a stimulus is associated with one or more responses, such that when the stimulus appears, the responses become active in proportion to their associative connection to the cue (represented by thickness of the line). In selection (a), the weaker response must be made, despite the existence of a strong competitor that becomes more active and threatens to capture control of behavior. In stopping (b), there is only one response, but it must be prevented. As shown in (c), sometimes the prepotent action is not the correct response, and a nondominant movement must instead be made (e.g., S–R compatibility and antisaccade tasks). As shown in (d), if no alternative response is warranted, the movement can simply be canceled (e.g., go/no-go, stop-signal, and countermanding saccade tasks). As shown in (e), sometimes inhibition must be initiated to selectively retrieve a memory with a weaker association to a cue that is shared by another trace (e.g., retrieving today's parking spot and suffering interference from the memory of yesterday's; RIF). In other circumstances (f), confronting a cue may activate an unwanted memory, leading the person to stop retrieval. For instance, when the sight of the World Trade Center initiates retrieval of the memory of the events of 9/11, retrieval might be stopped. This process can be assayed by TNT tasks. RIF, retrieval-induced forgetting; S–R, stimulus–response; TNT, think/no-think.

which direction the arrow is pointing by pressing one of two keys. If the instructions require subjects to press a key with their left hand in response to left-pointing arrows and a key with their right hand in response to right-pointing arrows, the S–R mappings are compatible. If, however, subjects must press a key with their right hand in response to a left-pointing arrow (doing the converse for the right-pointing arrow), the S–R mappings are incompatible. In a nonspatial variant, subjects are presented two consecutive color patches and asked to judge and report whether they are the same or different. In the incompatible mapping condition, subjects are instructed to say ‘same’ when the colors actually differ. The response selection requirement of such tasks is illustrated in [Figure 1\(c\)](#). The reduced accuracy and increased reaction time (RT) of stimulus-incompatible responses are the measurable costs of resolving the interference created by the prepotent compatible response.

Human imaging work suggests that the LPFC contributes to the resolution of this interference. Response selection appears to be subserved by both the DLPFC and VLPFC, together with a network of regions often observed in attentional control tasks, including the superior parietal cortex, anterior cingulate cortex (ACC), and lateral premotor cortex. A number of imaging studies have sought to differentiate the contributions of these areas, and converging evidence from S–R compatibility and other response selection designs is consistent with the view that the ACC contributes to the detection of response conflict, signaling the need for greater top-down control to the LPFC. In contrast, the LPFC – specifically, BA46 within the DLPFC – is thought to be instrumental in achieving response selection. Consistent with this, lesions and TMS of the human DLPFC compromise response selection. Intriguingly, cellular and neuroimaging studies in nonhuman primates emphasize the VLPFC over the DLPFC as the principal source of response selection. There is also conflicting evidence for the generality of response selection. Considerable behavioral evidence from dual-task interference indicates that response selection constitutes a central processing bottleneck spanning varied stimulus and response modalities. These findings are corroborated by neuroimaging findings that reveal overlapping neural activation across many stimulus and response demands. However, response selection appears in some situations to be lateralized according to stimulus characteristics, with spatial tasks associated with increased activation in the right hemisphere and nonspatial stimuli causing left lateralized activations. Thus, it is unclear whether response selection is a unitary process across all input and output

modalities, although most research points to the importance of the LPC in achieving this function.

Inhibitory control over motor action has also been studied in the context of oculomotor response selection. In human subjects, saccade termination similarly appears dependent on the DLPFC. In oculomotor inhibition paradigms, subjects intentionally try to override a reflexive foveal orientation to a stimulus, and the number of failed suppressions is measured. For example, in antisaccade tasks, subjects are instructed to look away from visual targets when they abruptly appear instead of toward them. This requires the inhibition of the visually triggered saccade that ordinarily orients subjects’ eyes to the onset stimulus. Although the DLPFC is not necessary to execute accurate saccades, numerous lesion studies show that damage to this area, and to BA46 in particular, markedly increases antisaccade errors, suggesting its importance in their cancellation. Similar patterns of errors have been reported in nonhuman primates following lesions of the DLPFC homolog (dorsal bank of the principal sulcus). Further, substantial neurophysiological work done in nonhuman primates has identified neurons within the DLPFC and frontal eye field (FEF) that show preferential activity during antisaccade trials. In human neuroimaging studies, increased activation for antisaccade trials has been found bilaterally in the DLPFC. Based on these findings, the DLPFC is believed to originate a top-down signal that acts on the FEF and possibly the superior colliculus (SC), which serve as the sites of the inhibition.

Taken together, research from these paradigms and others, including task-set switching, Stroop, and flanker tasks, consistently implicate the LPFC in implementing the top-down signal by which prepotent responses are suppressed to achieve selective motor response. Additional work is required to ascertain the relative involvement of the DLPFC and VLPFC, their respective roles, and the extent to which response selection is general or lateralized by content.

Inhibitory Control in Motor Stopping

Intended actions can be stopped, and some cognitive process must support this function, perhaps inhibition. To study stopping, many paradigms ask subjects to occasionally prevent a response they have been trained to complete, and then they measure the effectiveness or efficiency with which this is done. In the go/no-go (GNG) task, participants are presented with a stimulus to which they must make a motor response. On a minority of trials, a special no-go stimulus is presented, for which subjects must prevent their response. For example, people might be

presented with a series of letters on a screen. For every letter, they might be asked to press the same key as quickly as possible, unless they see the letter X, for which they must withhold their response. The percentage of no-go trials successfully withheld is a metric of inhibitory control ability. Another approach used to study motor stopping is the stop-signal paradigm developed by Gordon Logan, illustrated in [Figure 1\(d\)](#). In this paradigm, subjects typically perform a simple perceptual discrimination (e.g., deciding whether a letter is X or O), to which they must make a motor response (e.g., pressing the key corresponding to X or O) as quickly as possible. On a minority of the trials, a stop signal (typically a tone, but visual and tactile signals are sometimes used) occurs at some point after the stimulus, indicating that subjects should withhold their motor response (commonly a key press, although hand, arm, and eye movements; verbalization; and hand squeezes have been used). Over trials, the delay between the appearance of the stimulus and the stop signal is modulated by a dynamic tracking algorithm that adjusts the stop-signal delay (making it longer or shorter, depending on subjects' accuracy) until stopping performance is at chance. Using the average go trial RT and the average stop-signal delay latency required for an equal probability of successful and failed inhibition, the stop-signal RT (SSRT) can be computed. The SSRT, which is approximately 200 ms for manual responses, quantifies the speed of the stopping process itself and is commonly used as a measure of inhibitory control ability. Stop signal and GNG paradigms have been used to study inhibitory control across the life span, in neuropsychological patients, and as a way to study the neural basis of inhibitory control in nonhuman subjects such as monkeys and rats.

Considerable evidence from motor-stopping paradigms indicates that response inhibition is mediated by the VLPFC and DLPFC, with a right lateralization tendency, at least in humans. For example, work by Aron and colleagues showed that, in patients with damage to the right VLPFC or DLPFC (and not the left), SSRT is significantly slowed and the degree of slowing is correlated with the lesion volume. Work with a variety of other techniques yielded similar conclusions. For example, TMS over the right VLPFC disrupts motor stopping in human subjects, and lesions to a VLPFC homolog (the inferior frontal convexity) in nonhuman primates disrupts performance on GNG tasks. Electrophysiological studies in nonhuman primates have demonstrated a no-go potential originating in the dorsal bank of the principal sulcus (homologous to the DLPFC in humans) and in the rostroventral corner of the PFC (see [Figure 2](#)). The no-go potential is an electrical signature of the

behavioral no-go response. Strikingly, when stimulation is applied during go trials in which the monkey should respond, the response is cancelled or delayed, concomitant with reduced electrical activity in the motor cortex. The strength of the suppressive effect depends on the stimulation timing, with the maximal suppressive effect observed when the no-go potential would have peaked (75–125 ms), and occurs exclusively in the regions of the PFC in which the no-go potential is generated. As might be predicted from the foregoing findings, response inhibition activates the DLPFC and VLPFC in neuroimaging studies, very often right laterally, although sometimes bilaterally, and frequently accompanied by a network of areas implicated in attentional control. Further, direct comparisons of the neural correlates of three inhibitory tasks (the GNG and two response selection tasks, a S-R compatibility task and a flanker task) within-subjects revealed the DLPFC to be a region activated by these distinct cognitive control tests. Taken as a whole, these findings indicate that both the DLPFC and VLPFC contribute to a top-down signal for inhibiting prepotent motor responses, although some investigators have emphasized the primacy of the right VLPFC.

Although the lateral PFC appears to be the source of a top-down signal that suppresses prepotent motor responses, the site of action, and the circuit through which that site is influenced depends on the nature of the response. In the case of manual motor responses, stopping activates the expected control areas of the VLPFC and dorsomedial PFC, and the regions on which that control is exerted within the motor system. Subcortically, the control of movement within the basal ganglia is conceptualized using the brake-accelerator model. The accelerator is the direct pathway in which the cortex acts on the striatum and internal pallidum, increasing the activation of the motor cortex by the thalamus. Braking is accomplished by the same structures with the critical addition of the subthalamic nucleus (STN), which indirectly inhibits the thalamus and hence the motor cortex. Recent work suggests that a faster inhibitory mechanism, the cortico-subthalamo-pallidal hyper-direct pathway, may be contributing to response stopping. In this conception, the VLPFC interprets the stop signal and (circumventing the striatum) increases the activation of the STN, and thus the internal pallidum, resulting in the inhibition of the thalamus and, consequently, the motor cortex. Consistent with this possibility, a recent stop-signal neuroimaging study conducted by Aron and Poldrack revealed that the amount of activation in the STN (and not the striatum) predicted SSRT. Thus, in the case of manual motor response inhibition, the VLPFC may control action by exciting structures that inhibit motor cortex.

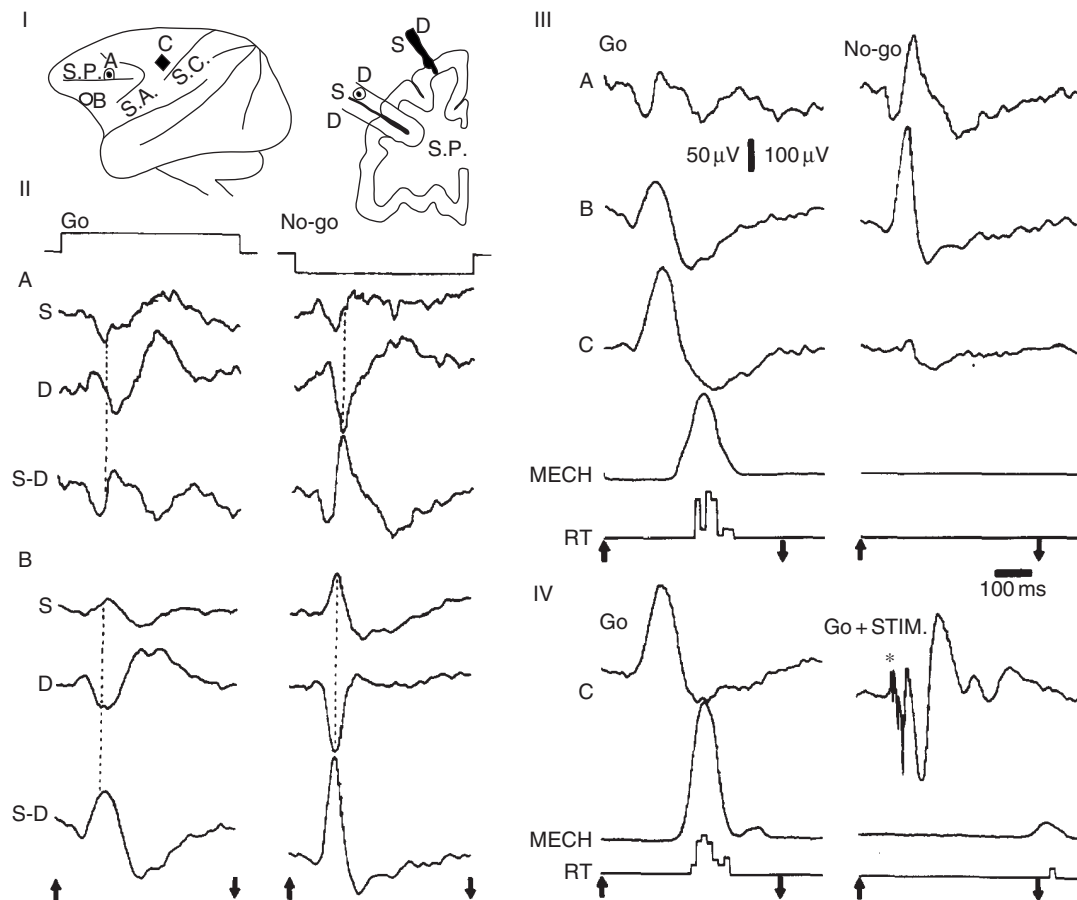


Figure 2 Stimulation of the DLPFC and VLPFC homologs suppresses motor responses in nonhuman primates. Monkeys were rewarded for completing manual responses to a light stimulus and learned to respond accurately. Responses to another light stimulus were unrewarded, and the monkeys learned to withhold their responses. No-go activity coincides with no-go behavior and is characterized by surface-negative, depth-positive field potentials generated 110–150 ms after presentation of the visual stimulus. Emergence of no-go potential is contingent on learned discrimination of light stimuli. Moreover, stimulation of specific lateral PFC loci induces no-go behavior. (I) Lateral (left hemisphere) and coronal (right hemisphere) views of the frontal lobe illustrate electrode localization. Surface (S) and depth (D) electrodes were placed in the monkey homologs of the DLPFC (dorsal bank of the principal sulcus; A, open circle with central dot), VLPFC (rostroventral corner of the prefrontal cortex; B, open circle), and forelimb area of the motor cortex contralateral to responding hand (C, filled diamond). (II) Field potentials consistent with no-go potential at S and D electrodes and S-D at prefrontal loci A and B during go (left column) and no-go (right column) trials for a single monkey. (III) S-D field potential data for each of the three recording regions across both conditions; A, B, and C in go (left column) and no-go trials (right column). Specificity of no-go potentials to regions A and B, illustrated by lack of potential in area C. In addition to field potentials, movement (as measured by mechanogram (MECH)), and reaction times (RT) are also reported for each condition. (V) Presentation of go stimulus produces typical field potentials, movement, and reaction times, whereas the go stimulus coupled with bilateral stimulation of areas A and B prevented response, as is typical of no-go trials (compare to III). Arrows indicate onset and offset of visual stimulus. DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; S.A., sulcus arcuatus; S.C., sulcus centralis; S.P., sulcus principalis; VLPFC, ventrolateral prefrontal cortex. Reproduced from [Sasaki K, Gemba H, and Tsujimoto T \(1989\)](#) Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. *Brain Research* 495(1): 100–107, with permission from Elsevier.

Suppressing unwanted eye movements, like suppressing manual responses, engages the LPFC, and in particular the DLPFC, as noted in the discussion of antisaccade research. The site acted on by LPFC, however, is different than in the case of manual responses. For instance, research on the cellular dynamics of motor inhibition with nonhuman primates points to the importance of the FEF. An adaptation of the stop-signal paradigm, called the countermanding saccade task, is often used. The monkeys learn a saccade

RT task and are subsequently trained to stop their saccadic eye movements whenever an infrequent stop signal is administered. Thus, the performance of this task requires two processes: (1) initiation of the intended saccades and (2) revocation of the to-be-cancelled saccade. Both of these processes are believed to be supported by the FEF, although movement cancellation is also supported by the SC and the supplementary eye fields. In particular, within the FEF and SC, movement neurons drive go processes,

whereas fixation neurons are implicated in stop processes. Whether a saccade is executed or not depends on the relative activity of these types of neurons. Increasing activation and the rate of that increase in movement neurons are predictive of commitment to saccade initiation and the timing of the initiation, respectively. In contrast, fixation neurons demonstrate activity that is reciprocal to that of movement neurons; their activity is gradually reduced before saccade initiation and increases with saccade suppression. Thus, movement and fixation neurons implement saccade initiation and termination in the FEF. Together with the work on antisaccade performance in human subjects, this suggests that inhibitory control of eye movements is implemented by an interaction between the DLPFC and regions of the FEF involved in initiating and canceling eye movement responses.

Thus, whereas the source of inhibitory control in LPFC may well be shared across different motor-stopping tasks, the site of action depends on the effector system being controlled. Next we discuss evidence indicating that this principle is not limited to the control of physical actions but also applies to the control of internal cognitive acts, such as long-term memory retrieval.

Inhibitory Control in Long-Term Memory

Inhibitory control over memory retrieval provides a model system for the role of inhibitory control in cognition; it has also been studied in selection and stopping. Human behavioral studies have revealed that overcoming the influence of prepotent traces in long-term memory retrieval yields an inhibitory aftereffect such that suppressed traces are subsequently less accessible. Neurobiological research indicates that retrieval suppression, like motor stopping, engages the LPFC, which modulates the activation in the hippocampus and other medial temporal regions associated with memory and emotion. The similarities between the systems engaged by memory and action control suggest that the same or perhaps isomorphic computational solutions may exist for solving response-override problems for physical and cognitive actions.

Inhibitory Control in Selective Retrieval

One procedure that has been designed to study inhibitory control is known as the retrieval-practice paradigm, developed by Anderson and colleagues. In a typical version of this procedure, subjects encode six exemplars from each of eight taxonomic categories (e.g., fruits-orange, fruits-banana, and drinks-gin) in a study phase. Following the initial study, subjects perform directed retrieval practice on a subset of

exemplars from some of the studied categories (e.g., three of the six fruits) via category-plus-stem cued recall tests (e.g., fruit or ____). Subjects are then tested on all exemplars from all categories. On the final test, subjects can either be cued with the category name and asked to recall all studied exemplars or be given a recognition memory test on all items. Of interest are the effects of practicing some category exemplars on the ability to recall the remaining unpracticed exemplars of those categories. Repeatedly retrieving some exemplars of the category impairs the subjects' ability to recall the remaining unpracticed exemplars, relative to their performance on baseline categories that were also studied, but none of whose exemplars were retrieved in the interim. This effect, known as retrieval-induced forgetting (RIF) is thought to reflect the consequences of an inhibitory process that suppresses unpracticed competitors during retrieval practice, causing enduring impairment of those items on subsequent tests. RIF has been induced with verbal and visuospatial stimuli, and across levels of complexity ranging from simple word pairs to complex factual knowledge and even eyewitness events. RIF affects episodic, semantic, and implicit memory as measured by conceptual fluency and lexical decision. Further, RIF appears on tests of episodic recall and recognition memory. Thus, RIF may be an example of inhibitory control aiding in the function of selection during the retrieval process by suppressing interfering items during retrieval of a target. The selection requirements of RIF are illustrated in [Figure 1\(e\)](#).

RIF exhibits functional properties that firmly establish the involvement of an inhibitory control process that overcomes interference. First, it is retrieval-specific; repeated study of some associates of a cue does not impair the recall of related items, even when repeated retrieval of those same items does. Further, RIF is interference-dependent, with larger RIF effects observed for competitors that cause interference during retrieval, consistent with the view that inhibitory control is engaged to suppress interfering competitors. Finally, RIF is cue-independent; the impairment of a competing memory item generalizes to novel cues used to test the inhibited items, indicating a generalized reduction in the accessibility of the suppressed trace. Thus, in the domain of memory control, theoretically focused behavioral research based on inhibitory aftereffects has firmly established the involvement of inhibition.

A large body of work establishes the role of the VLPFC in selective retrieval of verbal semantic knowledge under conditions of interference. Moreover, patients with LPFC damage show heightened susceptibility to proactive interference in long-term episodic memory retrieval, as revealed in work by Shimamura

and colleagues. Nevertheless, only recently has work begun to tie the LPFC to inhibitory aftereffects measured in RIF. Consistent with executive control literature, the ACC appears central to the detection of conflict between competing memories associated with a cue, signaling the need for top-down control to resolve competition; in contrast, the VLPFC appears to initiate control processes that resolve that conflict through inhibition. These principles can be seen in a study by Kuhl and colleagues, who hypothesized that because RIF is a consequence of resolving interference from competing items during target retrieval, inhibited items should cause less interference on later retrievals of the target items. Indeed, more activation was observed in the bilateral VLPFC and right DLPFC during early than during late retrieval practice trials, and the more activation decreased over trials in the right VLPFC and ACC, the more memory inhibition was found. Moreover, subjects showing higher inhibition exhibited elevated activation in the ACC and hippocampus during early trials that gradually diminished with repeated retrievals; low-inhibition subjects did not show this pattern. Thus, subjects who experience the greatest initial competition between the medial-temporal representations of the target and competitors (as indexed by medial temporal lobe (MTL) and ACC co-activation) show the greatest engagement of control and, consequently, the greatest RIF.

Similar conclusions have been reached using other techniques, such as electrophysiology. For example, more positive going event-related potentials (ERPs) are observed over frontal electrode sites during selective retrieval of target items than in a passive practice condition with the same targets. The magnitude of this retrieval-specific ERP effect on the PFC predicts the amount of RIF observed on the final test. These findings indicate that some functional requirement uniquely associated with retrieval, such as the need to resolve competition, engages the PFC and induces RIF, as before. Mounting evidence points to the involvement of the LPFC in the induction of RIF and the importance of this process in achieving selective retrieval, echoing the role of inhibitory processes in selective motor responding.

Inhibitory Control in Retrieval Stopping

Another method used to study inhibitory control of memory is known as the think/no-think (TNT) procedure, developed by Anderson and colleagues. Modeled after the GNG task, TNT measures the inhibitory aftereffects of stopping memory retrieval. Subjects learn a collection of cue-target pairs, so that whenever they are presented with the cue, they can recollect its associated target item. Following

encoding, subjects participate in the TNT phase, during which a single cue item from one of the earlier pairs is presented on each trial. For some of these cues, the subjects are directed to think of the associated target memory and keep it in mind for as long as the cue is on the screen. For other cues, subjects are directed to not think about the associated target memory, keeping it out of mind for as long as the cue is on the screen. The latter no-think task requires that the subject override the retrieval process and prevent the associated declarative memory from entering awareness, despite the tendency for the cue to elicit that memory (see [Figure 1\(f\)](#) for an example of memorial stopping). Subjects are then tested on their memory for all cue-target pairs. In the typical design, one-third of the original pairs participate in the think trials in the TNT phase, one-third in the no-think trials, and one-third are reserved as baseline items against which to measure the effects of retrieval and retrieval suppression on later memory performance.

Repeatedly presenting participants with reminders of an event and asking them to stop retrieval of that event has several notable effects. First, it eliminates the normally beneficial effects of reminders in enhancing a memory's later accessibility, so that reminders can be presented over a dozen times with little apparent benefit in accessibility of the associated traces. Second, stopping retrieval very often impairs the ability to recall the associated trace, relative to other baseline cue-reminder pairs that were trained at the same time but that did not have their reminders presented in the interim during no-think or think trials. Thus, repeated exposure to reminders coupled with an effort to stop declarative memory retrieval impairs access to the associated trace. Third, the impairment of the excluded trace occurs even when that trace is tested with a novel cue, indicating a generalized impairment of the trace, consistent with the idea that the trace has been inhibited. Most of these effects have been observed with both verbal cue-target pairs and visual pairs such as face-scene pairs, and the effects appear to generalize to target items with emotional content. Thus, stopping unwanted retrievals appears to be effected in part by suppressing the associated memory, consistent with inhibitory control. As such, the TNT paradigm provides an example of the role of inhibitory control that is analogous to the GNG and stop-signal paradigms.

Neuroimaging studies have established several key findings about the neural systems involved in stopping long-term memory retrieval. First, as can be seen in [Figure 3](#), suppressing retrieval of an episodic memory in response to a reminder engages the LPFC, including the VLPFC and DLPFC, often bilaterally,

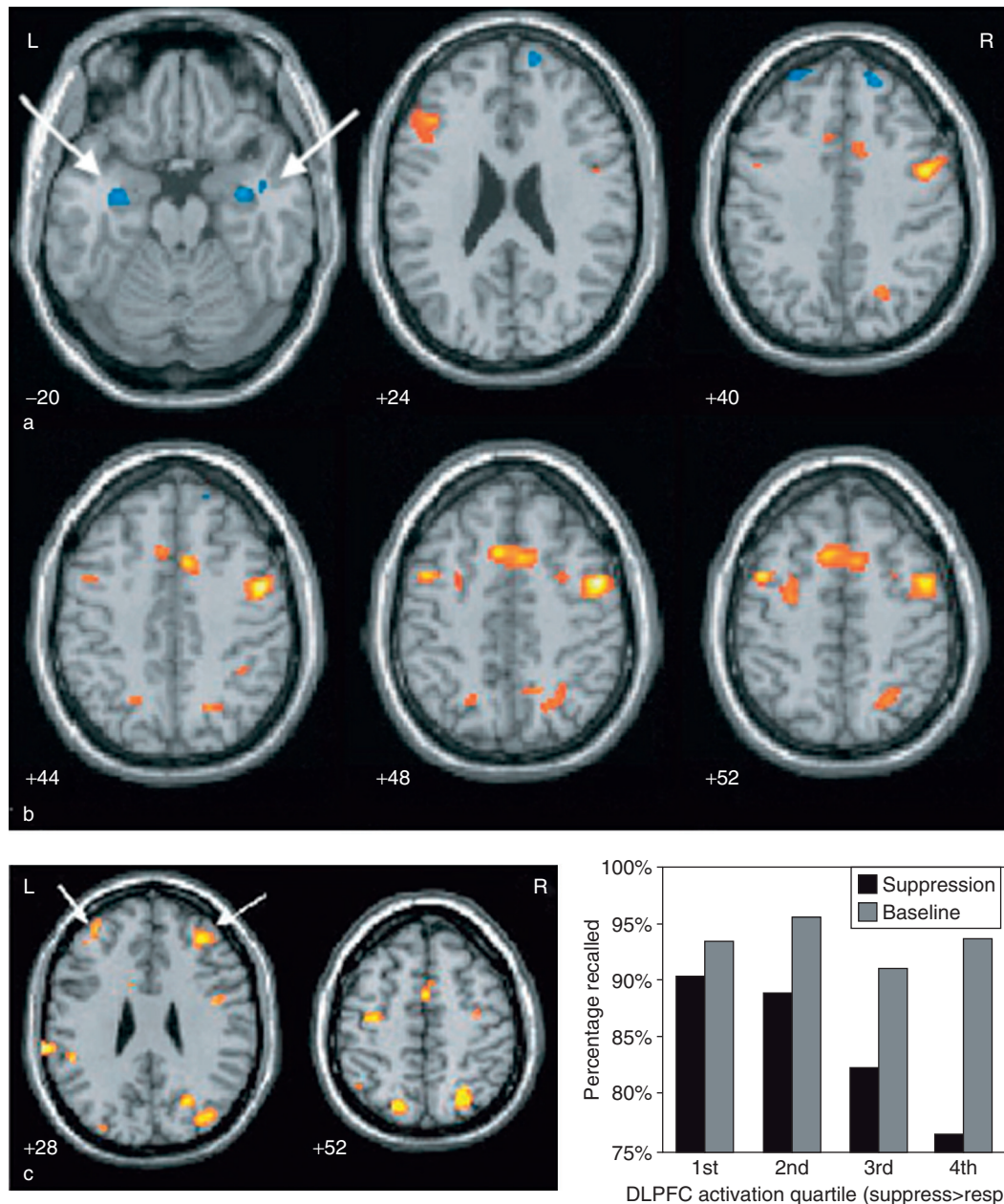


Figure 3 fMRI results during no-think trials and think trials: (a) brain regions that significantly differed in activation between the no-think trials and think trials during the TNT phase ($n = 24$); (b) successful recruitment of the DLPFC, which predicts individual differences in memory inhibition (the inhibitory aftereffect of stopping retrieval); (c) inhibitory aftereffects for four subject groups, differing in DLPFC activation. In (a), areas in yellow were more active during no-think trials than during think trials, whereas areas in blue were less active during no-think trials ($P < 0.001$). The white arrows highlight the reduced hippocampal activation in the no-think condition. In (b), plotted in warm colors are the regions that predict the magnitude of the inhibitory aftereffect observed on the final memory tests (the white arrows indicate the DLPFC; VLPFC was also observed in this study but not in a later study involving photographs). In (c), the greater the DLPFC activity shown by a subject group, the more impaired was the later recall of no-think items on the final test, compared to the recall of baseline items that were learned at the same time but that did not appear during the TNT phase. DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; TNT, think/no-think; VLPFC, ventrolateral prefrontal cortex. From Anderson MC, Ochsner KN, Kuhl B, et al. (2004) Neural systems underlying the suppression of unwanted memories. *Science* 303(5655): 232–235.

although sometimes with right lateralization. VLPFC engagement parallels the activations observed for RIF and for motor-response suppression, although the DLPFC appears to be more consistently engaged in retrieval stopping. Second, individual differences in

the engagement of the DLPFC (and sometimes the VLPFC) during suppression predict memory inhibition, with inhibition increasing with increasing activation, as might be expected if the DLPFC originated a top-down signal responsible for memory

impairment. Third, suppressing retrieval reduces activation in the hippocampus, compared to engaging retrieval, suggesting that inhibitory control modulates functional activity in structures involved in declarative memory. Recent work indicates that activation is reduced below the levels observed during passive fixation, with the extent of this reduction predicting memory failure. Finally, retrieval suppression engages the full network of regions associated with endogenous attention, including the lateral pre-motor cortex, ACC, and intraparietal sulcus, indicating common brain systems may support controlled attention during perception and memory tasks. With emotional memories, suppression also significantly reduces amygdalar activation, probably reflecting control over emotional aspects of the negative memories. Taken together, these findings indicate that functional interactions between the LPFC and MTLs support inhibitory control over memory retrieval.

As already discussed, imaging studies indicate that suppressing retrieval of an episodic memory significantly reduces activation in the hippocampus, compared to retrieval and a passive fixation baseline. The hippocampus has widely acknowledged involvement in episodic memory, and many studies indicate that it is also involved in the recollection of recently encoded events. As such, reduced hippocampal activation may reflect the successful control of conscious recollection by inhibitory control processes. Electrophysiological studies using the TNT procedure also support the conclusion that conscious recollection (as measured by an ERP component, the parietal old/new effect) may not merely be reduced, but may be eliminated by retrieval suppression. The extent of the modulation of this component predicts subsequent forgetting of no-think items, consistent with the view that regulating recollection induces later forgetting. Thus, both hemodynamic and electrophysiological measures converge on the conclusion that inhibitory control can be engaged to modulate the neural machinery responsible for generating episodic recollection.

The foregoing research illustrates the strong functional and neurobiological similarities between the control of action and memory. Both engage a common frontal region – the LPFC – to override the influence of unwanted neural activity in support of selection and stopping. What differs between motor and memory control (and, indeed, between different forms of motor control) appears to be the sites of control and, perhaps, the means of achieving that control (see the section titled ‘Neural architecture of inhibitory control’). The work on memory control adds the unique and theoretically significant contribution of showing that both selection and stopping induce inhibitory aftereffects on rejected representations, verifying and

quantifying the involvement of inhibition in achieving control. To the extent that memory control may be used as a model system for cognitive control, these findings suggest the existence of a domain general system for controlling action and thought via inhibition. Consistent with this possibility, the LPFC is engaged in an extraordinarily diverse collection of cognitive tasks, and Duncan and colleagues have shown that it predicts individual differences in fluid intelligence (gF, or psychometric g). A common theme running throughout these tasks appears to be the management of interference, consistent with the putative role of this region in inhibitory control. Nevertheless, it remains possible that there is not one mechanism of control in the LPFC but many content-specific ones, localized similarly, the differences between which cannot yet be ascertained in the absence of direct comparisons between cognitive and motor control. Even, so, lateral prefrontal-posterior interaction remains a valid organizing principle that characterizes our understanding of the networks underlying inhibitory control.

Neural Architecture of Inhibitory Control

Many investigators agree that inhibitory control supports the regulation of behavior by limiting the influence of undesired representations on ongoing behavior by functionally altering the state of the undesired representation. Although the brain clearly solves the computational problems of stopping and response selection, there is not yet widespread agreement on how they are solved or on whether they are solved in a unitary manner. There are two general views on how inhibition may be achieved: direct inhibition and biased competition. Direct inhibition hypothesizes that an inhibitory process targets the unwanted representation or system (either directly or by exciting inhibitory interneurons), degrading its control over behavior. In contrast, biased competition hypothesizes that attentional control signals facilitate the representations of desired actions and that, as a result, competing representations are inhibited through local reciprocal inhibitory projections. The evidence base for biased competition is well developed, and Miller and Cohen have argued that this computational principle may be a primary means of implementing executive control. It is established, however, that both types of inhibitory control take place in the nervous system. For example, as reviewed by Sotres-Bayon and colleagues, excitatory projections from the medial frontal cortex terminate on inhibitory interneurons in the amygdala that modulate the functioning and output of that structure and, correspondingly, suppress conditioned emotional

responding. Similarly, the frontal cortex excites inhibitory neurons in the reticular nucleus of the thalamus, which inhibit the thalamus, gating sensory input to the cortex. The fronto-subthalamic circuitry underlying motor-response suppression (discussed earlier) may be another such example. Thus, inhibitory control may often be accomplished, not by facilitating a competing response but by inhibitory modulation of the brain system underlying the undesired process. The types of situations in which these mechanisms of control operate are an interesting area for future study.

Concluding Comments

The capacity to override unwanted actions and memories is a fundamental component of the effective control of behavior and thought. The pervasiveness of selection and stopping as computational problems has led to the proposition that individual variation in the efficiency with which people inhibit may underlie differences in intellectual functions of many sorts (e.g., attention, working memory, long-term memory, reading, reasoning, and behavioral control) and may even be an important contributor to some psychological disorders. When a population exhibits perseverative tendencies, difficulties managing interference, or distractibility, investigators often consider the potential contribution of frontal lobe dysfunction (and, consequently, inhibitory dysfunction). These proposals, often referred to as inhibitory deficit theories, have been advanced to explain a range of phenomena. For example, because of the late development and early decline of the PFC in the life span, alterations in inhibitory control efficiency have featured prominently in theories of cognitive development and cognitive aging. Clinically, it has been proposed that inhibitory deficits contribute to psychopathologies, including obsessive-compulsive disorder, depression, schizophrenia, attention deficit/hyperactivity disorder, addiction, and chronic posttraumatic stress disorder. It seems unlikely that these diverse conditions are produced by the same deficit and, indeed, that even the various deficits within each population are produced by a single underlying deficiency. Nevertheless, the overlap between systems engaged during motor and memory inhibition suggests that generalized inhibitory control deficits are possible. If so, elucidating the neural systems that subserve inhibitory control is not merely of theoretical interest but has the potential for broad impact on problems of clinical importance.

See also: Computational Approaches to Motor Control; Cortical Control of Eye Movements; Episodic Memory; Assessment in Animals; Episodic Memory; Prefrontal

Cortex: Structure and Anatomy; Prefrontal Cortex; Saccadic Eye Movements; Semantic Memory; Strategic Control of Memory.

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