Published in final edited form as:
Exp Brain Res. 2009 January ; 192(3): 489–497. doi:10.1007/s00221-008-1642-z.

The prefrontal cortex and the executive control of attention

Andrew F. Rossi,
Division of Neuroscience and Basic Behavioral Science, NIMH, NIH, Bethesda, MD 20892, USA
rossia@mail.nih.gov

Luiz Pessoa,
Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, USA
lpessoa@indiana.edu

Robert Desimone, and
McGovern Institute for Brain Research at MIT, Cambridge, MA 02139, USA desimone@mit.edu

Leslie G. Ungerleider
Laboratory of Brain and Cognition, NIMH, NIH, Bethesda, MD 20892, USA ungerlel@mail.nih.gov

Abstract

We review two studies aimed at understanding the role of prefrontal cortex (PFC) in the control of attention. The first study examined which attentional functions are critically dependent on PFC by removing PFC unilaterally and transecting the forebrain commissures in two macaques. The monkeys fixated a central cue and discriminated the orientation of a colored target grating presented among colored distracter gratings in either the hemifield affected by the PFC lesion or the normal control hemifield. When the cue was held constant for many trials, task performance in the affected hemifield was nearly normal. However, performance was severely impaired when the cue was switched frequently across trials. The monkeys were unimpaired in a pop-out task with changing targets that did not require top-down attentional control. Thus, the PFC lesion resulted in selective impairment in the monkeys' ability to switch top-down control. In the second study, we used fMRI to investigate the neural correlates of top-down control in humans performing tasks identical to those used in the monkey experiments. Several fronto-parietal and posterior visual areas showed enhanced activation when attention was switched, which was greater on color cueing (top-down) trials relative to pop-out trials. Taken together, our findings indicate that both frontal and parietal cortices are involved in generating top-down control signals for attentive switching, which may then be fed back to visual processing areas. The PFC in particular plays a critical role in the ability to switch attentional control on the basis of changing task demands.

Introduction

For well over a century, the prefrontal cortex (PFC) has been thought to play a key role in the control of cognitive processes. Early behavioral studies of monkeys (Ferrier 1876; Bianchi 1922) and humans (Luria 1969) described the effects of frontal damage as a disruption of goal-directed behaviors. More recent studies of humans with lesions of PFC have further characterized the effects as impairments of "executive function", and, in particular, attention (Knight 1984; Duncan 1986; Shallice and Burgess 1991; Passingham 1993; Grafman 1994). Brain imaging studies have confirmed and extended these findings by identifying a distributed network of areas in frontal and parietal cortex that appear to be involved in the allocation of

Correspondence to: Leslie G. Ungerleider.

attention, including the frontal eye field (FEF), supplementary eye field, anterior cingulate cortex, middle frontal gyrus (MFG), intraparietal sulcus (IPS), and superior parietal lobule (see Hopfinger et al. 2000; Kastner and Ungerleider 2000; Corbetta and Shulman 2002).

Evidence from neurophysiology also supports the notion that PFC is integral to the control of cognitive function. Such studies have shown that patterns of neuronal activity in subregions of PFC are correlated with attentional state (for review, see Schall 2002), the control of eye movements (for review, see Schall 1997), as well as a variety of high-level behavioral functions, such as working memory (Goldman-Rakic 1987; Quintana et al. 1988; Fuster 1995; Miller et al. 1996), response strategies (Genovesio et al. 2005), and rule learning (Asaad et al. 1998, 2000; Rainer et al. 1998; White and Wise 1999), all of which suggest that PFC neurons might modulate responses in sensory areas according to attention and task demands (for review, see Miller and Cohen 2001). Moore and Armstrong (2003) provided direct evidence for this idea by demonstrating that visual responses in area V4 could be enhanced after brief stimulation of retinotopically corresponding sites within the FEF, and that stimulation of non-corresponding FEF representations could suppress V4 responses.

Taken together, these observations suggest the general hypothesis that PFC is one of a network of structures involved in the top-down control of attention by means of descending feedback signals that bias sensory processing in favor of information that is behaviorally relevant. Several influential theories of attention have proposed that sensory representations compete for neural resources (Grossberg 1980; Bundesen 1990; Desimone and Duncan 1995; Bundesen et al. 2005). For example, in the biased competition model (Desimone and Duncan 1995), competition among sensory representations is resolved either through top-down feedback from frontal and parietal areas or by bottom-up sensory properties such as relative stimulus strength.

Because PFC is thought to be one of several structures in a larger attentional network, a question remains as to which attentional functions are critically dependent on PFC. Here, we present two experiments in which we explored the role of PFC in visual attention. In the first experiment, we describe the effect of PFC lesions in monkeys on switching top-down control in a cued attention task, and we compare the results to those obtained in a task in which target selection is determined instead by bottom-up stimulus salience (Rossi et al. 2007). In the second experiment, we use fMRI to identify brain regions involved in top-down and bottom-up attentional switching in humans performing the same tasks (Pessoa et al., 2008).

Experiment 1: Deficits of attentional control in monkeys with lateral prefrontal lesions

Methods

Subjects and lesions—In two adult male macaque monkeys, we made unilateral aspiration lesions of the right lateral PFC (Fig. 1a). The lesion included the FEF (area 8), dorsolateral areas 9 and 46, and ventrolateral areas 45 and 12. In addition, the anterior commissure and corpus callosum were transected. As a result, visual processing in only the left hemisphere was potentially modulated by feedback from PFC, and we could assess the behavioral effects of the lesion by comparing visual performance in contralesional and ipsilesional hemifields in fixating monkeys (Fig. 1b).

Behavioral tasks and stimulus presentation—Monkeys were trained to fixate a central cue on a display monitor and discriminate the orientation of the target grating presented among distracters in the periphery (Fig. 1c). Monkeys responded by either releasing a bar for a vertical grating or holding for non-vertical gratings and received a juice reward for all correct responses. The monkey's threshold for discriminating a vertical from a non-vertical target grating was

determined using a staircase procedure (Wetherill and Levitt 1965) that adjusted the magnitude of the orientation difference (from vertical) based on the monkey's previous performance. The stimulus array of target and distracters was presented in either the left or right visual hemifield.

The monkeys were trained on two variations of the orientation discrimination task: a color cueing task and a pop-out task. For the color cueing task, monkeys were trained to fixate a central cue and discriminate the orientation of a colored target grating presented among two colored distracter gratings. The color of the central cue (red, green, or blue) identified the target on each trial (see Fig. 1c). The cue appeared when the monkey held a lever to initiate a trial and remained present throughout the trial. On each trial, the relative positions of the colored gratings were randomly assigned. In addition, the two distracters always differed in color and orientation from each other, to prevent the target from being identified solely on the basis of a feature difference from the distracters. We tested each monkey on four conditions of cue repetition: 1, 5, 10, and 100 trials. For example, for a cue repetition of 1, the cue changed every trial, whereas for a cue repetition of 100, the cue changed every 100 trials. For trials when the cue changed, the new color was randomly chosen from the two distracter colors in the previous trial.

For the pop-out task, the monkeys were trained to fixate centrally and discriminate the orientation of the odd grating as defined by color pop-out (see Fig. 2a). Grating stimuli were the same as described in the color cueing task. Two additional distracters were added in this experiment to increase the salience of the target. The relative positions of the target and distracters were randomly assigned on each trial. Possible target positions were limited to the three most central locations nearest the horizontal meridian, as in the color cueing task. The identity of the target was systematically varied by changing either the color of the target, or both the color of the target and distracters. As in the color cueing task, we tested each monkey on four conditions of target repetition: 1, 5, 10, and 100 trials. The data were analyzed using ANOVA and post-hoc *t*-tests. Additional details of these methods and procedures have been reported in Rossi et al. (2007).

Results

The goal of the color cueing experiment was to investigate the effects of lateral PFC lesions on a monkey's ability to switch top-down control in a cued attention task. The behavioral measure, the orientation threshold for the target, served as a measure of both acuity in the discrimination task and the monkey's ability to attend to the target in the presence of distracters. In other words, the target orientation threshold was used as an indirect measure of the monkey's ability to select the target as defined by the cue.

The results are shown in Fig. 1d, where the average orientation threshold is plotted as a function of cue repetition for one monkey. The same pattern of results was observed in the second monkey. Performance in the control hemifield is shown in white, and in the hemifield affected by the lesion in black. For both monkeys, the average orientation threshold across all levels of cue repetition was significantly greater in the lesion hemifield compared to the control hemifield ($P < 0.001$) when the target was presented with distracters. Both monkeys also showed a small elevation in orientation discrimination thresholds in the lesion-affected hemifield compared to the control hemifield when the target was presented without distracters (e.g., see “no distracters” condition in Fig. 1d). However, in the presence of distracters, the average magnitude of the threshold impairment was significantly larger (compared to no distracters) for all but the longest cue repetition value (i.e., cue changes every 100 trials) in one monkey (Fig. 1d) and for all cue repetition values in the second monkey, consistent with the idea that the lesion caused an attentional impairment.

Although the lesion appeared to cause an attentional impairment, the magnitude of this impairment was strongly dependent on the rate of cue repetition. The threshold difference between the lesion and control hemifield in one monkey was 23.2° and 28.7° in the second monkey when the cue changed every trial (repetition 1); however, this threshold difference dropped to 1.1° and 7.6°, respectively, when the same cue was repeated for 100 trials. Both monkeys exhibited a systematic and significant increase in discrimination thresholds as the frequency of the cue change increased in the lesion hemifield ($P < 0.001$) but not in the control hemifield ($P > 0.1$), and there was a significant interaction between hemifield and cue repetition for both monkeys ($P < 0.001$). In sum, the major effect of the PFC lesion was an impairment in flexibly switching attention when the target identity changed frequently across trials.

We next considered whether the impairment in switching attention to a new target across trials was due to a problem in guiding top-down attention based on information derived from the cue, or whether the impairment would be found in any task in which the target identity changed over trials, even if the "top-down" attentional requirement were reduced. We therefore trained the monkeys to perform a variation of the task in which the target was defined by color pop-out (see Fig. 2a), i.e., the monkeys were rewarded for discriminating the orientation of the grating that differed in color from all of the other gratings on a given trial. Thus, the target was defined by "bottom-up" stimulus features rather than the "top-down" information about the cue used in the task. The identity of the target was systematically varied across trials by changing either the color of the target, or the color of both the target and distracters.

Average discrimination thresholds on the pop-out task are shown for one monkey in Fig. 2b. The same pattern of results was observed in the second monkey. The thresholds in the control hemifield were larger than we observed in the color cueing task, possibly because of the larger number of distracters. The target was also bounded on both sides by grating distracters on every trial in this task, unlike most of the trials in the color cueing task. Both monkeys' thresholds were significantly higher in the lesion hemifield compared to the control hemifield ($P = 0.004$), although the magnitude of the threshold increase for the lowest repetition values (1 and 5) was signifiantly smaller than in the color cueing task ($P < 0.0001$). Thus, while performance in the pop-out attentional task was moderately impaired, this impairment was not related to the frequent switching of "bottom-up" attention to different salient targets across trials.

The stability of the behavioral effects found in Experiment 1 was confirmed by comparing orientation thresholds between test sessions occurring about 2 years apart.

Discussion

In the color cueing task, the animals' ability to use a central color cue to attend to a matching colored grating among distracters was impaired by PFC lesions, particularly when the cue/target changed frequently over trials. As the cue switch frequency increased, the discrimination threshold for the target grating increased. Control experiments without distracters showed little or no impairment, arguing against a loss of acuity or a general inability of the monkey to attend. Rather, the PFC lesion seemed to mainly impair the ability of monkeys to cognitively switch top-down control of attention from one target feature to another across trials, e.g., to attend to the red grating on one trial and to the green grating on the next. An analysis of errors (see Rossi et al. 2007) supports this interpretation, in that the monkeys seemed to perseverate in attending to the same target color from one trial to the next, even when the central cue indicated that they should attend to a different target color on that trial.

The results from the pop-out task also support this interpretation of a top-down attentional switching impairment. We considered the pop-out task to be mainly a "bottom-up" task because the target was defined as the grating that differed in color from all of the others. The critical feature of the pop-out task we used was that there was no information about target identity

available to the animal at the start of the trial, and, thus, no “top-down” information about the target could be used to find it. We found that the animals did show a moderate impairment in this task, but it did not increase with the frequency of the target color change. This non-specific decrease in pop-out performance in the lesion-affected visual field is consistent with reports of a widespread reduction of neural activity in the ipsilesional hemisphere of human subjects with PFC damage (Barcelo et al. 2000; Blasi et al. 2002). Therefore, findings from both experiments suggest that PFC is critical to the monkey's ability to flexibly reallocate top-down attention to a target stimulus, whereas guidance of attention by means of bottom-up stimulus salience is not critically dependent on PFC.

Experiment 2: Dynamic attentional control in humans measured with fMRI

Although our experiment in monkeys revealed that some part of lateral PFC is important for top-down attentional control, it was not possible to more precisely localize the region(s) responsible for the deficit. In addition, because the lesions were confined to the PFC, it was unclear whether other brain regions, such as parietal cortex, were involved in top-down attentional switching in the task. In this second experiment, we sought to answer these questions in humans, using the same tasks as before, but modified slightly for the fMRI environment.

Methods

In the main experimental condition (color cueing), which was guided by top-down control, a central cue indicated the color of a peripheral grating on which the subjects performed an orientation judgment. The central cue was a red, green, or blue square. For switch trials, the color of the cue in the current trial was different from the color in the previous one. For non-switch trials, the color of the cue in the current trial was the same as the color in the preceding trial. Switch and non-switch trials occurred in random order. Because the cue was present in every trial, the contrast of switch and non-switch trials was expected to reveal brain regions involved in the updating of cue-related information. In addition, based on the results in our monkeys, we expected such endogenous cue updating to engage different regions relative to those that would be observed when targets were determined in a bottom-up fashion. To test this prediction, we included a pop-out condition in which the target grating was defined by color contrast, i.e., target selection was guided by bottom-up saliency. Specifically, the target grating was the color singleton appearing within an array of like-colored gratings. For the pop-out condition, the central cue was thus uninformative. Again, both switch and non-switch trials occurred.

The trial structure for both color cueing and pop-out trials was identical. An initial central fixation square was shown for 500 ms, followed by a 500-ms display containing a central cue and a peripheral array of five gratings. Potential targets only comprised the central three locations; the two additional extreme gratings were fixed and were included to equate sensory stimulation for the two tasks. For color cueing trials, the fixation square turned color and indicated the color of the target grating on which the subject was to perform an orientation judgment. For pop-out trials, the fixation square remained white and the target on which subjects performed the orientation judgment was the grating whose color differed from that of the remaining four gratings. On all trials, subjects indicated with a button press whether the target grating was vertical or not. The trial then ended with a 1,500-ms blank screen. The target location was randomized on each trial, irrespective of whether the trial was a switch or non-switch trial.

Color cueing and pop-out trials occurred in a blocked fashion and only one condition occurred during an fMRI run. Within individual runs, each block consisted of 40 trials, and during each block, five to ten switch trials occurred at random. Twenty normal, healthy subjects performed alternating runs containing blocks of either color cueing or pop-out trials, and fMRI data were

collected using a 3T scanner. Analysis of fMRI data employed standard multiple regression methods; condition (color cueing and pop-out) and trial type (switch and non-switch) were fixed factors and participant was a random factor in a mixed-effects analysis.

Results

First, we investigated the main effect of task on brain activation by contrasting color cueing vs. pop-out conditions. We found stronger responses during color cueing trials in several bilateral fronto-parietal regions, including the inferior parietal lobule, FEF, MFG, and inferior frontal gyrus (IFG). We did not observe any regions in which responses evoked during pop-out trials were stronger than during color cueing trials. Next, we compared switch to non-switch trials (pooled across conditions; see Fig. 3a). Stronger responses evoked during switch trials were observed in the left IPS and left MFG/IFG. These activations were quite extensive; smaller foci of activation included the right IPS and left FEF, as well as the left middle occipital gyrus (MOG) and bilateral inferior occipital gyrus (IOG). Finally, stronger responses for non-switch trials relative to switch trials were observed in the right insula.

We also probed for task by trial type interactions (Fig. 3b), i.e., regions for which the difference of switch vs. non-switch trials was greater during color cueing trials relative to pop-out trials. These included the following frontoparietal sites: left IPS, left FEF, left MFG/IFG, and right IFG. Interestingly, several sites in visual cortex also showed this interaction effect, including left MOG and IOG, left inferior temporal gyrus, right fusiform gyrus (FG; not illustrated), and right middle temporal gyrus. No other significant interactions were observed (e.g., those involving non-switch > switch trials).

Discussion

A central goal of this experiment was to determine brain regions in humans engaged during target selection based on the updating of an endogenous cue (i.e., during the color cueing task). To probe this question, we determined brain activations associated with the interaction of task and trial type. Specifically, we determined regions in which the difference between switch and non-switch trials was greater during the color cueing task relative to the pop-out task. Because both types of trials involved a change in the target grating, such a contrast isolated regions that are important for endogenous updating.

Task by trial type interactions were observed in several fronto-parietal regions, including the IPS, FEF, MFG, and IFG. As stated in “Introduction”, these regions are thought to be important sites involved in the control of attention. Our findings further reveal that these regions are also important for the updating of endogenous cue information. Importantly, the FEF, MFG, and IFG were all removed in the region ablated in our monkeys with deficits in top-down attentional control, but the IPS was not. Thus, in addition to lateral PFC, the IPS may also contribute to this function.

Task by trial interactions were observed not only in fronto-parietal “control” areas, but also in several visual regions, namely, the left MOG, left IOG, and right FG. Therefore, such visual activations were not simply due to the task performed or trial type, but depended instead on the combination of the color cueing task and switch trials. We suggest that these visual areas were the recipients of top-down signals from fronto-parietal control regions that are generated when cue information is updated. For anterior visual areas with bilateral visual inputs, these top-down signals may go to visual areas in either or both hemispheres.

Single-cell recording studies have shown that spontaneous (baseline) firing rates are 30–40% higher for neurons in areas V2 and V4 when a monkey is cued to attend covertly to a location within the neuron's receptive field (RF) in expectation of a stimulus but before it is presented

there; that is, in the absence of visual stimulation (Luck et al. 1997). This increased baseline activity, termed the “baseline shift”, has been suggested to reflect top-down signals that feed back from higher-order control areas to lower-order visual processing areas. Such a shift in baseline activity in visual cortex would presumably “sensitize” neurons with RFs at the attended location, so that when a stimulus subsequently appears at that location there would be enhanced visually evoked activity. Similar effects have also been observed in neuroimaging studies (Kastner et al. 1999), in which “baseline” effects have been observed in human areas V1, V2, V4, and TEO. Increases in baseline activity are not only spatially specific, but also appear to depend on the type of visual feature attended to (Chawla et al. 1999). If our interpretation is correct, then top-down signals influence visual processing not only during sustained directed attention to a stimulus’ location and features, but also during the updating of the information conveyed by endogenous cues.

General discussion

In Experiment 1, we found that monkeys with lesions of lateral PFC were impaired in their ability to use a central color cue to attend to a matching colored grating presented among distracters. The magnitude of this impairment increased when the cue/target identity changed frequently over trials. When target identity changed due to bottom-up stimulus salience in the color pop-out task, we found that the monkeys showed a moderate impairment, but it did not increase with the frequency of the target color change. There was little or no impairment in performance when distracters were not present, indicating that the monkeys’ capacity to both orient to a solitary target and discriminate its orientation remained intact. This pattern of results suggests that PFC is necessary for flexible switching of top-down control of attention.

The results from the human functional brain imaging in Experiment 2 complement these lesion findings and provide additional insights into the cortical architecture of cognitive control. The regions of human PFC that exhibited significant increased activation for switch trials in the color cueing task (relative to the color pop-out task) are homologous to the ablated regions of monkey lateral PFC that resulted in deficits in top-down switching of attention. Thus, in both monkeys and humans, important PFC sites included the FEF as well as mid- and inferior PFC regions. However, in addition to differential activation of human prefrontal areas, the IPS also exhibited increased activation during switch vs. non-switch trials that was greater for color cueing than for pop-out tasks. This pattern of parietal and frontal activation in Experiment 2 agrees with the notion, recently advanced by Petersen and colleagues (Dosenbach et al. 2008), that the lateral PFC does not constitute the sole top-down controller in the brain (Miller and Cohen 2001). Instead, functionally and anatomically distinguishable regions of frontal and parietal cortex contribute specific individual control functions as nodes within separate control networks. This putative role of parietal cortex may also account for our monkeys’ ability to maintain set information across non-switch trials in the color cueing task, despite the absence of lateral PFC.

The idea that PFC plays a predominant role in the ability to flexibly switch top-down attention is compatible with human lesion data, which show that large lateral PFC lesions typically cause a long-lasting perseveration, either on a stimulus or on a response (Milner 1963; Walker et al. 1998; Manes et al. 2002; Aron et al. 2004). As with our monkeys, these studies show that PFC lesions typically do not result in a permanent loss of the ability to attend selectively. Likewise, fMRI studies in humans often show activation of PFC in attentional tasks, but the activation is greatest when subjects must switch between responses, switch between tasks, or switch their attention between different stimuli (Dove et al. 2000; Monchi et al. 2001; Dreher and Berman 2002; Dreher et al. 2002; Brass et al. 2003; Braver et al. 2003; Dreher and Grafman 2003; Smith et al. 2004; Hampshire and Owen 2006; Loose et al. 2006; Slagter et al. 2006; Yeung et al. 2006). In monkeys, PFC cells switch their response properties between different tasks,

and even between different phases of the same task (e.g., Hoshi et al. 1998; White and Wise 1999; Asaad et al. 2000; Buschman and Miller 2007). The present results support the idea that PFC lesions in monkeys, like those in humans, have long-lasting effects on attentional switching, which other brain structures apparently cannot fully compensate for over time (Mishkin 1964; Knight 1984; Dias et al. 1996a, b; Chao and Knight 1997; Rushworth et al. 1997).

As mentioned in the “Introduction”, several popular theories of attention have proposed that sensory representations compete for neural resources (Grossberg 1980; Bundesen 1990; Desimone and Duncan 1995; Bundesen et al. 2005). A common feature of these theories is that endogenous attention is accomplished through top-down feedback from frontal and parietal areas. That our monkeys with PFC lesions performed as well as they did lends some support for the role of parietal cortex in attentional control. Indeed, one could argue for a broader interpretation of top-down control that could, depending on the cognitive demands of the task, include the contribution of any number of cortical and subcortical areas. Rather than limiting the domain of attentional control to frontal and parietal areas, structures outside of these regions may well contribute to control depending on the task and response strategy.

It is possible, for example (perhaps even likely), that the monkeys in our study changed their strategy on the color cueing task following the surgical lesion and split brain procedure. Indeed, both monkeys needed an extended period of retraining in the contralesional hemifield with a simpler version of the color cueing task to attain consistent levels of performance. Assuming the PFC lesion disrupted the ability of the monkeys to integrate the cue information in the context of the task, the monkeys could have defaulted to a “win-stay lose-shift” response strategy when being tested in the contralesional hemifield. Using this strategy, the monkey would ignore the cue and attend to whichever colored grating was recently rewarded until an error occurred, then switch to one of the other two colored gratings. The adoption of this strategy can explain why the monkeys performed as well as they did in the contralesional hemifield with large values of cue repetition and why errors increased as the cue changed more frequently. This scenario raises the intriguing possibility that top-down control over sensory representations in early visual areas is normally accomplished by the recruitment of any number of cortical and subcortical regions involved in a given task. For a win-stay lose-shift strategy, one can speculate that brain structures involved in stimulus-reward associations and error (e.g., orbitofrontal cortex, amygdala, ventral tegmentum, ventral striatum, and cingulate cortex) would participate in the attentional control of sensory information. This broader interpretation of top-down control of attention does not discount the contributions of prefrontal and parietal cortex, but extends the anatomical substrates beyond the “frontal-parietal network” to better account for the tremendous flexibility of primate behavior.

References

Aron AR, Monsell S, Sahakian BJ, Robbins TW. A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. Brain 2004;127:1561–1573. [PubMed: 15090477]

Asaad WF, Rainer G, Miller EK. Neural activity in the primate prefrontal cortex during associative learning. Neuron 1998;21:1399–1407. [PubMed: 9883732]

Asaad WF, Rainer G, Miller EK. Task-specific neural activity in the primate prefrontal cortex. J Neurophysiol 2000;84:451–459. [PubMed: 10899218]

Barcelo F, Suwazono S, Knight RT. Prefrontal modulation of visual processing in humans. Nat Neurosci 2000;3:399–403. [PubMed: 10725931]

Bianchi, L. The mechanism of the brain and the function of the frontal lobes. E. & S. Livingstone; Edinburgh: 1922.

Blasi V, Young AC, Tansy AP, Petersen SE, Snyder AZ, Corbetta M. Word retrieval learning modulates right frontal cortex in patients with left frontal damage. Neuron 2002;36:159–170. [PubMed: 12367514]

Brass M, Ruge H, Meiran N, Rubin O, Koch I, Zysset S, Prinz W, von Cramon DY. When the same response has different meanings: recoding the response meaning in the lateral prefrontal cortex. Neuroimage 2003;20:1026–1031. [PubMed: 14568472]

Braver TS, Reynolds JR, Donaldson DI. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 2003;39:713–726. [PubMed: 12925284]

Bundesen C. A theory of visual attention. Psychol Rev 1990;97:523–547. [PubMed: 2247540]

Bundesen C, Habekost T, Kyllingsbaek S. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol Rev 2005;112:291–328. [PubMed: 15783288]

Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 2007;315:1860–1862. [PubMed: 17395832]

Chao LL, Knight RT. Prefrontal deficits in attention and inhibitory control with aging. Cereb Cortex 1997;7:63–69. [PubMed: 9023433]

Chawla D, Rees G, Friston KJ. The physiological basis of attentional modulation in extrastriate visual areas. Nat Neurosci 1999;2:671–676. [PubMed: 10404202]

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–215. [PubMed: 11994752]

Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995;18:193–222. [PubMed: 7605061]

Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 1996a;380:69–72. [PubMed: 8598908]

Dias R, Robbins TW, Roberts AC. Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. Behav Neurosci 1996b;110:872–886. [PubMed: 8918991]

Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. Trends Cogn Sci 2008;12:99–105. [PubMed: 18262825]

Dove A, Pollmann S, Schubert T, Wiggins CJ, von Cramon DY. Prefrontal cortex activation in task switching: an event-related fMRI study. Brain Res Cogn Brain Res 2000;9:103–109. [PubMed: 10666562]

Dreher JC, Berman KF. Fractionating the neural substrate of cognitive control processes. Proc Natl Acad Sci USA 2002;99:14595–14600. [PubMed: 12391312]

Dreher JC, Grafman J. Dissociating the roles of the rostral anterior cingulate and the lateral prefrontal cortices in performing two tasks simultaneously or successively. Cereb Cortex 2003;13:329–339. [PubMed: 12631562]

Dreher JC, Koechlin E, Ali SO, Grafman J. The roles of timing and task order during task switching. Neuroimage 2002;17:95–109. [PubMed: 12482070]

Duncan J. Disorganization of behaviour after frontal lobe damage. Cogn Neuropsychol 1986;3:270–290.

Ferrier, D. The functions of the brain. Smith Elder and Company; London: 1876.

Fuster, JM. Memory in the cerebral cortex. MIT Press; Cambridge: 1995.

Genovesio A, Brasted PJ, Mitz AR, Wise SP. Prefrontal cortex activity related to abstract response strategies. Neuron 2005;47:307–320. [PubMed: 16039571]

Goldman-Rakic, P. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory.. In: Plum, F., editor. Handbook of physiology: the nervous system. American Physiological Society; Bethesda: 1987. p. 373-417.

Grafman, J. Alternative frameworks for the conceptualization of prefrontal lobe functions.. In: Boller, FG.; Grafman, J., editors. Handbook of neuropsychology. Elsevier; Amsterdam: 1994. p. 187-202.

Grossberg S. How does a brain build a cognitive code? Psychol Rev 1980;87:1–51. [PubMed: 7375607]

Hampshire A, Owen AM. Fractionating attentional control using event-related fMRI. Cereb Cortex 2006;16:1679–1689. [PubMed: 16436686]

Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. Nat Neurosci 2000;3:284–291. [PubMed: 10700262]

Hoshi E, Shima K, Tanji J. Task-dependent selectivity of movement-related neuronal activity in the primate prefrontal cortex. J Neurophysiol 1998;80:3392–3397. [PubMed: 9862940]

Kastner S, Ungerleider LG. Mechanisms of visual attention in the human cortex. Annu Rev Neurosci 2000;23:315–341. [PubMed: 10845067]

Kastner S, Pinsk MA, De Weerd P, Desimone R, Ungerleider LG. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 1999;22:751–761. [PubMed: 10230795]

Knight RT. Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 1984;59:9–20. [PubMed: 6198170]

Loose R, Kaufmann C, Tucha O, Auer DP, Lange KW. Neural networks of response shifting: influence of task speed and stimulus material. Brain Res 2006;1090:146–155. [PubMed: 16643867]

Luck SJ, Chelazzi L, Hillyard SA, Desimone R. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J Neurophysiol 1997;77:24–42. [PubMed: 9120566]

Luria, AR. Frontal lobe syndromes.. In: Vinken, PJ.; Bruyn, GW., editors. Handbook of clinical neurology. Elsevier; New York: 1969. p. 725-757.

Manes F, Sahakian B, Clark L, Rogers R, Antoun N, Aitken M, Robbins T. Decision-making processes following damage to the prefrontal cortex. Brain 2002;125:624–639. [PubMed: 11872618]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202. [PubMed: 11283309]

Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci 1996;16:5154–5167. [PubMed: 8756444]

Milner B. Effects of different brain lesions on card sorting. Arch Neurol 1963;9:100–110.

Mishkin, M. Perseveration of central sets after frontal lesions in monkeys.. In: Warren, JM.; Akert, K., editors. The frontal granular cortex and behavior. McGraw-Hill; New York: 1964. p. 219-241.

Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J Neurosci 2001;21:7733–7741. [PubMed: 11567063]

Moore T, Armstrong KM. Selective gating of visual signals by microstimulation of frontal cortex. Nature 2003;421:370–373. [PubMed: 12540901]

Passingham, R. The frontal lobes and voluntary action. Oxford University Press; Oxford: 1993.

Pessoa L, Rossi A, Japee S, Desimone R, Ungerleider LG. Attentional control during the transient updating of cue information. Brain Res. 2008 (in press)[Epub]

Quintana J, Yajeya J, Fuster JM. Prefrontal representation of stimulus attributes during delay tasks. I. Unit activity in cross-temporal integration of sensory and sensory-motor information. Brain Res 1988;474:211–221. [PubMed: 3208130]

Rainer G, Asaad WF, Miller EK. Selective representation of relevant information by neurons in the primate prefrontal cortex. Nature 1998;393:577–579. [PubMed: 9634233]

Rossi AF, Bichot NP, Desimone R, Ungerleider LG. Top down attentional deficits in macaques with lesions of lateral prefrontal cortex. J Neurosci 2007;27:11306–11314. [PubMed: 17942725]

Rushworth MF, Nixon PD, Eacott MJ, Passingham RE. Ventral prefrontal cortex is not essential for working memory. J Neurosci 1997;17:4829–4838. [PubMed: 9169541]

Schall, JD. Visuomotor areas of the frontal lobe.. In: Rockland, KS.; Kaas, JH.; Peters, A., editors. Cerebral cortex. Plenum Press; New York: 1997. p. 527-628.

Schall JD. The neural selection and control of saccades by the frontal eye field. Philos Trans R Soc Lond B Biol Sci 2002;357:1073–1082. [PubMed: 12217175]

Shallice T, Burgess PW. Deficits in strategy application following frontal lobe damage in man. Brain 1991;114(Pt 2):727–741. [PubMed: 2043945]

Slagter HA, Weissman DH, Giesbrecht B, Kenemans JL, Mangun GR, Kok A, Woldorff MG. Brain regions activated by endogenous preparatory set shifting as revealed by fMRI. Cogn Affect Behav Neurosci 2006;6:175–189. [PubMed: 17243354]

Smith AB, Taylor E, Brammer M, Rubia K. Neural correlates of switching set as measured in fast, event-related functional magnetic resonance imaging. Hum Brain Mapp 2004;21:247–256. [PubMed: 15038006]

Walker R, Husain M, Hodgson TL, Harrison J, Kennard C. Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. Neuropsychologia 1998;36:1141–1159. [PubMed: 9842760]

Wetherill GB, Levitt H. Sequential estimation of points on a psychometric function. Br J Math Stat Psychol 1965;18:1–10. [PubMed: 14324842]

White IM, Wise SP. Rule-dependent neuronal activity in the prefrontal cortex. Exp Brain Res 1999;126:315–335. [PubMed: 10382618]

Yeung N, Nystrom LE, Aronson JA, Cohen JD. Between-task competition and cognitive control in task switching. J Neurosci 2006;26:1429–1438. [PubMed: 16452666]

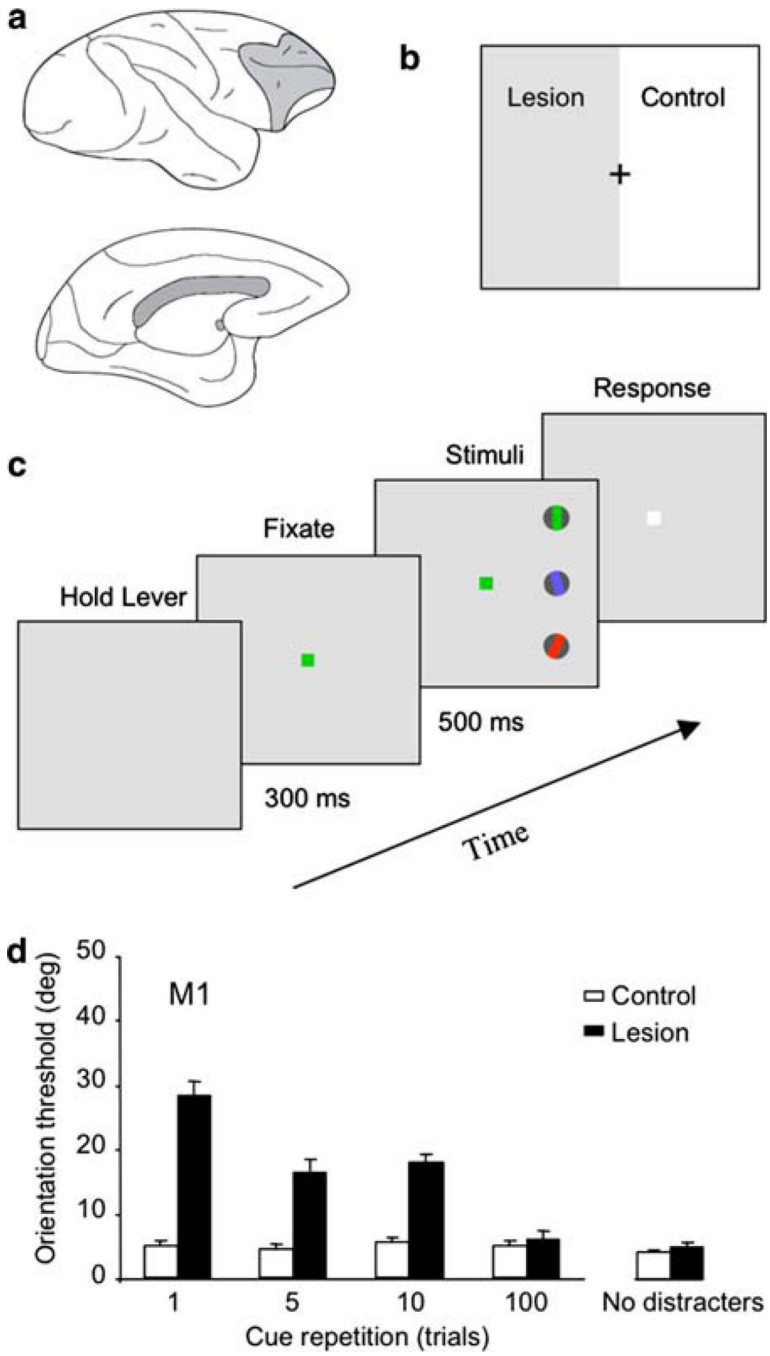

Fig. 1.

Color cueing experiment. **a** Combination of unilateral PFC lesion and split brain. *Upper*: The lateral view of the right hemisphere showing a lesion of the lateral surface of the right PFC (*gray shading*). *Lower*: The medial surface of the left hemisphere shows the transection, in *gray*, of the corpus callosum and anterior commissure. **b** The combined lesion and split brain resulted in the contralesional visual hemifield, shown as *gray*, being processed without PFC and the ipsilesional visual hemifield serving as an experimental control. The effect of the lesion was assessed by comparing visual performance in the two hemifields. **c** The temporal sequence of stimulus presentation in the color cueing task. The monkey fixated centrally and discriminated the orientation of the peripheral target grating that was cued by the color of the

fixation spot. The relative positions of the colored gratings were randomly assigned each trial. The frequency at which the color cue changed was varied to examine the effect of increasing or decreasing the "top-down load" of the task. **d** The average orientation threshold is plotted as a function of cue repetition in the color cueing task for monkey M1. Performance in the control hemifield is shown in *white*, and in the lesion-affected hemifield in *black*. Error bars represent the standard error of the mean. Each bar represents the average of between 40 and 60 thresholds for that condition. Adapted from Rossi et al. (2007)

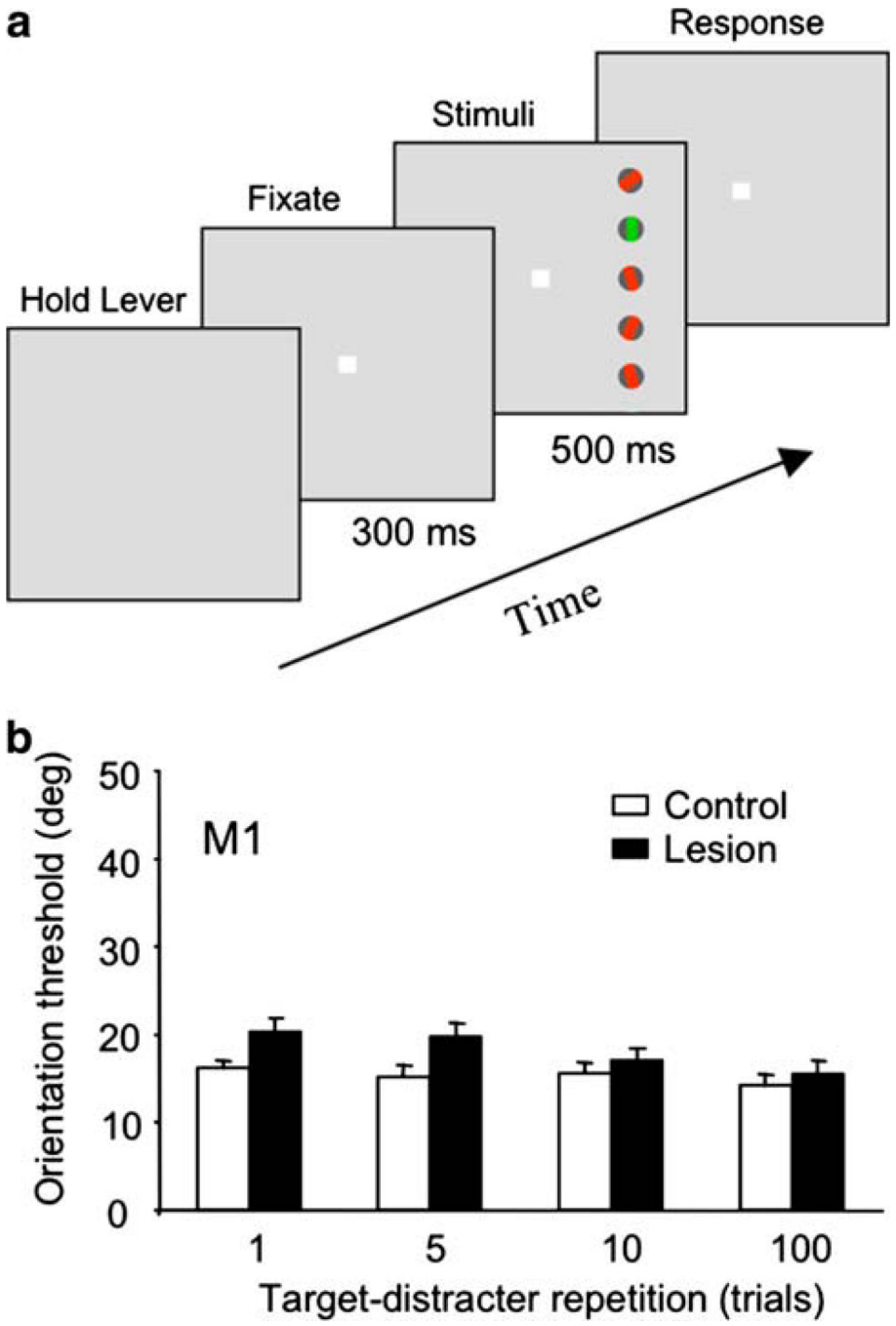

Fig. 2.

Effects of target-distracter repetition on grating orientation discrimination in a color pop-out task. **a** The temporal sequence of stimulus presentation in the color pop-out display. The monkey fixated centrally and discriminated the orientation of the target grating as defined by color pop-out. The frequency at which the target and distracter colors changed was varied to examine the effect of changes in target identity on task performance. **b** The average orientation threshold is plotted as function of cue repetition for monkey M1. Performance in the control hemifield is shown in *white*, and in the lesion-affected hemifield in *black*. Error bars represent the standard error of the mean. Each bar represents the average of between 50 and 60 thresholds for that condition. Adapted from Rossi et al. (2007)

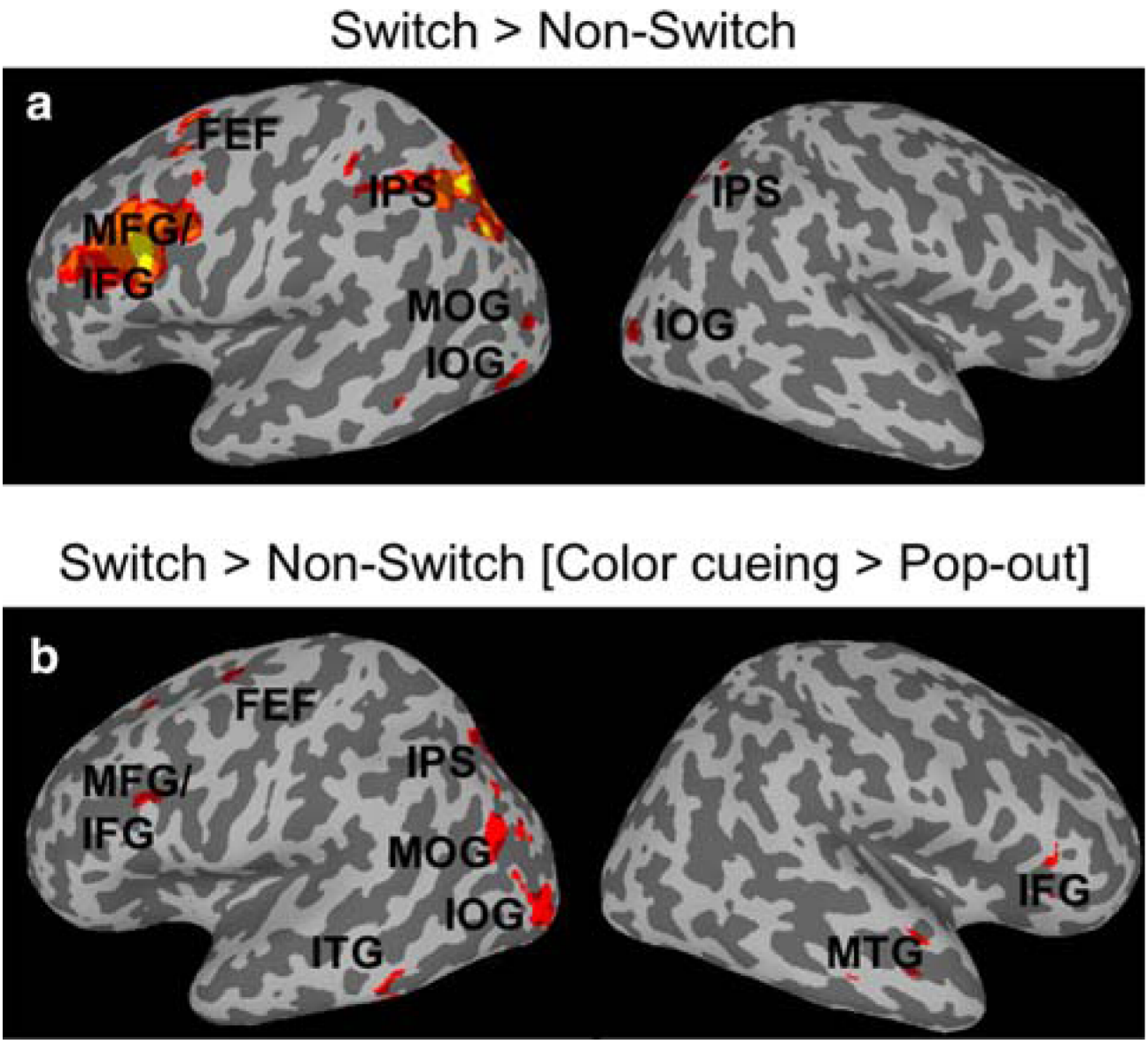

Fig. 3.

Results from Experiment 2. **a** Group activation maps displaying switch > non-switch trials across both color cueing and pop-out conditions. **b** Group activation maps displaying switch > non-switch trials for color cueing > pop-out conditions (i.e., task × trial type interaction effect). Data are illustrated on inflated brains. Adapted from Pessoa et al. (2008)