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Recent advances in understanding neural systems that support inhibitory control

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Although it is agreed that the right lateral prefrontal cortex plays a prominent role in inhibitory control, the exact psychological processes it implements remain unclear, as do the precise neural substrates of such control. Recently debated is the issue of whether the right inferior cortex is specifically involved in inhibition of action, or whether this region monitors the environmental context to provide information as to which goals are attainable under current conditions. Another issue of debate is whether there is a common neural substrate for inhibitory control or whether different neural systems are involved in inhibitory control in different domains — motoric, cognitive, and emotional. The present review examines the current state of thought on these two important issues.

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Introduction

One of the most prominent aspects of cognitive control has been characterized as 'inhibition' or inhibitory processing. Inhibition is generally considered the ability to override, interrupt, or abort ongoing processes, especially when those processes are well engrained. Furthermore, there is general agreement that inhibitory processes involve frontal regions of the brain, more specifically lateral regions of the right prefrontal cortex [1]. Interest in the neural bases of inhibitory processing is high because these processes have been found to be disrupted in a number of psychiatric disorders, including ADHD [2] and substance abuse disorders [3].

This review focuses on two issues that recently have spurred debate. While there is agreement that right lateral prefrontal regions play a prominent role in inhibitory control, the exact nature of the specific computation or process that is being implemented by this region, especially that of the right inferior frontal gyrus (rIFG), is being debated (see Figure 1). The second issue revolves around the degree to which 'inhibition' is a unitary construct, which relies on a central shared brain mechanism regardless of the domain — motoric, cognitive, or emotional — in which inhibition is exerted, or whether there are separate neural mechanisms for inhibitory control in each of these domains.

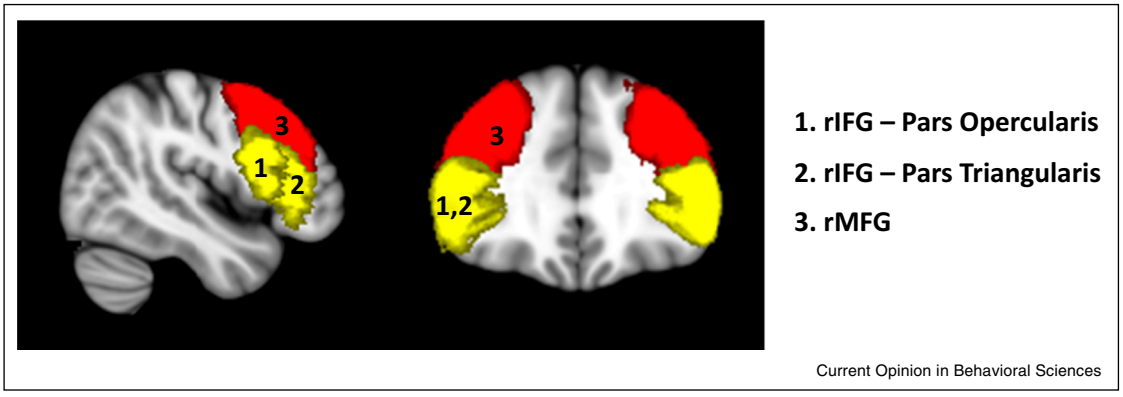
What computation is the rIFG implementing in inhibition?

Typically, inhibitory control is indexed by asking an individual to override, interrupt, or suppress an ongoing cognitive, emotional or behavioral response. Classically this ability has been measured by paradigms that assess inhibition in the motoric domain, such as the Go/No-Go paradigm, which induces a prepotent bias to respond, and which must be overridden when certain specific stimuli are present. Similarly, in the Stop-Signal paradigm, individuals make a forced-choice decision on the majority of trials, but on a minority a specific sensory signal (e.g., auditory tone, perceptual cue) indicates that an ongoing process of responding must be aborted or interrupted [4].

Approximately a decade ago, it was proposed that the rIFG (also sometimes referred to as right ventrolateral cortex) plays a prominent role in inhibiting motor responses by sending a signal to the subthalamic nucleus of the basal ganglia, which in turn suppresses thalamocortical output so as to preclude motor responding [5•]. Since that time, compelling work using a variety of converging methods including that performed with patients with focal lesions, alteration of brain activation (rTMS, tDCS), neuroimaging and electrophysiological evidence has supported such a viewpoint [6••]. An expansion of this viewpoint suggests two distinct forms of motor inhibition, one invoked for stopping all responses, and another that is more selective, only stopping certain responses but not others [7]. It has been proposed that the global stopping mechanisms may be mediated by a hyperdirect pathway from the rIFG → STN → Globus Pallidus → Thalamus.

Recently, however, other evidence suggests that rIFG may be involved not in inhibition *per se*, but rather monitors information in the external environment to determine which goals are compatible with current environmental conditions and what actions can be implemented to

Figure 1

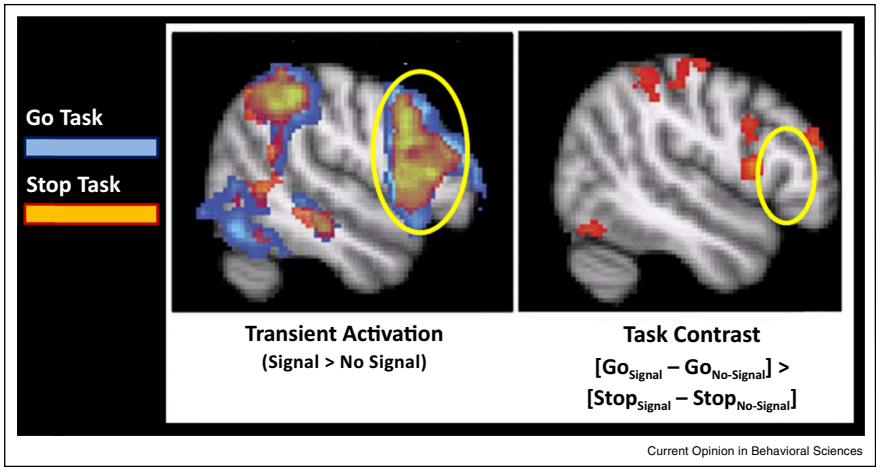


Areas of the right lateral prefrontal cortex commonly activated as assessed by fMRI during inhibitory tasks. 1 (yellow) depicts the pars opercularis of the right inferior frontal gyrus (rIFG); 2 (yellow) depicts the pars triangularis of the right inferior frontal gyrus (rIFG); and 3 (red) depicts the right middle frontal gyrus (rMFG). Areas as defined by the Harvard–Oxford Cortical Structural Atlas.

meet those goals. The main evidence for this viewpoint comes from studies indicating that the rIFG is involved when environmental stimuli signal a change in responding, either when a response must be aborted or withheld, or when a different response must be made [8,9••].

For example, Chatham and colleagues [9••] compared brain activation as assessed by fMRI between a classic stop signal condition, in which a stimulus indicated that a response should be aborted, and one in which a stimulus indicated that an additional response should be emitted, referred to as a Double-Go trial. The Stop or Double-Go trials were embedded within separate blocks. As in a classic Stop Signal paradigm, these trials were a minority (i.e., 25%) of trials as compared to standard trials in which the subject made a forced-choice response. If rIFG plays a specific role in inhibitory processing, then one would predict rIFG activation on Stop but not Double-Go trials. However, brain activation within block for each of these conditions separately versus forced choice Go (i.e., signal) trials showed that both engendered activity in rIFG and that the patterns were overlapping (see Figure 2, left hand panel). Moreover, a comparison between blocked activation for Double-Go versus Stop blocks did not reveal any significant difference in activation for the rIFG (see Figure 2, right hand panel). These findings are clearly at

Figure 2



Areas of activation associated with Stop versus Double-Go trials as assessed by fMRI. Left hand panel; shown here are areas activated during a Stop Signal paradigm in an event-related contrast within blocks of Double-Go (blue) and Stop trials (orange), respectively. Activation is determined in both cases compared to no signal trials within the same block, which are those trials in which a simple forced-choice decision is made and need not be modified. Notice the highly overlapping pattern of activation in right lateral prefrontal cortex, as indicated by the region within the yellow oval. Right hand panel; shown here is the difference in activation for the Double-Go versus Stop trials. Notice that in no area is there greater activity for Stop than Double-Go trials, and that no difference between tasks is found in anterior portions of the rIFG (yellow oval).From Ref. [9••].

odds with the idea that rIFG plays a specific role in response inhibition.

One potential problem with such findings is that they rely on a pattern of null results (no difference between the Stop and Double-Go trials). However, multiple lines of evidence from the studies performed by Chatham *et al.* overcome this objection, suggesting that similar processes are being invoked on Stop and Double-Go trials. They used multi-voxel pattern analysis across the rIFG to classify each subject's pattern of responding on the Double-Go condition. If the rIFG is implementing a similar computational process during the Stop condition, then the multi-voxel pattern in rIFG on Double-Go trials should be able to reliably distinguish amongst individuals on Stop trials, which it did. Notably, however, a classifier trained on Double-Go trials for the motor cortex could not reliably predict an individual's response on Stop trials, as the motor cortex is likely implementing different computations on Double-Go versus Stop trials. Similarly, in an ERP study, the amplitude of a component called the Stop P3 [10], which is a fronto-central component observed after the onset of a stimulus that signals motor stopping, was highly correlated in amplitude for Stop and Double-Go trials across the 38 individuals in that study, once again suggesting that similar processes are being invoked on both No-Go and Double Go trials. In addition, pupillometry, a measure of mental effort and a formal model of reaction time distributions, also was consistent with this conclusion.

The suggestion that the common process implemented by rIFG does not involve inhibition *per se* is consistent with a recent review [11], which involved a meta-analysis of patterns of brain activation as measured by fMRI during the performance of a Go/No-Go task. This analysis identified a common network of brain regions that show greater activation on No-Go than Go trials. The authors then categorized these studies into simple versus complex based on three attributes: first, the difficulty in identifying No-Go signals, second, the frequency of No-Go signals among Go signals, and third, working memory load as instantiated in whether the stimulus-response contingency always remained the same across trials (simple) or whether the stimulus-response contingency was based on information that had to be maintained in working memory (complex). Activation driven by the complexity of these three processes substantially overlapped with the typical right lateralized system thought to be involved in inhibition, including the rIFG. As a result the authors argue that the neural systems involved in inhibitory control, at least in the Go/No-Go task, actually represent more general aspects of cognitive control.

The idea that inhibitory processing is not a unique and separable aspect of cognitive control that is localized to rIFG is consistent with a variety of other evidence. Analysis of deficits observed in patients with focal prefrontal lesions either suggests that inhibitory deficits are not localized to a specific region [12] or that lesions to right lateral cortex disrupt monitoring [13], which would be needed for analyzing contextual factors that affect which goals can be implemented under current conditions. In addition, analyses of patterns of performance across different individuals suggest that executive function (EF) abilities vary on three main dimensions: general EF, which is common across all EF tasks and has been hypothesized to represent the ability to hold a goal online, and two more specific functions: working memory updating, and task switching. Notably tasks of inhibitory control, such as the anti-saccade task, load on the common EF factor without distinct and unique variance for inhibition *per se* [14].

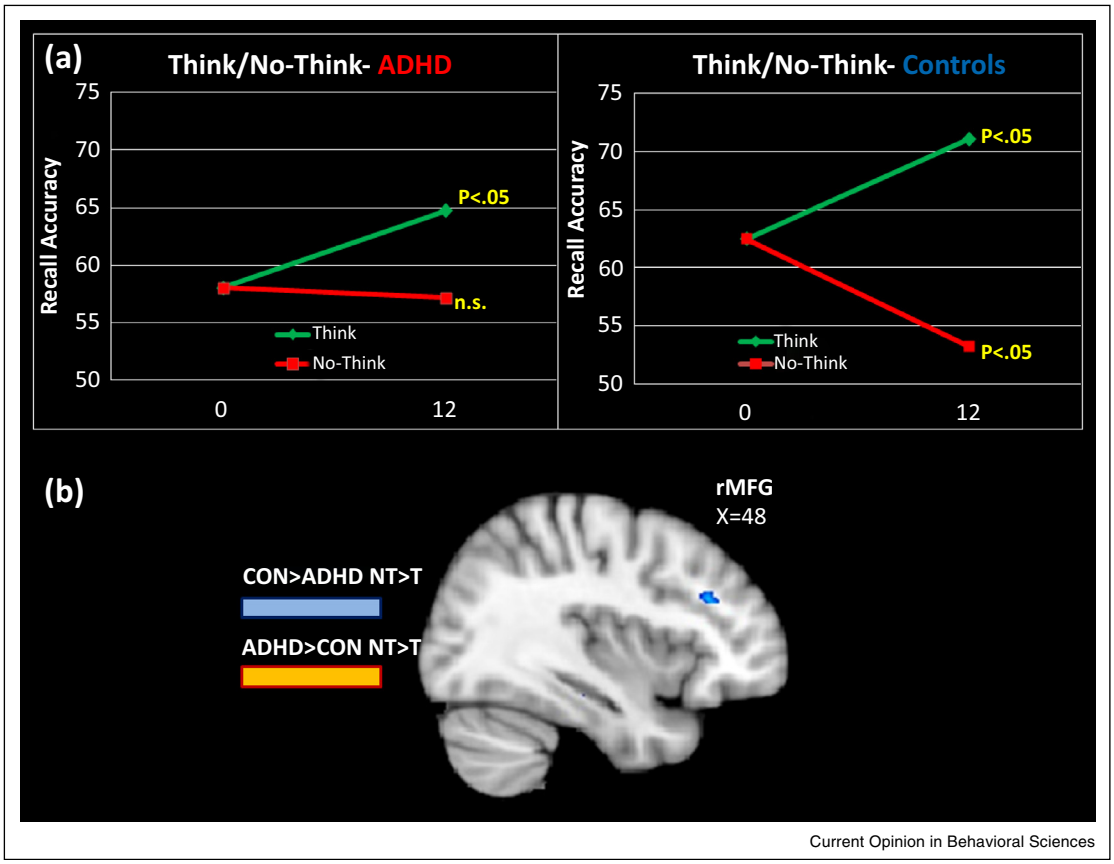
As can be seen from the discussion above, there is no current consensus as to what specific role rIFG plays in cognitive control, with suggestions ranging from those discussed above such as inhibitory control over motor output [6••] and providing contextual information for goal selection and maintenance [9••], to others such as detecting behaviorally relevant stimuli [15]. Future work should help to refine our understanding of this issue.

Is there a central or common neural system for inhibitory control?

It has been suggested that the critical role of lateral prefrontal regions in what is typically perceived to be inhibitory function is instead to maintain goals and then modulate activity of other brain regions [16], consistent with some of the evidence discussed above. As such, one might expect that there would be a central neural system involved in inhibitory control. To evaluate such a prospect, it is informative to consider the neural bases of inhibitory control in other domains beside the motoric domain.

Research suggests that right lateral prefrontal regions also play a prominent role when the retrieval of information from episodic memory must be inhibited. Anderson and colleagues [17] devised a mental analog of the Go/No-Go task, called the Think/No-Think task, in which individuals learn associations between cue-target item pairs. In the critical phase of the task, participants are shown just the cue. For some cues, participants are signaled to remember the associated item. For other cues, participants are signaled to inhibit thinking about the associated item. Behavioral results indicate that the more chances an individual has to remember an item associated with a cue, the better the recall compared to items in which no retrieval from memory has been prompted. Likewise, the more chances an individual has to inhibit retrieval, the poorer the recall compared to items in which no retrieval from memory has been prompted. Hence, the Think/No-Think task focuses on inhibition of retrieval

Figure 3



Evidence for a role of rIFG in inhibiting retrieval from episodic memory. **(a)** Behavioral results of the Think/No-Think paradigm indicating individuals with ADHD have no deficit in elaborating recall (Think condition; green), whereas inhibiting memory retrieval is impaired (No-Think condition; red), as compared to controls who show both significant elaboration (Think condition; green) and inhibition (No-Think condition; red). **(b)** Areas of activation for the contrast of No-Think versus Think trials as assessed by fMRI for ADHD versus control individuals. Notice that ADHD individuals show less activation in the rMFG, an area that has been shown to downregulate the hippocampus to preclude retrieval of information from memory. From Ref. [23].

from memory, akin to the inhibition of a motor response in the Go/No-Go task.

Neuroimaging work has shown that the right lateral prefrontal cortex plays a prominent role in inhibiting memory retrieval by down-regulating activity in the hippocampus [18••] as well as sensory regions (e.g., ventral visual processing areas) that support the originally encoded memory (e.g., of a visual scene) [18••,19•]. The region so identified, right middle frontal gyrus (rMFG), is a bit more superior to that identified in motor inhibition. Similarly, when individuals are directed to encode and then forget certain items or lists in the directed forgetting paradigm, right hemisphere regions, including lateral prefrontal cortex, become more active (e.g., [20,21] and see [22] for review of neural mechanisms involving inhibitory effects on memory including those at encoding). The rMFG is implicated as being especially important based on a number of findings. For example, activation of rMFG predicts the degree to which individuals are successful at inhibition of memory retrieval, and those individuals with a more negative correlation between activation of the rMFG and the hippocampus are better at suppressing memory retrieval [18••]. In addition, although young adults with ADHD are no worse at retrieving memories (i.e., have equivalent performance on Think trials), they have a specific deficit in the inhibition of memory (i.e., have a poorer ability to inhibit retrieval on No Think trials) (Figure 3a). Importantly, the only brain region in which they show reduced activity as measured by fMRI compared to controls on No-Think trials is the rMFG [23] (Figure 3b), implicating this region as playing a central role in inhibiting memory retrieval.

Likewise right prefrontal regions are implicated in the inhibition of emotional responses or reactions. The ability to inhibit emotional responses is generally measured by a paradigm in which individuals view an emotional scene or

are asked to retrieve an emotional memory (typically negative in valence) and then are either told to not think about the item or to distance themselves from the emotion it conveys. Such inhibition over emotional information generally involves activation of a wide variety of right prefrontal regions including the right superior, middle and inferior gyri (see [24] for meta-analysis and review). Moreover, suppression of emotional responses specifically engages right dorsolateral and ventrolateral (i.e., inferior) regions as compared to re-appraisal of emotion (e.g., reframing one's thoughts about a graphic picture of a surgical procedure as indicating that someone will be cured of an ailment, rather than focusing on the degree of injury) [25].

At face value, many of these same regions are those implicated in the inhibition of a motoric response. Moreover, additional evidence hints at a common mechanism of inhibitory control across domains. For example, decreased activity in rIFG in individuals with ADHD during inhibition of memory retrieval is associated with poorer performance on a motoric test of inhibitory function, the stop-signal task [23]. As yet another example, suppressing emotional reactivity impairs performance on a subsequent task of cognitive control, the Stroop task, and leads to decreased activity in right lateral prefrontal cortex during performance of the Stroop task [26]. Finally, behavioral data suggest that these aspects of inhibitory function may be somewhat shared yet also dissociable [27].

As such, a central question remains as to whether there is a central and common right hemisphere system that is involved in inhibitory control regardless of the domain in which such control is exhibited, or whether there are indeed fractionations within the right hemisphere with regards to regions that play a role in inhibitory function over motoric, cognitive, and emotional domains respectively. If inhibitory control really is a by-product of top-down mechanisms that actively maintain goals and modulate the activity of other brain regions to meet those goals, one would suspect a high degree of overlap across domains. To the degree that there are special systems for inhibitory control in particular domains (e.g., rIFG for inhibition of motor responses), then the critical regions would be predicted to be distinct.

Why does the right hemisphere play a predominant role in inhibitory function?

One of the striking aspects of the studies reviewed above is the clear lateralization of function, with right prefrontal regions differentially engaged as compared to left prefrontal regions across most aspects of inhibitory control. As of yet, the underlying reason for this rather dramatic degree of lateralization remains unclear. At least some evidence suggests that the right hemisphere plays an important role in surveillance of the external environment, especially as relating to potential threat [28]. Hence, it is particularly sensitive to the surrounding environmental context. In addition, evidence suggests that inferior right prefrontal regions may play a role in interrupting goal-oriented behavior when salient stimuli capture attention, leading to a re-orienting of behavior [29]. Finally, the right hemisphere has also been implicated in avoidance as compared to approach behaviors, including motivations [30]. The confluence in the right hemisphere of subsystems sensitive to environmental context, that can evaluate whether context accords (or does not) with current goals and can re-orient behavior, along with a tendency toward control of avoidance behaviors and motivation may help to explain the predominant role of the right hemisphere in inhibitory function. Clearly, more work is needed to determine the degree to which these three aspects of right-lateralized function are related to the right hemisphere predominance in inhibitory control.

Conclusions

Currently, there is clear evidence that the right hemisphere plays a critical role in inhibitory function. However, there remain questions as to the functional neuroanatomy of such inhibitory control, as well as the degree to which specific regions of the right hemisphere are involved in specific aspects of inhibitory control, depending on the domain in which that control is exhibited — motoric, cognitive, or emotion. Ascertaining the answer to these questions is of practical important due to the large number of psychiatric and neurological disorders in which inhibitory control is compromised. Understanding the underlying neurobiology of inhibitory control may lead to more effective and focused interventions.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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