17   Rostral Prefrontal Brain Regions (Area 10): A Gateway between Inner Thought and the External World?

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17.1   Introduction

This chapter reviews recent evidence from our laboratory (and others) that suggests that the most anterior parts of the frontal lobes of the brain support cognitive processes which are critical to complex volitional behavior in humans. We conclude by proposing a simple preliminary hypothesis about the role of this region in cognition.

17.2   Introduction to the Rostral Prefrontal Cortex

The part of the frontal lobes that is foremost in the brain has many names. The most common of these are "anterior prefrontal cortex," "the frontal pole," "frontopolar cortex," and "rostral prefrontal cortex" (rostral PFC). Of these, we favor the use of the term "rostral" since the term is equivalent to others that are used to denote regions of the brain (e.g., caudal, dorsal, lateral, medial, ventral). However, these terms all refer to a region which broadly corresponds to the cytoarchitectonic area known as Brodmann Area (BA) 10. There is very good reason for suspecting that this brain region plays a critical role in human cognition. For instance, it is large in humans: in volumetric terms probably the largest single architectonic region of the frontal lobes (Christoff et al. 2001), which themselves account for approximately 30 percent of the total cortical surface. Given that the brain may consume as much as 20 percent of the oxygen we extract from the air that we breathe (Raichle et al. 2001), there must be some evolutionary advantage to such a large brain region. Moreover, the rostral PFC regions are of unique proportional size in humans; they are for instance double the relative size in humans compared with chimpanzees (Semendeferi et al. 2001). And finally, this region is possibly the last to achieve myelination, and it has been argued that tardily myelinating areas engage in complex functions highly related to the organism's experience (Fuster 1997, p. 37). These are all good reasons to imagine that the rostral PFC may support cognitive processing which is especially important to humans.

However, until recently there has been very little evidence which might speak to the cognitive functions of this brain region.

17.3   Outline of the Arguments

Before outlining a potential theoretical resolution, this chapter seeks to explain why it is that we know so little and sets out the problems facing current theorists. In doing so, we will make the following points (for fuller exposition of the theoretical conclusion alone, readers are referred to Burgess, Simons, Dumontheil, and Gilbert, in press):

1. There are very few data concerning the putative functions of rostral PFC other than from functional imaging and a small number of human lesion studies.
2. Functional imaging data provide few constraints on theorizing because rostral PFC activation is found in such a wide variety of tasks.
3. Human lesion data rule out many aspects of the theories from functional imaging.
4. The most promising approach for functional imaging is therefore to start with the possible explanations emerging from lesion data.
5. Functional imaging studies that start from this base suggest that the role of rostral PFC is in the attentional control between stimulus-independent and stimulus-oriented thought.

Let us now consider these points in turn.

17.3.1   There Are Very Few Data Concerning the Putative Functions of Rostral PFC Other Than from Functional Imaging and a Small Number of Human Lesion Studies

There are many reasons why we know so little about the cognitive functions of rostral PFC. For instance, animal studies of this region are problematic: The very fact of the structural difference between humans and other animals creates doubt as to the transferability of findings from one species to another, and animal lesion studies of this region are in any case hindered by practical anatomical considerations. Other cognitive neuroscience methods also face limitations. For instance, electrophysiological methods do not presently have the required spatial resolution to separate subregions of the frontal lobes, and transcranial magnetic stimulation studies of certain aspects of rostral PFC (i.e., medial Area 10) may be difficult for anatomical reasons. Thus, virtually the only significant evidence one might call upon comes from two methods: functional imaging and human lesion studies. Human lesion studies are, however, difficult and costly: Area 10 lesions (e.g., tumors or strokes) are neither common nor do they typically produce "hard" neurological signs (such as hemiparesis, marked aphasia, etc.), and so unless they are the result of trauma, they are often not detected until they are large, affecting other brain regions in addition to Area 10. This then raises the question of which of the symptoms can be attributable specifically to the rostral

aspect of the lesion, usually necessitating a group study using the overlapping lesion method. However, since there is no straightforward pathology–lesion site correspondence, the pattern will typically be made more difficult by issues of the effects of different pathologies. These issues are not insurmountable (see, e.g., Burgess et al. 2000; Burgess, Veitch, and Costello, submitted) but will necessitate careful and lengthy data collection and analysis, often taking several years. In this context, the functional imaging method, where data collection can be scheduled in advance and takes only a few hours, is understandably attractive to researchers.

17.3.2 Functional Imaging Data Provide Few Constraints on Theorizing because Rostral PFC Activation Is Found in Such a Wide Variety of Tasks

Functional brain imaging, principally positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI), has shown that local hemodynamic (e.g., blood flow; blood oxygenation) changes occur in rostral PFC during the performance of a very wide variety of cognitive tasks (Grady 1999), from the simplest (e.g., conditioning paradigms; Blaxton et al. 1996) to highly complex tests involving memory and judgment (e.g., Burgess et al. 2001, 2003; Frith and Frith 2003; Koechlin et al. 1999) or problem solving (e.g., Christoff et al. 2001).

Indeed, one can find activation of the rostral PFC in just about any kind of task, for example, verbal episodic retrieval (Rugg et al. 1996; Tulving et al. 1996), nonverbal episodic retrieval (Roland and Gulyas 1995; Haxby et al. 1996), semantic memory (Martin et al. 1995; Jennings et al. 1997), language (Bottini et al. 1994; Klein et al. 1995), motor learning (Jenkins et al. 1994), shock/tone conditioning (Hugdahl et al. 1995), nonverbal working memory (Gold et al. 1996; Haxby et al. 1995), verbal working memory (Petrides et al. 1993), spatial memory (N. Burgess et al. 2001), auditory perception (Zatorre et al. 1996), object processing (Kosslyn et al. 1994, 1995), Tower of London Test (Baker et al. 1996), Wisconsin Card Sorting Test (Berman et al. 1995), reasoning tasks (Goel et al. 1997), and intelligence tests such as Raven's Progressive Matrices (Christoff et al. 2001; Prabhakaran et al. 1997).

Perhaps a meta-analysis of the tasks which most reliably produce rostral PFC activation would isolate the critical processing component in these tasks that this region supports? Grady (1999) provides just such an analysis. She reviewed 90 PET studies showing prefrontal regional cerebral blood flow (rCBF) changes and concluded that the most heavily represented function of BA 10 is episodic memory, on the grounds that most of the experiments reporting BA 10 activation were using episodic memory paradigms. This was a very useful and carefully conducted review. However, it didn't take into account the predominance of episodic memory investigations in functional imaging studies. If one takes this into account, a quite different picture emerges. Thus 37/90 (41%) of the studies that Grady considered in her review investigated episodic memory, and 47/90 (52%) of the studies she considered implicated BA 10. However,

only 68 percent of the episodic memory studies were found to cause BA 10 activations, and just 25 (53%) of the paradigms that caused BA 10 activations were episodic memory ones. Furthermore, 7/90 of the studies that Grady considered were investigations of "working memory," and 6 of these (86%) showed BA 10 activation. And finally, 6/90 studies investigated conditioning or motor learning, and all 6 (100%) reported BA 10 activation. Thus, whatever role it is that BA 10 functions play in cognition, it is doubtful indeed that they are especially active when people are involved in episodic memory tasks. This is, of course, *not* to say that the processing BA 10 facilitates is unimportant to episodic memory (the findings are too consistent for this to be the case; see, e.g., Simons and Spiers 2003) but, rather, that whatever processing it supports is probably also used in many other types of situations.

On the need for convergent evidence from differing methods, this raises the issue of how one might progress in theorizing about the functions of BA 10, for example, by "narrowing down" the possibilities. One option is to rely upon converging evidence from different methods. Functional imaging as a method has some interesting properties as a way of developing and testing theories in cognitive neuroscience. However, it may be that it is not "equipotential" for all types of brain function, with the inferences getting harder as one attempts to evaluate more putatively "central" cognitive processes. This becomes especially important when one is trying to discover what is the function of a brain region rather than the brain regions that are involved in a particular function. A full examination of this issue is beyond this chapter. However, this is an important matter when trying to understand the scientific development of ideas about the functions of rostral PFC. What one would ideally like of a method in cognitive neuroscience in the current situation is that it can both "rule in" and "rule out" the involvement of a particular brain region in a particular function. However, functional imaging is essentially a correlative method, and therefore (in common with all correlative methods), invites inferential mistakes due to (among other possibilities) the influence of mediator variables and the like.

To illustrate this point, let us briefly consider how functional imaging might "rule in" the processes supported by a brain region in performing a particular task. Prima facie, a consistent relation between performance of task A and activation in brain region B suggests that region B supports processing important for task A performance. However, any "thought" will cause cerebral hemodynamic changes, whether they are strictly related to performance of the task or not. For the sake of argument, if we supposed that the function of rostral PFC is to support "stimulus-independent thought," one can begin to see how it might be easy to mistake activations associated with this for activations provoked by one's experimental task. Let us make this argument more concrete: Imagine that the principal information-processing role of the processes supported by brain region X is in facilitating daydreaming. If one were to devise a cognitive task (task Y) so easy and boring that subjects would sometimes daydream at the

same time as performing it, one might easily find oneself suggesting on the basis of one's functional imaging data that region X is involved in performance of task Y. But if performance of task Y actually bears no necessary relation to daydreaming, this would be a false assumption. This is an especially relevant argument when one is investigating the functions of rostral PFC, since at least one study (McGuire et al. 1996) has indeed associated rostral activation with self-report of stimulus-independent thoughts (i.e., thoughts unrelated to the tasks subjects were instructed to perform or to their immediate sensory environment).

In this way, efforts to "rule in" a brain region on the basis of functional imaging data alone should be treated with caution, and the behavioral data from task performance requires close examination. But this is a relatively small problem compared with the difficulty of "ruling out" the involvement of a region in a particular task. This would likely rely upon a lack of significant activation in a brain region, and of course negative findings are not of equal power to positive ones for theorizing, since there will always be more reasons for not finding a statistically significant result than for finding one.

Compare the difficulty of these inferences for theorizing with the results one would attain from a lesion study. If damage to brain region X consistently causes severe impairment in task Y, then it is difficult to argue that brain region X does not support some process/system/pathway which is important to task Y (although this is not to say that it is a simple matter to determine what the exact processing contribution is). Similarly, if obliteration of brain region X consistently does *not* cause impairment in task Y, it is difficult to argue that that brain region plays some critical role in performance of that task. Thus, lesion studies, in theory, can both "rule in" and "rule out" the involvement of a brain region in performance of a particular task and, as a consequence, are potentially a much more powerful way of determining the functions of a brain region than functional imaging studies. A recent demonstration of this point is given by Bird et al. (2004), who describe a fascinating case study of a neurological patient who had suffered extensive damage to the medial rostral PFC bilaterally following a rare form of stroke. The areas damaged in this case included all those repeatedly implicated by functional imaging studies as critical for "theory of mind" tasks (i.e., those involving the attribution of mental states to other agents). However, their patient actually showed no impairment on a wide range of theory of mind tasks, although she was impaired on certain tests of executive function (most notably the Six Element Test and the Hayling Test, part 2 (Burgess et al. 1996; Burgess and Shallice 1996, 1997). Bird et al. (2004) rightly caution against the use of functional imaging as the sole method of establishing cognitive neuroanatomy. Bearing this in mind, we will now look at the theories of rostral PFC function that have emerged from functional imaging and then "test" these theories by considering the empirical evidence from lesion studies.

Perhaps because of the widespread findings of BA 10 involvement in functional imaging studies, theories of the possible function of this brain region predicated on these data tend to be quite general. For instance, one influential theory of the functions of *medial* rostral PFC is that it supports an "organized mode of brain function" that is present as a baseline or default state and attenuated during specific goal-directed behaviors (Gusnard et al. 2001; Raichle et al. 2001). This is argued to explain repeated findings by this group of medial rostral PFC "deactivations" when subjects are performing various cognitive tasks (compared with resting with one's eyes closed). This is referred to below as the "default mode hypothesis."

By contrast, other investigators have concerned themselves primarily with the functions of *lateral* Area 10. Christoff and Gabrieli (2000) have argued that "the frontopolar cortex is a functionally distinct prefrontal region that may be selectively involved in active processing, such as evaluation, monitoring or manipulation, performed on internally generated information" (p. 183). There is some broad agreement in framework here with the views of Koechlin and colleagues (e.g., Koechlin et al. 1999; Dreher et al. 2002; Koechlin, Ody, and Kouneihaer 2003). They maintain that (lateral) rostral PFC "selectively mediates the human ability to hold in mind goals while exploring and processing secondary goals" (Koechlin et al. 1999, p. 148), with the frontal lobes organized along a posterior to anterior axis as the task being performed becomes more endogenously guided (Dreher et al. 2002), with the highest level of this control being exerted by (lateral) rostral PFC according to the temporal episode in which the stimulus occurs (Koechlin, Ody, and Kouneihaer 2003). Koechlin was also one of the first people to demonstrate a possible medial-lateral dissociation in rostral PFC function, with a study that implicated medial rostral regions in situations where a subject encounters predictable sequences of stimuli, and lateral polar regions when the subject performed tasks in sequences contingent upon unpredictable events (Koechlin et al. 2000).

What predictions do these accounts make about the pattern of impairment that would be expected following rostral PFC lesions? If rostral PFC supports cognitive processes that are fundamental to a wide range of functions (e.g., the "default mode" hypothesis) or functions used in a wide range of conditions such as those involved in processing of internally generated information, it would be natural to expect that damage to this region in neurological patients should lead to marked cognitive impairment in many domains (e.g., problems with memory, language, perception, etc.). But what pattern actually occurs?

17.3.3   Human Lesion Data Rule out Many Aspects of the Theories from Functional Imaging

The available evidence shows emphatically that it is *not* the case that patients with rostral lesions show deficits on a wide range of cognitive tasks. Consider, for instance,

Table 17.1

AP's Neuropsychological Test Performance.

Measure	Data	
	Shallice and Burgess (1991)	metzler and Parkin (2000)
Intellectual Functioning		
NART FSIQ	124	123
WAIS FSIQ	130	133[a]
PIQ	138	129
VIQ	124	128
Memory Tests		
Doors and People (%iles):		
Verbal Memory		99
Visual Memory		75
Recall		84
Recognition		98
AVLT (SS)		12
Recognition (SS)	10 (words)	
	14 (faces)	
Executive Function Tests		
FAS Verbal Fluency	70	56
WCST Categories	6	6
Perseverations	0	0
Cognitive Estimates	2	2
Stroop %ile	OK	100

[a]WAIS–R.

the case of AP from Shallice and Burgess (1991), who was called "NM" when he was investigated by Metzler and Parkin (2000). AP was involved in a serious road-traffic accident when he was in his early twenties, and sustained an open head injury, leading to virtually complete removal of the rostral PFC. But consider his performance on standard neuropsychological tests shown in table 17.1. This shows the results of both the Shallice/Burgess and Metzler/Parkin testing sessions, administered approximately 10 years apart. On standard neuropsychological measures of intellectual functioning, memory, and perception and even traditional tests of executive function, AP performs within the superior range.

This is not, however, to say that AP was unimpaired in other regards (Shallice and Burgess 1991; Metzler and Parkin 2000). The most noticeable of these impairments in everyday life was a marked multitasking problem. This manifested itself as tardiness and disorganization, the severity of which ensured that despite his excellent intellect and social skills, he never managed to make a return to work at the level he had

enjoyed premorbidly. Shallice and Burgess (1991) invented two new tests of multi-tasking to assess these problems. One was a real-life multitasking test based around a shopping exercise (the "Multiple Errands Test"), and the second was a multitasking test for use in the laboratory or clinic (the "Six Elements Test"). Despite excellent general cognitive skills, AP and the other cases reported by Shallice and Burgess all performed these tasks below the 5% level compared with age- and IQ-matched controls.

There are now a number of cases reported in the literature of individuals who show similar everyday behavioral impairments (see Burgess 2000 for a review), and there is a remarkably consistent finding of involvement of Area 10 among them. For instance, in the six cases reviewed by Burgess, all had rostral PFC involvement of either the left or right hemispheres (or both). Moreover, all cases to whom the Shallice/Burgess multitasking tests have been administered have failed at least one of them. In addition to these cases, we might now also add that of Bird et al. (2004), described above, who failed the Six Elements Test.

Of course, anatomical–behavioral associations made on the grounds of data from single case studies should be treated with caution, since individual cases might be anatomically atypical (see Owen, this volume). However, two recent group human lesion studies also convincingly demonstrate that patients with rostral PFC damage do *not* necessarily have widespread cognitive deficits. Thus, Burgess et al. (2000) examined a series of 60 acute neurological patients (approximately three-quarters of whom were suffering from brain tumors) and 60 age- and IQ-matched healthy controls on a multitasking test called the Greenwich Test. In this test, subjects are presented with three different simple tasks and told that they have to attempt at least some of each of the tasks in 10 minutes, while following a set of rules. One of these rules relates to all subtests ("in all three tasks, completing a red item will gain you more points than completing an item of any other color"), and there are four task-specific rules (e.g., "in the tangled lines test you must not mark the paper other than to write your answers down"). Thus, this is a multitasking test where the majority of the variance in performance of the test comes from rule infractions rather than task-switching problems (see Burgess 2000 for a specification of the more general characteristics of a multitasking test). The Greenwich Test was administered in a form that allowed consideration of the relative contributions of task rule learning and remembering, planning, plan following, and remembering one's actions to overall multitasking performance. Specifically, before participants began the test, their ability to learn the task rules (by both spontaneous and cued recall) was measured; this measure was called "Learn." They were then asked how they intended to do the test, and a measure of the complexity and appropriateness of their plans was gained (a variable called "Plan"). The participants then performed the task itself, and by comparing what they did with what they had planned to do, a measure of "Plan Following" was made.

Multitasking performance (the number of task switches minus the number of rule breaks) was referred to as the test "Score." After these stages were finished, subjects were asked to recollect their own actions by describing in detail what they had done (variable name: "Recount"). Finally, delayed memory for the task rules was examined ("Remember").

If rostral aspects of the frontal lobes support processes which are critical to performance in many situations, one might expect that patients with lesions to this region would be impaired at all stages of this test, with perhaps the impairment profile reflecting the differing sensitivities of the measures (e.g., delayed memory would be worst, since delayed free recall measures are usually among the most sensitive to nonspecific neurological damage). However, this was not the case at all. Patients with left hemisphere rostral lesions, when compared with patients with lesions elsewhere, showed a significant multitasking impairment (i.e., the variable "Score") despite no significant impairment on remembering task rules (the"Remember" variable). Indeed, the left rostral prefrontal cases showed *no* significant impairment on any variable except the one reflecting multitasking performance. In other words, despite being able to learn the task rules, form a plan, remember their actions, and say what they should have done, they nevertheless showed a multitasking problem.

A further recent human group lesion study underlines these results (Burgess, Veitch, and Costello, submitted). In this study, a new version of the Burgess et al. (1996) Six Elements Test of multitasking was given to 69 acute neurological patients with circumscribed focal lesions and 60 healthy individuals, using the administration framework of Burgess et al. (2000). The Six Elements Test differs from the Greenwich Test in that the multitasking score reflects mainly voluntary time-based switching rather than rule following. Compared with other patients, those whose lesions involved the rostral prefrontal regions of the right hemisphere made significantly fewer voluntary task switches, attempted fewer subtasks, and spent far longer on individual subtasks. They did not, however, make a larger number of rule breaks (in contrast to the left rostral patients in the Burgess et al. 2000 study). As with the study of Burgess et al. (2000), these multitasking deficits could not be attributed to deficits in general intellectual functioning, rule knowledge, planning, or retrospective memory.

17.3.4 The Most Promising Approach for Functional Imaging Is Therefore to Start with the Possible Explanations Emerging from Lesion Data

In this laboratory we have therefore taken the constraints presented by human lesion data as a scientific starting point for our functional imaging studies. The multitasking failures in our patients clearly had as a root cause problems with prospective memory (i.e., failure to carry out a delayed intention), so the first step was to investigate the brain regions involved in prospective memory as indicated by functional imaging. In the first study, Burgess, Quayle, and Frith (2001) used PET to investigate rCBF changes

in eight participants performing four different tasks, each under three conditions. The first condition (baseline) was subject paced and consisted of making judgments about two objects appearing together (e.g., which of two digits is the largest, or which of two letters comes nearer the start of the alphabet). The second condition consisted of the baseline task, but subjects were also told that if a particular combination of stimuli appeared (e.g., two vowels, two even numbers) they were to respond in a different way (press a particular key combination). However in this condition ("expectation"), none of these stimuli actually appeared. In the third condition, participants were given the same instructions and stimuli as in the first, except that the expected prospective memory stimuli did occur (after a delay, and on 20% of trials), and participants had the chance to respond to them ("execution" condition). In the terminology of prospective memory researchers, the last two conditions were "prospective memory" conditions in that they involved a delayed intention (see Burgess, Quayle, and Frith 2001 for an outline of the further characteristics of prospective memory tasks).

Burgess et al. (2001) considered the rCBF changes between conditions that were common across the four tasks. Relative to the baseline condition, rCBF increases were seen in the frontal pole (BA 10) bilaterally, right DLPFC (BA 45/46) and right inferior parietal regions (BA 7, 19, 39, 40), precuneus, plus decreases in left fronto-temporal regions (BA 38, 47 and insula) when the participants were expecting to see a stimulus, even though it did not occur. Further increases were seen in the thalamus when the intention cues were seen and acted upon, with a corresponding decrease in right dorsolateral PFC. It was concluded that at least some of the rCBF changes in the expectation condition were most likely associated with intention maintenance, with those in the execution condition associated with recognizing and responding to prospective memory cues. This result corresponded well with that of Okuda et al. (1998), who were the first to demonstrate a role for BA 10 in prospective memory using functional imaging.

Thus, there seems to be both within- and cross-method support for a role of BA 10 in prospective memory functions. And the Burgess, Quayle, and Frith (2001) study suggests that this role is material- and stimulus nonspecific, and probably involved more with maintenance rather than execution of the delayed intention.

However one possible explanation for the Burgess, Quayle, and Frith (2001) findings is that the activations seen in the expectation condition could be due to task difficulty or increased stimulus processing demands rather than anything to do with delayed intentions per se. This hypothesis was examined in a second PET experiment (Burgess, Scott, and Frith 2003). Three different tasks were administered under four conditions: baseline simple reaction time (RT), attention-demanding ongoing task only, ongoing task plus a delayed intention (unpracticed), ongoing task plus delayed intention (practiced). Under prospective memory conditions, Burgess et al. (2003)

found significant rCBF decreases in the superior medial aspects of the rostral PFC (BA 10) relative to the baseline or ongoing task only conditions. However, more lateral aspects of Area 10 (plus the mediodorsal thalamus) showed the opposite pattern, with rCBF increases in the prospective memory conditions relative to the other conditions. These patterns were broadly replicated over all three tasks. Since (a) both the medial and lateral rostral regions showed instances where rCBF was lower during a more effortful condition (as estimated by increased RTs and error rates) than in a less effortful one, and (b) there was no correlation between rCBF and RT durations or number of errors in these regions, a simple task difficulty explanation of the rCBF changes in the rostral aspects of the frontal lobes during prospective memory tasks was rejected. Instead, the favored explanation concentrated upon the particular processing demands made by these situations irrespective of the precise stimuli used or the exact nature of the intention, in particular the requirement to hold a thought in mind (i.e., stimulus-independent thought) while carrying out other operations on presented stimuli.

Significantly for the current account, there was good correspondence between the findings of this second PET study and the findings of the human group lesion study of Burgess et al. (2000). The left rostral region which showed significant decreases when a delayed intention was added to an ongoing task is (a subsection of) the same left rostral region which, when damaged, caused prospective memory impairments on the Greenwich Test of multitasking. This correspondence is shown in figure 17.1.
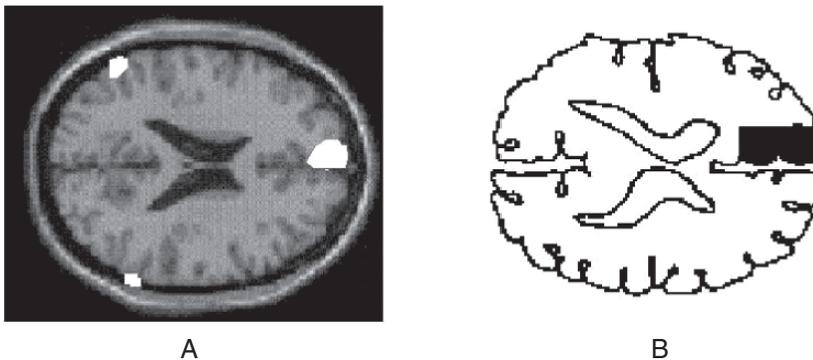

A   B

Figure 17.1
Comparison between the positron-emission tomography findings of Burgess, Scott, and Frith (2003) and the group lesion study of Burgess et al. (2000). Panel A shows the rostral prefrontal cortex (PFC) region which showed significant regional cerebral blood flow decrease in prospective memory conditions, and panel B shows the rostral PFC region which, when damaged, caused multitasking impairments on the Greenwich Test.

17.3.5   Functional Imaging Studies That Start from This Base Suggest That the Role of Rostral PFC Is in the Attentional Control between Stimulus-Independent and Stimulus-Oriented Thought: Introducing the "Gateway" Hypothesis of Rostral PFC

It is axiomatic of situations requiring prospective memory that there is a requirement to maintain a thought (or "internal representation") in the absence of external reminders (e.g., cues). Additionally, one is engaging in the ongoing task, which requires processing of externally presented stimuli. These are, of course, other requirements of multitasking, where one is "bearing in mind" that a task has to be performed (or returned to) while performing another task and may be using other internally maintained criteria (such a differing priorities) to determine behavior. And it would appear that rostral PFC is implicated in supporting processes critical to this behavior (see also Koechlin et al. 1999 for further evidence). But what exactly might this role be?

It is unlikely that rostral PFC is critical for all forms of stimulus-directed thought: Shallice and Burgess's (1991) three patients, all of whom had rostral PFC damage, performed ongoing tasks (e.g., arithmetic) as well as controls, and Bird et al.'s (2004) case similarly performed many tasks at a normal or near-normal level. So perhaps an explanation of their problems can be given by the opposing explanation from the functional imaging literature: that rostral PFC is involved in *stimulus-independent* thought, such as occurs in daydreaming, self-reflection, and other situations involving self-generated and maintained thought (e.g., McGuire et al. 1996; Christoff et al. 2001, 2003; Johnson et al. 2002; Zysset et al. 2002).

However, this explanation also fails as a good explanation of the pattern of cognitive deficits in lesion patients. Although a task such as mental arithmetic performed on a sum presented on a display undoubtedly involves processing externally presented material, it is equally true that the calculation itself must involve at least some "stimulus-independent thought" (i.e., the actual calculation itself) once past the early stages of visual processing and so forth. This would be even more the case with tasks with a large component of "internally generated thought" (cf. Christoff et al. 2001) such as theory of mind tasks. Thus, if the root of the rostral patients' problems were an incapacity for any form of stimulus-independent thought, they should again show cognitive impairment in a wide range of situations, and tasks involving judgment, theory of mind, and so forth, which have a large component of reflective thought, should be impaired. But they do not. Thus, a simple account in which rostral PFC is critical for all stimulus-independent thought can be rejected.

17.4   The Gateway Hypothesis

As we have seen, the idea which is at the center of most accounts of rostral PFC function is the notion of the contrast between stimulus-directed and stimulus-

independent thought (e.g., Christoff and Gabrieli 2000; McGuire et al. 1996; Christoff et al. 2001, 2003; Koechlin et al. 1999; Frith and Frith 2003; Gusnard et al. 2001; Johnson et al. 2002; Zysset et al. 2002). As we have seen, absolute versions of this position (i.e., of the kind: rostral PFC supports all stimulus-independent thought) are unsupportable. However, one possible position that maintains this useful framework is to suggest that rostral PFC plays a role in the goal-directed *coordination* of both modes of thought without being directly responsible for the information transformations involved in either. A simple analogy might be a railway track switch-point, where we imagine the train as representing packets of information within the brain, and the tracks as the pathways that carry that information. The switch point will have no influence upon the train itself (i.e., does not effect an information transformation, aslo known as thought) but merely determines the direction of the flow. In this analogy, one "track" governed by the switch point may lead back to the specialist regions from which the information came, and another governs the flow of information to and from basic input/output systems (e.g., visual processing, motor effector systems, speech and language systems, etc.) via these central representations (see fig. 17.2 for a simple analogical representation of how such a system might operate). In a model of this type, there would be competition for activation of central representations between the two pathways (i.e., either input to central representations from more basic systems or reciprocal activation from currently active central representations), and much of cognition could occur naturally through this competition without influence from the processes supported by rostral PFC. It would only be either when one pathway has to be consistently biased or when there has to be rapid switching between the bias of the two that influence from the "switch point" would be needed. This biasing would typically occur in situations that were novel or where a specific demand for it has been determined (e.g., "I must pay special attention to . . ."; "I must think about . . .")—in other words, those situations which have been identified as requiring the operation of a "supervisory attentional system" (see Shallice and Burgess 1996 for details).

This account has some pleasing similarities with Raichle et al.'s default mode hypothesis. However, on the present account it is *not* the case that medial rostral PFC must be *deactivated* in order that goal-directed behavior may take place, as proposed by the default mode hypothesis. For instance, if one is asked to solve a series of arithmetic problems, we assume that the cognitive system effects its own bias between taking in information from the senses (e.g., basic visual and number processing systems) and internally generated thought (e.g., the products of step 1 of the sum being then operated on at step 2). Biasing from rostral PFC processes would only be required if an extra, novel requirement were added (e.g., "When you have done 20 sums, press key X") which requires maintaining the internal representation of the intention during the ongoing arithmetic task. Similarly, the state of conscious "rest,"
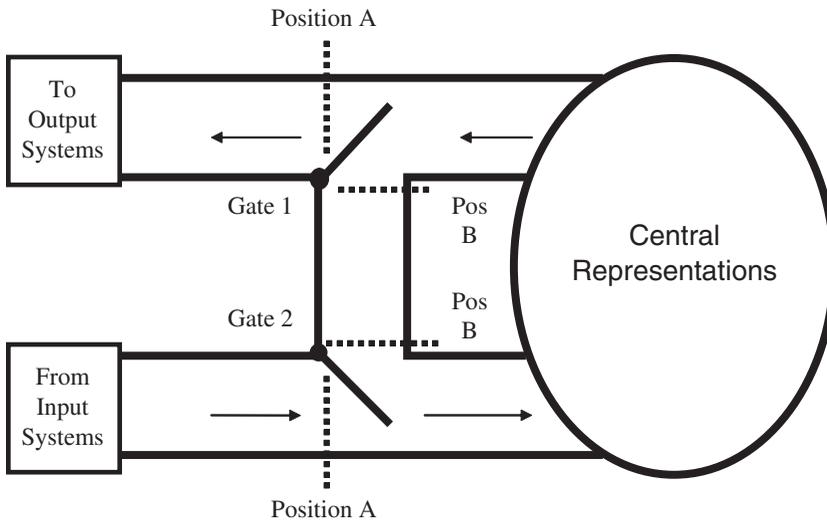
Figure 17.2
Stylized representation of the "Gateway Hypothesis, Version 1" of rostral prefrontal function. Rostral regions are hypothesized to bias the flow of information between basic systems and central representations. Gates are currently shown in a neutral position (bias freely determined by context). If both gates are at position A, stimulus-independent thought is favored. If both gates are at position B, full engagement with (external) stimuli is effected. Other combinations have further experiential correlates.

as investigated in functional neuroimaging studies, may involve continual selection between the various internal and external events that could serve as objects for further cognitive processing, in the absence of any specified task (Zuckerman, Albright, Marks, and Miller 1962). Or perhaps medial rostral PFC supports processes which are more active in conditions that require attending to the environment in the absence of stimuli (e.g., a general state of "preparedness"). Either account could explain the relatively high level of medial rostral PFC activity during the resting state.

In developing this account, we were mindful of the requirement in a first hypothesis to make the minimum of assumptions. The advantage of the current account is that it does not require the assumption that rostral PFC facilitates particular processing transformations, merely that it makes these possible by the simple action of directing the flow of the information between regions where transformations occur. Thus, it should be possible to observe rostral PFC activation associated with this function in a wide variety of tasks, involving many different types of information-processing transformations. This makes the hypothesis more readily testable.

17.5 Direct Empirical Support for the Gateway Hypothesis

In our laboratory, we recently conducted a series of experiments which lend support to this overall framework. These studies consistently find that areas of rostral PFC are involved in coordinating attention between externally presented and internally represented information. Thus Gilbert, Frith, and Burgess (2005) asked subjects either to perform three separate tasks that were provoked by stimuli presented to them visually or to do the same tasks "in their heads," while undergoing fMRI. In one task, subjects either tapped a response button in time with a visually presented clock or ignored the visual display (which now presented distracting information) and continued to tap at the same rate as before. The second task required subjects either to navigate around the edge of a visually presented shape or to imagine the same shape and continue navigating as before. In the third task, subjects performed a classification task on letters of the alphabet that followed a regular sequence. They either classified visually presented letters or mentally continued the sequence and classified the letters that they generated internally. Thus all three tasks alternated between phases where subjects attended to externally presented information and phases where they ignored this information and attended to internally represented information instead. We investigated both the sustained neural activity that differed between two phases, and transient activity at the point of a switch between these two phases. Consistently, across all three tasks, medial rostral PFC exhibited sustained activity that differed between the two phases, in all three cases showing greater activity when subjects attended to externally presented information. By contrast, right lateral rostral PFC exhibited transient activity when subjects switched between these phases, regardless of the direction of the switch. This dissociation between medial and lateral rostral PFC regions was confirmed statistically in all three tasks. Thus, the results of the study strongly support the hypothesis that rostral PFC supports selection between externally and internally oriented cognitive processes, and they suggest dissociable roles of medial and lateral rostral PFC in this selection process.

In a follow-up study (Gilbert, Simons, Frith, and Burgess, in press), we replicated the finding of greater medial rostral PFC activity during attention to externally presented versus internally represented information. In addition, we found that activity in this region was correlated on a trial-by-trial basis with faster RTs (i.e., there was a negative correlation) in a simple RT (SRT) baseline task. This finding is important for two reasons. First, it rules out an explanation of the activity we observe in medial rostral PFC in terms of "daydreaming" during simple tasks. If this were the case, greater medial rostral PFC activity (and hence the occurrence of daydreaming) would reflect disengagement from the baseline task and should show a positive correlation with RT. Second, this finding helps to constrain theorizing on the functional role of this brain region. By demonstrating that rostral medial PFC activity correlates with better

performance in an SRT baseline task, we can point to a task requiring focused attention (in this case, focused attention toward intermittent visual targets) to which medial rostral PFC makes a functional contribution. Thus, contrary to the default mode hypothesis, it does not seem that any task requiring focused attention will lead to "deactivation" of this area. Rather, we propose that this region plays a specific role in particular types of focused attention tasks (i.e., deliberate biasing of attention toward externally presented or internally represented information), which it may also play during the state of conscious rest.

Evidence from our laboratory additionally suggests that rostral PFC is not only involved in selecting at the present moment between externally and internally oriented cognitive processing but is also involved in differentiating between memories of previous events that had an external or internal origin. Simons, Owen, Fletcher, and Burgess (in press) investigated an area of human cognition which previous studies have often (although inconsistently) associated with BA 10: the recollection of past events along with associated contextual information. Previously, it has not been clear how to account for the anomaly that some functional imaging experiments of contextual recollection observed activation in BA 10 (e.g., Rugg et al. 1999; Dobbins et al. 2002) whereas others did not (e.g., Nyberg et al. 1996; Henson et al. 1999). One possible explanation is that the studies which did find BA 10 activation involved recollecting which of two tasks was undertaken with target items ("task context"), whereas the other studies focused on externally derived features of context (e.g., recollecting the position on a monitor screen in which target items were presented: "position context"). Simons et al. investigated the possibility that BA 10 might be differentially involved in recollecting internally generated versus externally derived contextual information by contrasting directly the recollection of task context and position context within participants. They observed a functional dissociation within rostral prefrontal cortex, with lateral regions associated with recollection of both task- and position-based contextual details and a more medial region showing significantly greater activation during recollection of task context than position context. This lateral versus medial dissociation was apparent regardless of whether words or famous faces were being remembered, suggesting that the region is involved in central, stimulus-independent executive control processes and was unrelated to task difficulty as estimated by accuracy and RT. Thus, the results further support the view that the processes supported by rostral PFC involve mediating attentional engagement between internally generated and externally derived information, which is important for successful contextual recollection.

17.6 The Gateway Hypothesis and the Medial Versus Lateral Rostral PFC Distinction

The results of these studies strongly support a role of rostral PFC in coordinating internally and externally oriented information. There is also strong evidence for functional

dissociations between medial versus lateral rostral PFC across a number of tasks (see also Koechlin et al. 2000; Burgess et al. 2003). However, the precise operating dynamics of this system have yet to be determined. The difficulty of this task has been highlighted by two recent studies carried out by Jiro Okuda in this lab and at Tamagawa University in Tokyo, both of which concerned the distinction between time- and event-based prospective memory. In the first PET study, he contrasted a task involving voluntary uncued time-based delayed intentions (clasping your hands twice during a 30-second period while performing an ongoing task) with ones cued by an event (clasping hands to a specific cue while performing the same ongoing task). Okuda et al. (2002) found that contrasts involving the time-based intention (i.e., (time + event > ongoing task only; or time > ongoing only) were associated with increased activation in *lateral* left rostral PFC regions. However, in a second PET study, Okuda, Frith, and Burgess (2004) contrasted maintaining a time-based intention ("respond after time *X*," when a clock was visible while performing an ongoing task) with maintaining an event-based intention ("respond if you see cue *X*") while also performing an ongoing task. In this study, relative to the event-based condition, the time-based condition was associated with increases in *medial* Area 10. One possibility under the terms of the current framework is that the medial rostral activation reflects the difference in the *source* of the time information between the two experiments, with the first experiment relying upon self-generated estimates of time but the second using externally derived information (a clock). Thus, these intriguing findings clearly suggest future experimentation. It may well be that evidence from other methodologies may be yet again required to constrain the hypotheses that the fascinating functional imaging data provokes.

17.7 Summary

We have presented evidence concerning the functions of rostral PFC (principally frontopolar Area 10) which suggests that this area is critical for carrying out intended actions after a delay, which is one important form of volitional behavior. In neurological patients with rostral PFC damage, this deficit is particularly noticeable in situations requiring multitasking. These functions are common in everyday life (e.g., shopping, preparing a meal, etc.) so rostral PFC lesions can cause impairments which are very disabling, despite normal intellect, retrospective memory, and other cognitive abilities.

There also appears to be a potential dissociation in these impairments. People may quite independently show problems in carrying out delayed novel actions associated with particular events (e.g., "when *X* happens, do *Y*"), or problems with remembering after a delay all of the things they intended to do within a set time or "retrieval context." The involvement of rostral PFC (principally BA 10) in these kinds of "prospective memory" functions has also been confirmed by functional brain imaging.

The results from this method suggest a dissociation between medial and lateral aspects of Area 10.

This chapter also presents a new information-processing hypothesis of rostral PFC function and some empirical supporting evidence. The framework makes a distinction between stimulus-oriented (i.e., provoked by, or directed toward) and stimulus-independent thought and suggests that rostral PFC acts as a "gateway" which biases the priority of information from each stream. The strength of this hypothesis is that it is a starting position (in other words, a description of a set of starting assumptions) which (a) makes the minimum number of assumptions (since the proposal is that rostral PFC is involved in cognitive processes that apply across a wide variety of task domains), (b) makes predictions that are more readily testable empirically than alternative theories, and (c) introduces a potentially unifying explanation of the previous findings involving both medial and lateral rostral PFC that is independent of "task difficulty."

If this account is correct, it makes interesting predictions about the potential involvement of this brain region in psychological or psychiatric disorders. Thus, one might suppose that some forms of dysfunction of a mechanism of this kind might lead to an inability to distinguish between one's thoughts and one's experiences, which could be a plausible account of hallucinatory phenomena in schizophrenia. Similarly, for instance, an account using this framework could be constructed for symptoms linked to unwanted (intrusive) thoughts. This speculation remains to be tested, however, and would have to compete with the excellent contrasting views described by, among others, Nitschke and Mackiewicz; Liddle; Frith; Jeannerod; Proust; and Spence and Parry in chapters in this volume.

Acknowledgments

References

Baker, S. C., R. D. Rogers, A. M. Owen, C. D. Frith, R. J. Dolan, R. S. J. Frackowiak, and T. W. Robbins. 1996. Neural systems engaged by planning: A PET study of the Tower of London task. *Neuropsychologia*, *34*, 515–526.

Berman, K. F., J. L. Ostrem, C. Randolph, J. Gold, T. E. Goldberg, R. Coppola, R. E. Carson, P. Herscovitch, and D. R. Weinberger. 1995. Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: A positron emission tomography study. *Neuropsychologia*, *33*, 1027–1046.

Bird, C. M., F. Castelli, O. Malik, U. Frith, and M. Husain. 2004. The impact of extensive medial frontal lobe damage on "Theory of Mind" and cognition. *Brain*, *127*, 914–928.

Blaxton, T. A., T. A. Zeffiro, J. D. E. Gabrieli, S. Y. Bookheimer, M. C. Carrillo, W. H. Theodore, and J. F. Disterhoft. 1996. Functional mapping of human learning: A positron emission tomography activation study of eyeblink conditioning. *Journal of Neuroscience*, *16*, 4032–4040.

Bottini, G., R. Corcoran, R. Sterzi, E. Paulesu, P. Schenone, P. Scarpa, R. S. J. Frackwoiak, and C. D. Frith. 1994. The role of the right hemisphere in the interpretation of figurative aspects of language. *Brain*, *117*, 1241–1253.

Burgess, N., E. A. Maguire, H. J. Spirs, and J. O'Keefe. 2001. A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage*, *14*, 439–453.

Burgess, P. W. 2000. Strategy application disorder: The role of the frontal lobes in human multitasking. *Psychological Research*, *63*, 279–288.

Burgess, P. W., N. Alderman, J. J. Evans, B. A. Wilson, H. Emslie, and T. Shallice. 1996. *The Modified Six Element Test*. Bury St. Edmunds, U.K.: Thames Valley Test.

Burgess, P. W., A. Quayle, and C. D. Frith. 2001. Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia*, *39*, 545–555.

Burgess, P. W., S. K. Scott, and C. D. Frith. 2003. The role of the rostral frontal cortex (Area 10) in prospective memory: A lateral versus medial dissociation. *Neuropsychologia*, *41*, 906–918.

Burgess, P. W., and T. Shallice. 1996. Response suppression, initiation, and strategy use following frontal lobe lesions. *Neuropsychologia*, *34*, 263–273.

Burgess, P. W., and Shallice, T. 1997. *The Hayling and Brixton Tests*. Bury St. Edmunds, U.K.: Thames Valley Test.

Burgess, P. W., J. S. Simons, I. Dumontheil, and S. J. Gilbert. In press. The gateway hypothesis of rostral PFC function. In *Speed, Control and Ageing: In Honour of Patrick Rabbitt*, ed. J. Duncan, L. Phillips, and P. McLeod. Oxford: Oxford University Press.

Burgess, P. W., E. Veitch, A. Costello, and T. Shallice, T. 2000. The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia*, *38*, 848–863.

Burgess, P. W., E. Veitch, and J. Costello. Submitted. The role of the right rostral prefrontal cortex in multitasking: The Six Elements Test.

Christoff, K., and J. D. E. Gabrieli. 2000. The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology*, *28*, 168–186.

Christoff, K., V. Prabhakaran, J. Dorfman, Z. Zhao, J. K. Kroger, K. J. Holyoak, and J. D. E. Gabrieli. 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. *Neuroimage*, *14*, 1136–1149.

Christoff, K., J. M. Ream, L. P. T. Geddes, and J. D. E. Gabrieli. 2003. Evaluating self-generated information: Anterior prefrontal contributions to human cognition. *Behavioral Neuroscience*, *117*, 1161–1168.

Dobbins, I. G., H. Foley, D. L. Schacter, and A. D. Wagner. 2002. Executive control during episodic retrieval: Multiple prefrontal processes subserve source memory. *Neuron*, *35*, 989–996.

Dreher, J.-C., E. Koechlin, S. O. Ali, and J. Grafman. 2002. The roles of timing and task order during task switching. *Neuroimage*, *17*, 95–109.

Frith, U., and C. D. Frith. 2003. Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London B*, *358(1431)*, 459–473.

Fuster, J. M. 1997. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*. Philadelphia: Lippincott-Raven.

Gilbert, S. J., C. D. Frith, and P. W. Burgess. 2005. Involvement of rostral prefrontal cortex in selection between stimulus-oriented and stimulus-independent thought. *European Journal of Neuroscience*, *21*, 1423–1431.

Gilbert, S. J., J. S. Simons, C. D. Frith, and P. W. Burgess. In press. Performance-related activity in medial rostral PFC (Area 10) during low demand tasks. *Journal of Experimental Psychology: Human Perception and Performance*.

Goel, V., B. Gold, S. Kapur, and S. Houle. 1997. The seats of reason? An imaging study of deductive and inductive reasoning. *Neuroreport*, *8*, 1305–1310.

Gold, J. M., K. F. Berman, C. Randolph, T. E. Goldberg, and D. R. Weinberger. 1996. PET validation of a novel prefrontal task: Delayed response alternation. *Neuropsychology*, *10*, 3–10.

Grady, C. L. 1999. Neuroimaging and activation of the frontal lobes. In *The Human Frontal Lobes: Function and Disorders*, ed. B. L. Miller and J. L. Cummings, pp. 196–230. New York: Guilford Press.

Gusnard, D. A., E. Akbudak, G. L. Shulman, and M. E. Raichle. 2001. Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*, 4259–4264.

Haxby, J. V., L. G. Ungerleider, B. Horwitz, J. M. Maisog, S. I. Rapoport, and C. L. Grady. 1996. Storage and retrieval of new memories for faces in the intact human brain. *Proceedings of the National Academy of Sciences*, *93*, 922–927.

Haxby, J. V., I. G. Ungerleider, B. Horwitz, S. I. Rapoport, and C. L. Grady. 1995. Hemispheric differences in neural systems for face working memory: A PET–rCBF study. *Human Brain Mapping*, *3*, 68–82.

Henson, R. N. A., T. Shallice, and R. J. Dolan. 1999. Right prefrontal cortex and episodic memory retrieval: A functional MRI test of the monitoring hypothesis. *Brain*, *122*, 1367–1381.

Hugdahl, K., A. Beradi, W. I. Thomson, S. M. Kosslyn, R. Macy, D. P. Baker, N. M. Alpert, and J. E. LeDoux. 1995. Brain mechanisms in human classical conditioning: A PET blood flow study. *Neuroreport*, *6*, 1723–1728.

Jenkins, I. H., D. J. Brooks, P. D. Nixon, R. S. J. Frackowiak, and R. E. Passingham. 1994. Motor sequence learning: A study with positron emission tomography. *Journal of Neuroscience*, *14*, 3775–3790.

Jennings, J. M., A. R. McIntosh, S. Kapur, E. Tulving, and S. Houle. 1997. Cognitive subtractions may not add up: The interaction between semantic processing and response mode. *Neuroimage*, *5*, 229–239.

Johnson, S. C., L. C. Baxter, L. S. Wilder, J. G. Pipe, J. E. Heiserman, and G. P. Prigatano. 2002. Neural correlates of self-reflection. *Brain*, *125*, 1808–1814.

Klein, D., B. Milner, R. J. Zatorre, E. Meyer, and A. C. Evans. 1995. The neural substrates underlying word generation: A bilingual functional-imaging study. *Proceedings of the National Academy of Sciences*, *92*, 2899–2903.

Koechlin, E., G. Basso, P. Pietrini, S. Panzer, and J. Grafman. 1999. The role of the anterior prefrontal cortex in human cognition. *Nature*, *399*(6732), 148–151.

Koechlin, E., G. Corrado, P. Pietrini, and J. Grafman. 2000. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. *Proceedings of the National Academy of Sciences*, *97*, 7651–7656.

Koechlin, E., C. Ody, and R. Kouneiher. 2003. The architecture of cognitive control in the human prefrontal cortex. *Science*, *302*, 1181–1185.

Kosslyn, S. M., N. M. Alpert, and W. L. Thompson. 1995. Identifying objects at different levels of hierarchy: A positron emission tomography study. *Human Brain Mapping*, *3*, 107–132.

Kosslyn, S. M., N. M. Alpert, W. L. Thompson, C. F. Chabris, S. L. Rauch, and A. K. Anderson. 1994. Identifying objects seen from different viewpoints: A PET investigation. *Brain*, *117*, 1055–1071.

Martin, A., J. V. Haxby, F. M. Lalonde, C. L. Wigges, and L. G. Ungerleider. 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. *Science*, *270*, 102–105.

McGuire, P. K., E. Paulesu, R. S. J. Frackowiak, and C. D. Frith. 1996. Brain activity during stimulus independent thought. *NeuroReport*, *7*, 2095–2099.

Metzler, C., and A. J. Parkin. 2000. Reversed negative priming following frontal lobe lesions. *Neuropsychologia*, *38*, 363–379.

Nyberg, L., A. R. McIntosh, R. Cabeza, R. Habib, S. Houle, and E. Tulving. 1996. General and specific brain regions involved in encoding and retrieval of events: What, where, and when. *Proceedings of the National Academy of Sciences*, *93*, 11280–11285.

Okuda, J., C. D. Frith, and P. W. Burgess. 2004. Organisation of time- and event-based intentions in rostral prefrontal cortex. Abstract for the 10th Annual Meeting of the Organization for Human Brain Mapping, June 2004, Budapest, Hungary. Available on CD-ROM in *NeuroImage*, *22*.

Okuda, J., T. Fujii, H. Ohtake, T. Tsukiura, A. Umetsu, M. Suzuki, and A. Yamadori. 2002. Brain mechanisms underlying human prospective memory. In *Frontiers of Human Memory*, ed. A. Yamadori, R. Kawashima, T. Fujii, and K. Suzuki, pp. 79–96. Sendai: Tohoku University Press.

Okuda, J., T. Fujii, A. Yamadori, R. Kawashima, T. Tsukkiura, R. Fukatsu, K. Suzuki, M. Ito, and H. Fukuda. 1998. Participation of the prefrontal cortices in prospective memory: Evidence from a PET study in humans. *Neuroscience Letters*, *253*, 127–130.

Petrides, M., B. Alivisatos, E. Meyer, and A. C. Evans. 1993. Functional activation of the human frontal cortex during the performance of verbal memory tasks. *Proceedings of the National Academy of Sciences*, *90*, 878–882.

Prabhakaran, V., J. A. Smith, J. E. Desmond, G. H. Glover, and J. D. Gabrieli. 1997. Neural substrates of fluid reasoning: An fMRI study of neocortical activation during performance of the Raven's Progressive Matrices test. *Cognitive Psychology*, *33*, 43–63.

Raichle, M. E., A.-M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman. 2001. A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*, 676–682.

Roland, P. E., and B. Gulyas. 1995. Visual memory, visual imagery, and visual recognition of large field patterns by the human brain: Functional anatomy by positron emission tomography. *Cerebral Cortex*, *5*, 79–93.

Rugg, M. D., P. C. Fletcher, P. M. L. Chua, and R. J. Dolan. 1999. The role of the prefrontal cortex in recognition memory and memory for source: An fMRI study. *NeuroImage*, *10*, 520–529.

Rugg, M. D., P. C. Fletcher, C. D. Frith, R. S. J. Frackowiak, and R. J. Dolan. 1996. Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain*, *119*, 2073–2084.

Semendeferi, K., E. Armstrong, A. Schleicher, K. Zilles, and G. W. Van Hoesen. 2001. Prefrontal cortex in humans and apes: A comparative study of Area 10. *American Journal of Physical Anthropology*, *114*, 224–241.

Shallice, T., and P. W. Burgess. 1991. Deficits in strategy application following frontal lobe damage in man. *Brain*, *114*, 727–741.

Shallice, T., and P. W. Burgess. 1996. The domain of supervisory processes and temporal organisation of behaviour. *Philosophical Transactions of the Royal Society of London B*, *351*, 1405–1412.

Simons, J. S., and H. J. Spiers. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience*, *4*, 637–648.

Simons, J. S., A. M. Owen, P. C. Fletcher, and P. W. Burgess. In press. Anterior prefrontal cortex and the recollection of contextual information. *Neuropsychologia*.

Tulving, E., H. J. Markowitsch, F. I. M. Criak, R. Habib, and S. Houle. 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex*, *6*, 71–79.

Zatorre, R. J., A. R. Halpern, D. W. Perry, E. Meyer, and A. C. Evans. 1996. Hearing in the mind's ear: A PET investigation of musical imagery and perception. *Journal of Cognitive Neuroscience*, *8*, 29–46.

Zuckerman, M., R. J. Albright, C. S. Marks, and G. L. Miller. 1962. Stress and hallucinatory effects of perceptual isolation and confinement. *Psychological Monographs: General and Applied*, *76*, 1–15.

Zysset, S., O. Huber, E. Ferstl, and D. Y. Von Cramon. 2002. The anterior frontomedian cortex and evaluative judgement: An fMRI study. *Neuroimage*, *15*, 983–991.