Executive Function and Higher-Order Cognition: Neuroimaging

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Executive Function

The terms executive function and cognitive control refer to cognitive processes associated with the control of thought and action. Putative control functions include the ability to (1) selectively attend to relevant information while filtering out distracting information (selective attention and interference suppression), (2) work with information that is currently being held in working memory (manipulation), (3) flexibly switch between tasks (task switching), (4) inhibit inappropriate response tendencies (response inhibition), and (5) represent contextual information that determines whether a thought is relevant or whether an action is appropriate (e.g., task-set representation).

Although a number of control processes have been proposed, it is unclear which of these putative processes are distinct from one another. Thus, an important challenge in cognitive control research is to identify a set of elemental control processes and to understand the brain mechanisms underlying each of these processes. One approach that has proven useful for dissociating cognitive processes is the study of patients with various forms of neurological disease and damage. This approach, however, is not without its limitations. As such, convergent evidence from brain imaging techniques is proving increasingly useful.

Probing Executive Function with Neuroimaging Techniques

Functional magnetic resonance imaging (fMRI) has proven useful for identifying brain regions involved in cognitive control. As such, this technique allows us to test whether tasks involving putatively distinct control processes recruit separable brain networks. On the other hand, fMRI allows us to determine whether different tasks that involve a common control process recruit some of the same brain regions.

Prefrontal cortex (PFC) has long been implicated in executive function. Indeed, in 1895, the Italian physiologist Bianchi observed that experimental ablations of the frontal lobes destroyed the ability to synthesize incoming percepts together and to integrate these with outgoing motor commands. Since this early work more than a century ago, countless experiments have been conducted with a variety of techniques to better understand how PFC exerts control over other brain regions.

It is now clear that PFC should not be considered a monolithic structure; indeed, this expansive region constitutes roughly one-third of the human brain and consists of a number of different subregions. Each of these subregions is thought to provide a distinct contribution to cognition via different cellular characteristics and anatomical connectivity. As such, the use of a technique with high spatial resolution, such as fMRI, is essential for determining whether two executive tasks rely on the same or different PFC subregions.

Additionally, it is clear that if we want to understand cognitive control mechanisms, we must examine how PFC interacts with other brain regions. Some information about these interactions can be gleaned from functional connectivity analyses of fMRI data, although fMRI provides little information about the timing of these interactions. For several decades, event-related potential (ERP) data from electroencephalography (EEG) studies have contributed to our knowledge about the timing of control mechanisms. The ERP research of Robert Knight, involving patients with PFC lesions and healthy controls, demonstrated that PFC is necessary for top-down enhancement of relevant information in primary sensory regions.

Tasks Used to Study Executive Function

The most common type of executive task requires participants to override a prepotent response tendency. In the widely used Stroop task, one must override the impulse to read a word out loud and instead indicate the name of the color in which the word is printed (Figure 1a). In the go/no-go paradigm, one must press a button in response to a series of rapidly presented visual stimuli but must inhibit responding to a particular stimulus (Figure 1b). The continuous performance test known as AX-CPT is similar to go/no-go but additionally has a monitoring component because one must respond to an X followed by an A, but not to an X followed by a B. In the flanker paradigm, one must press one of two buttons in response to a central target stimulus while overriding the response specified by distracters on either side of the target (Figure 1c). In a task-switching paradigm, one must switch abruptly from one task rule to another (Figure 1d). This type of paradigm is thought to involve both suppression of the prior task rule and retrieval of the new rule. Here, several experimental paradigms are discussed in-depth.

Selective Attention

Goal-directed behavior hinges on the ability to focus on relevant information and ignore distracters, a

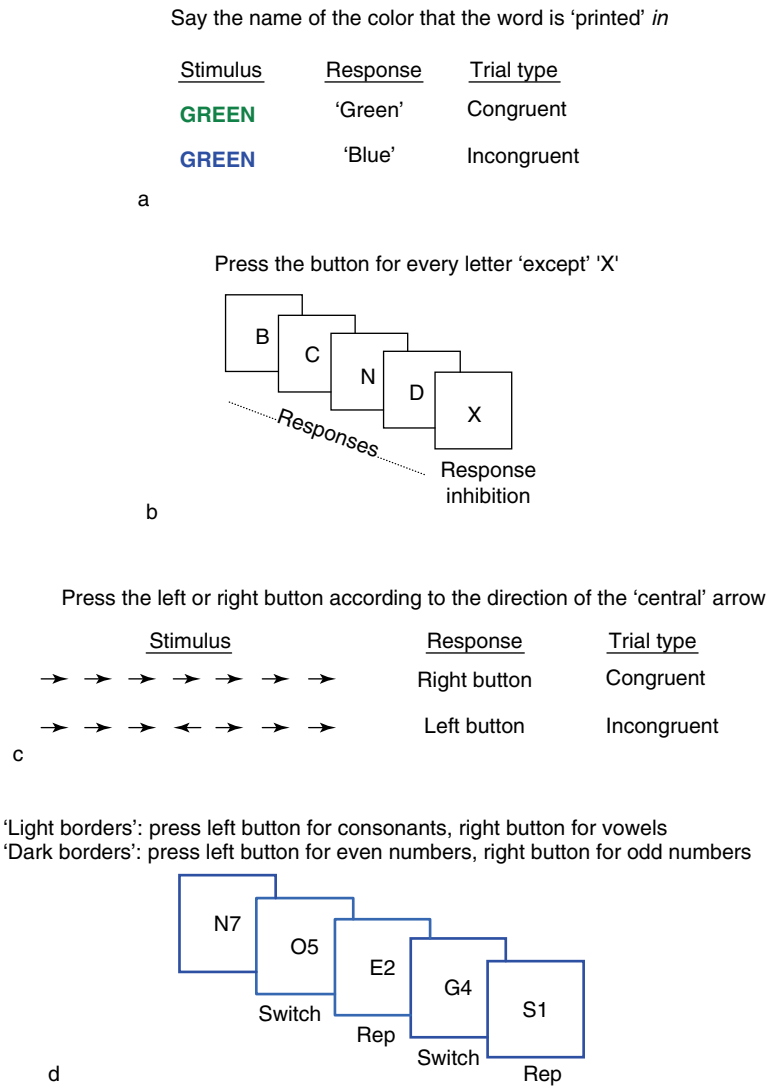

Figure 1 Standard versions of several tasks commonly used to study executive function: (a) the Stroop task, (b) the go/no-go task, (c) the Flanker task, and (d) an example of a task-switching paradigm. Variants of these basic paradigms have been used in a number of brain imaging studies.

function referred to as selective attention and/or interference suppression. Although the neural mechanisms are not yet fully understood, a widely accepted model proposed by Desimone and Duncan postulates that selective attention relies on top-down biasing mechanisms. The model proposes that long-range excitatory projections from PFC to posterior cortical regions enhance the activation of relevant representations, which in turn serve to suppress irrelevant representations through local inhibitory interactions. Herd et al. adapted this model in such a way that it can better account for performance and brain activation data from the Stroop task.

Building on earlier behavioral and fMRI work by Lavie and collaborators, Gazzaley and colleagues have conducted fMRI and ERP studies that provide compelling evidence for separable top-down enhancement and suppression effects in a selective attention paradigm. In their task, participants viewed a series of pictures of faces and scenes pseudorandomly intermixed. They were instructed to (1) remember the faces and ignore the scenes, (2) remember the scenes and ignore the faces, (3) remember both, or (4) passively view the stimuli.

The researchers found that a region involved in processing faces – the fusiform face area (FFA) – exhibited enhanced activation relative to the other conditions when participants selectively attended to faces. They further showed that FFA activation was lower relative to the passive view condition when participants ignored faces and attended to scenes instead. The opposite pattern of results was found for the parahippocampal place area (PPA), a region involved in processing scenes (Figure 2).

An ERP study involving the same paradigm also showed an enhancement of face processing-related neural activity (the face-selective N170 component)

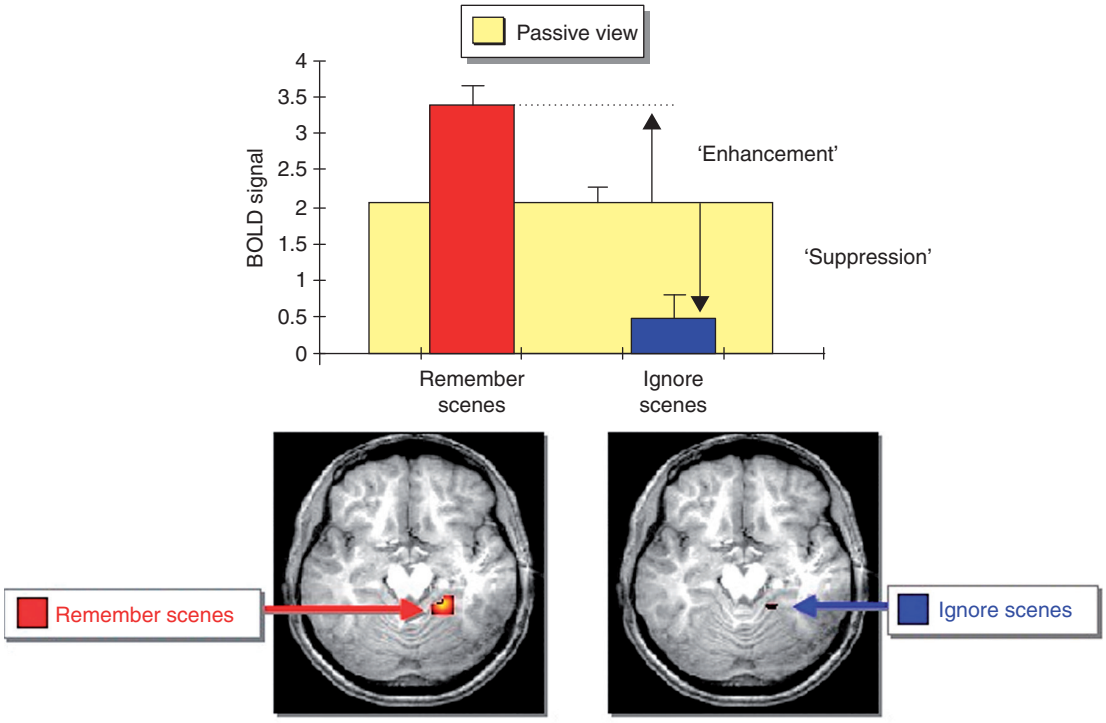

Figure 2 Data from 18 adults aged 19–30 years in an fMRI study on selective attention by Gazzaley and colleagues. These data show that the PPA was more active when participants selectively attended to scenes rather than faces than when they passively viewed both scenes and faces. Additionally, the PPA was less active when participants selectively attended to faces (ignored scenes) than in the passive viewing condition. Participants view the same number of scenes across tasks, and therefore the modulation observed in PPA must be mediated by top-down mechanisms. BOLD: Blood-oxygen level dependent. Courtesy of Adam Gazzaley.

when subjects were instructed to selectively attend to faces. The ERP data further revealed that attention to faces led to faster face processing: indeed, the peak latency of the N170 component was shifted 10 ms earlier for the 'remember faces' condition than for 'ignore faces.' Taken together, these fMRI and ERP results provide strong evidence for top-down modulation of posterior cortical representations as a function of goal relevance.

A large behavioral literature suggests that older adults have difficulty ignoring irrelevant information, but it is unclear from these data whether this deficit is rooted in a specific deficit in top-down suppression of irrelevant information, top-down enhancement of relevant information, or both. As such, Gazzaley and colleagues used the paradigm discussed previously to study selective attention in older adults. Their fMRI data revealed that in older adults, the PPA was not suppressed in the 'ignore scenes' condition relative to the 'passive view' condition (Figure 3). In contrast, the PPA did exhibit enhancement for the 'remember scenes' condition relative to 'passive view.' These data indicate that older adults showed a specific deficit in top-down suppression. In addition to providing insight into cognitive changes during aging, this finding lends credence to the idea that suppression and enhancement mechanisms are neurally separable.

Response Inhibition

The ability to inhibit a contextually inappropriate response tendency is central to goal-directed behavior. Numerous brain imaging studies have been conducted in an effort to identify the brain structures that mediate response inhibition. In the go/no-go paradigm, participants must respond to the presentation of each of a rapidly presented stream of visual stimuli, thereby building up a prepotent response tendency. Participants are also instructed to withhold their response to a particular stimulus (the 'no-go' stimulus), which will be presented without warning from time to time (Figure 1b). fMRI studies involving the go/no-go paradigm have revealed a network of largely right-hemispheric brain regions associated with successful response inhibition, including right ventrolateral PFC. The go/no-go paradigm has been used not only to study inhibitory control in healthy young adults but also to probe the neural basis of inefficient inhibitory control in children and in patient populations.

Another paradigm used to study response inhibition is the stop-signal task. In the most common variant of this paradigm, participants press a button in response to visual stimuli but must on some occasions (e.g., if they hear a tone) inhibit their response at the last moment (Figure 4a). This task is thought to tax

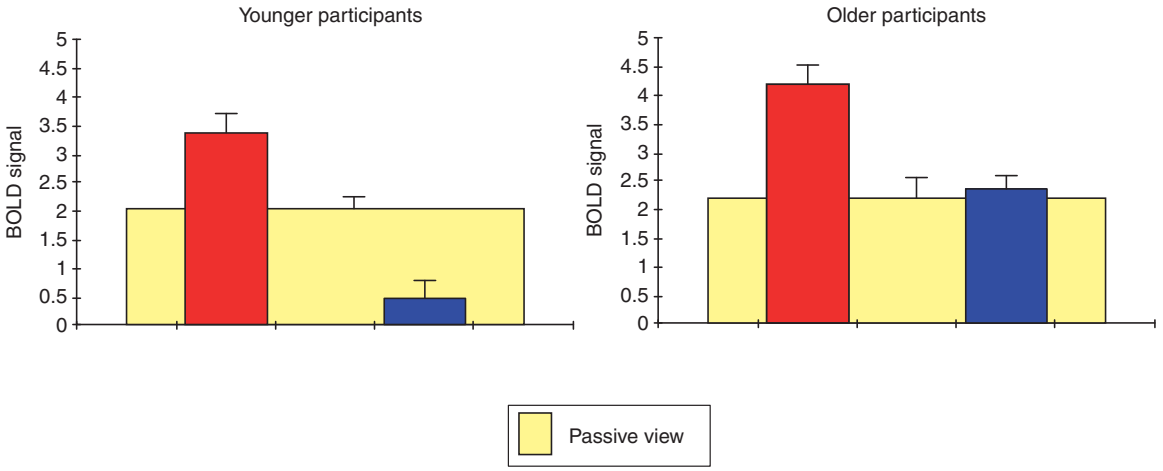

Figure 3 The data from younger adults in **Figure 2** are replotted here as a point of comparison for PPA activation in 16 older adults, aged 60–77 years. For the older adults, like the younger adults, activation in PPA was greater during selective attention to scenes than during passive viewing. In contrast, PPA activation for older adults did not differ between the ignore scenes condition and the passive viewing condition. Thus, the older participants exhibited top-down enhancement of PPA activation but failed to demonstrate top-down suppression. Blood-oxygen level dependent. Courtesy of Adam Gazzaley.

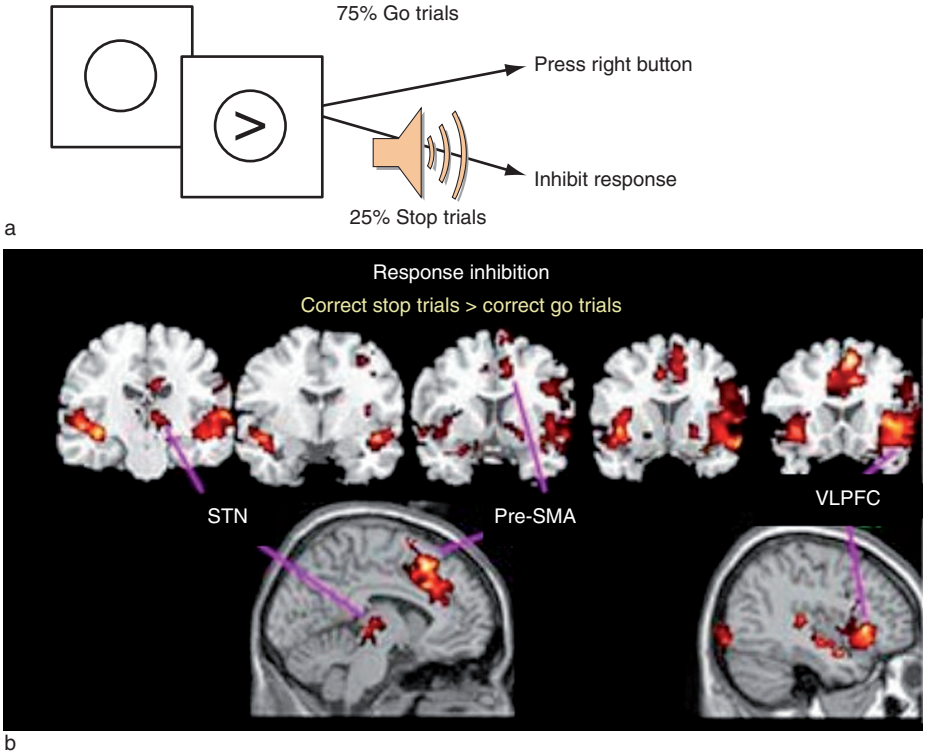

Figure 4 (a) A simplified illustration of the stop-signal paradigm used by Aron and Poldrack. (b) The neural correlates of successful inhibition of motor programs are shown in these activation maps. In particular, three regions – all in the right hemisphere – have been associated with stopping: the subthalamic nucleus (STN), pre-supplementary motor area (pre-SMA), and ventrolateral prefrontal cortex (VLPFC). This pattern of activation suggests that stopping behavior relies on the hyperdirect pathway from PFC to the STN.

response inhibition more heavily than the go/no-go paradigm because participants must override a motor response that they have already initiated. The stop-signal paradigm has an advantage over other response inhibition paradigms for use in clinical and developmental brain imaging studies: the task difficulty varies dynamically on a trial-by-trial basis to ensure a fixed level of performance across participants. As such, differences in brain activation between groups cannot simply be attributed to differences in performance.

In an fMRI study involving the stop-signal paradigm, Aron and Poldrack proposed that stopping is

achieved through excitation of the subthalamic nucleus by PFC (Figure 4b). From prior work in animals, it is known that the subthalamic nucleus is inhibitory, and that excitation of this nucleus should result in a dampening of activity in the thalamus and cortex. This fMRI study provides evidence in humans for hyperdirect inhibition, bypassing the slower, indirect loop through the basal ganglia. It is likely that some response inhibition paradigms engage the hyperdirect pathway, whereas others engage either the indirect pathway through the basal ganglia or cortico-cortical projections that result in top-down biasing of posterior representations. Further brain imaging research is needed to determine whether various types of response inhibition are indeed neurally separable.

Task-Set Representation

The majority of research on cognitive control focuses on the issue of how PFC controls thought and behavior. An equally interesting question is how PFC 'knows' which thoughts and behaviors to facilitate or suppress. Until we have a satisfactory answer for this question, we will continue to treat PFC as a homunculus – a little man inside the brain who mysteriously knows everything and can direct our thoughts and actions accordingly.

Computational modelers have attempted to decompose or decentralize the homunculus. However, more neuroanatomically detailed computational models will be needed to account for the roles of distinct PFC subregions and other parts of the brain. Such models await a larger body of research on context representations – that is, the information that is used to decide on an appropriate course of action. Context representations could include information about current goals, motivational state, the current situation, rules for behaving in this situation, etc.

The type of context representation that can perhaps be most readily operationalized and studied is the representation of a currently relevant task rule. Research in our laboratory is focused on understanding how rules for behavior are stored in long-term memory, retrieved, maintained online during task preparation, and implemented. Along the same lines, Sakai and Passingham have conducted several elegant studies examining the role of anterior prefrontal cortex (APF; lateral Brodmann area 10) in task preparation.

In these studies, Sakai and Passingham provide evidence from functional connectivity analyses that APF interacts with different brain regions during task preparation, depending on the type of task to be performed. Their first study, in 2003, showed that when participants prepared to perform either a challenging verbal or spatial working memory task, APF activation was strongly correlated with regions involved in verbal or spatial working memory, respectively. Their second study, in 2006, focused exclusively on the verbal domain, and it showed that when participants prepared to perform either a semantic or phonological task, APF was correlated with distinct regions in ventrolateral PFC that have been associated with either semantic or phonological processing. These studies show that APF coordinates task performance by interacting with brain regions that are needed to perform an upcoming task.

Current and Future Directions

During the past decade of brain imaging research, the emphasis has been on using fMRI to localize individual brain regions engaged in various tasks. These endeavors have given us a fairly good idea of the key players in cognitive control and have allowed us to test specific hypotheses regarding their contributions. Furthermore, fMRI studies focusing on adult-individual differences have shown that task performance can be tightly correlated with level of engagement of specific brain regions. Similarly, developmental and clinical fMRI studies have identified brain regions for which differences in level of activation across groups may underlie performance differences.

The next generation of brain imaging techniques will need to combine high-resolution spatial and temporal information. Additionally, further research is needed to better characterize neuropharmacological and genetic influences on brain activation. Several methods that hold promise for the next wave of studies probing executive function are discussed here.

Combined fMRI and EEG Methodology

fMRI and EEG are complimentary techniques in that the former allows for the precise spatial localization of active brain regions, and the latter provides exquisite timing information about the onset and offset of neural activity. To push our understanding of cognitive control mechanisms to the next level, it will be necessary to acquire data with high spatial and temporal resolution.

One approach is to acquire fMRI and EEG data on the same group of participants, in separate sessions. The set of brain regions identified from the fMRI data can then be used to constrain the source localization of the ERP data. Another, more technically challenging, approach is to simultaneously acquire fMRI and EEG data from the same participants. This latter approach has been used successfully in a study on performance monitoring by Debener and colleagues. Several groups are working on multimodal imaging approaches, including combined fMRI/EEG, and the further development of these methods should provide new insights into the neural mechanisms of executive function.

Event-Related Optical Signals

Gratton and Fabiani and their colleagues have developed an optical imaging technique with high spatial and temporal resolution known as EROS, or the event-related optical signal. The standard analytic approach for optical imaging data analysis is to focus on changes in optical properties of the cortical brain tissue associated with changes in blood flow, which are only indirectly related to changes in neural activity. Given the sluggish blood flow response to neuronal activity, optical imaging – like fMRI – typically has poor temporal resolution. In contrast, with EROS, the optical changes that are being analyzed are directly related to neural activity. In addition to having high temporal resolution, the EROS signal also has a high degree of spatial resolution; it can be localized to an area of less than a cubic centimeter. The main drawback of this method is that it can only be used to measure activity within 3–5 cm of the surface of the brain.

The developers of EROS have used it to study response competition in a Stroop task. They showed that both left and right motor cortices were active in response to an incongruent Stroop stimulus, even though participants were instructed to respond to the stimulus by pressing a button with only one hand. In contrast, congruent Stroop stimuli, which did not elicit response competition, elicited activation of only the contralateral motor cortex. Since this validation study was performed approximately 5 years ago, the technique has been further fine-tuned and validated. Although only a few published studies have employed EROS thus far, the use of this technique may spread as more researchers become aware of its potential.

See also: Attentional Networks; Cognition: An Overview of Neuroimaging Techniques; Cognitive Control and Development; Electroencephalography (EEG); Event-Related Potentials (ERPs) and Cognitive Processing; Executive Function and Higher-Order Cognition: Assessment in Animals; fMRI: BOLD Contrast; Neuroimaging; Optical Imaging of Intrinsic Signals; Prefrontal Cortex: Structure and Anatomy.

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