Special Lecture

A gateway between mental life and the external world: Role of the rostral prefrontal cortex (area 10)

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Abstract: There are many reasons for supposing that rostral PFC (approximating brain area 10 in humans) might play a critical role in human cognition. For instance, it is the largest single subsection of the prefrontal cortex, and is also relatively bigger in humans than in any other animal. It also matures very late, and has an unusual architecture. However until very recently virtually nothing was known about the functions of this brain region. But evidence from neuroimaging and human neuropsychology together are now providing critical constraints for theorizing. In particular, although activations of rostral PFC are found in neuroimaging studies of a very wide variety of functions, the deficits experienced by patients with damage to this brain region seem remarkably specific. Rostral PFC lesions need not impair intellect, simple memory functions, or many other abilities. However they can lead to a syndrome of high-level behavioural disorganization, in which impairments in multitasking and prospective memory are a central, but by no means exclusive, feature. This paper reviews this evidence, and proposes that one explanation for these findings is that rostral PFC supports a cognitive mechanism whose purpose is to attenuate the degree to which one either attends to stimuli in the environment, or to self-generated thoughts. This notion is called the “gateway hypothesis” of area 10 function. We present a series of experiments, using fMRI, which demonstrate the plausibility of this account in three ways. First, by showing area 10 activations both during the performance of tasks specifically designed to tap this hypothetical resource. Second, by showing BA 10 activations during tests of functions which putatively should require the operation of such a mechanism (prospective memory and context memory). Third, by showing that a prediction about activation-behaviour relationships that follows from this hypothesis is supported by neuroimaging meta-analysis. We conclude that although the gateway hypothesis is unlikely to provide a complete account of the role of the processes supported by rostral PFC, it may prove a useful tool for interpreting some of the existing evidence.


Key words: ★★★★★★★

Introduction

Area 10 of the brain (also termed “rostral prefrontal cortex (PFC)”, or “anterior PFC”) presents one of the most fascinating puzzles in cognitive neuroscience. For instance, it is a very large
brain region in humans, covering approx. 25-30 cubic centimetres, and is in relative terms larger in the human brain than in any other animal, including the great apes (Semendeferi et al., 2001; Holloway, 2002). It also has an unusual cell structure, in that Area 10 in humans has more space available for connections with higher-order association areas than in other animals. Furthermore, rostral PFC is probably the last brain region to achieve myelination (Semendeferi et al., 2001; Fuster, 1997, p. 37). On these grounds, it is a reasonable hope that understanding the role of this region in human cognition may provide a key understanding of how the brain enables some of the behaviors peculiar to humans, and therefore the symptoms that accompany its dysfunction (e.g. certain forms of mental illness).

Until less than 10 years ago, however, virtually nothing was known about the functions of this region, and the available evidence presented a conundrum. Activation of rostral PFC (as evidenced by haemodynamic changes) could be found in just about any kind of task (for review, see Grady, 1999; Ramnani and Owen, 2004).

This was a problem since the sheer multiplicity of these results provided little constraint for theorizing about the functions of this region. But it was also a problem since one might predict that if the processing that Area 10 supports is involved in performance of a wide range of cognitive tasks, lesions to this region would cause deficits on correspondingly wide range of tasks. However we will argue that this is not the case. Instead, we suggest that neurological patients with circumscribed rostral prefrontal cortex involvement do not typically show impairments of intellect, language, perception or recognition memory. Nor in fact may they fail traditional “frontal lobe” tests of executive function (e.g. WCST etc., Burgess, 2000). Instead, we argue that patients with rostral PFC damage show a characteristic impair-

ment in multitasking and in dealing with other “ill-structured” situations (Shallice and Burgess, 1991; Burgess et al., 2000; Goel and Grafman, 2000).

The endeavour to understand the functions of Area 10 has thus been for us the process of coming to an appreciation of the nature of these patients’ problems. This paper describes that research endeavour, and the progress we have made so far. This has come about largely through dovetailing human neuropsychology investigations with functional neuroimaging ones. We hope that our research will serve two aims. First that it will give us a fundamental insight into how the brain works. Second, that it will enable us to help people with the characteristic symptoms of rostral PFC lesions. This is especially important since, for anatomical reasons, damage to this region is very common following traumatic brain injury.

**Behavioural disorganization in the context of apparent preservation of intellect: the early investigations.**

Seventy years ago, Penfield and Evans (1935) described the symptoms that Penfield’s sister was experiencing after the removal of a right frontal glioma: “She had planned to get a simple supper for one guest and four members of her family. She looked forward to it with pleasure and had the whole day for preparation. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long continued effort alone”.

This impairment in carrying out daily activities would not have been remarkable were it the case that the patient was suffering from serious disabilities in basic cognitive systems (e.g. classic dense amnesia, visuo-spatial/perceptual or ag-
nosic problems, disorders of motor control and so forth). However this was not the case, either with Penfield and Evans’ patient, nor with others which were soon reported (e.g. Brickner, 1936; Ackerly and Benton, 1947). These established, at least on the grounds of clinical observation alone, that this kind of behavioural disorganisation can be seen in the absence of these kinds of impairments.

However it was not until 50 years after Penfield and Evans’s paper that an attempt was made to isolate the critical cognitive deficit underpinning this disorder. Eslinger and Damasio (1985) described the case of EVR, who had undergone surgical removal of a large bilateral frontal menigioma. At the time of his operation EVR was a financial officer with a small company and a respected member of his community. He was married and the father of two children; his brothers and sisters considered him a role model and a natural leader. After the operation however, EVR lost his job, went bankrupt, was divorced by his wife, and moved in with his parents. He subsequently married a prostitute and was divorced again within two years. Extensive psychological evaluations found no deficit; in fact, he was superior or above average on most tests (e.g., Verbal IQ of 125; Performance IQ of 124; no difficulty on Wisconsin Card Sorting Test). He was also able to discuss intelligently matters such as the economy, foreign affairs, financial matters, or moral dilemmas. Despite these normal findings, EVR was often unable to make simple everyday decisions, such as which toothpaste to buy, what restaurant to go to, or what to wear. He would instead make endless comparisons and contrasts, often being completely unable to come to a decision at all. Further, Eslinger and Damasio report prospective memory problems: “...it was as if he forgot to remember short- and intermediate-term goals...” (1985, p. 1737). (“Prospective memory” refers to the act of carrying out an intended action at a point distant from when one first thought of it, and where one has been engaged since in some other task, e.g. remembering to mail a letter the following day.)

Eslinger and Damasio’s paper was important because it was the first formal demonstration that this level of behavioural disorganisation could occur in the context of intact intellect, and intact performance on some tests traditionally thought to be sensitive to deficits in “frontal lobe” executive functions. However scientific progress was limited at that time by two interlinked shortcomings: (1) No qualitative assessment had yet been undertaken of these kind of patients’ everyday life problems, and (2) no laboratory task had been developed which a priori reflected these difficulties. Without (1) one could not begin to determine the range of behaviours under examination, or the characteristics of the situations which presented problems for the patients, and without (2) there was no simple “model of the world” which could form the basis for scientific investigation of the disorder at an information processing level.

**Disorganisation in everyday life: the development of empirical measures.**

Shallice and Burgess (1991) however addressed these issues. They described the neuropsychological performance of three people who had all suffered frontal lobe damage in a traumatic brain injury (in this case, road traffic accidents). All three had no significant impairment on formal tests of perception, language and intelligence and two performed well on a variety of traditional tests of executive function. This is not however to say that they were unimpaired in other regards (Shallice and Burgess, 1991; see also case NM by Metzler and Parkin, 2000; Wood and Rutterford, 2004). The most noticeable of these in everyday life was marked multitasking and prospective
memory problems. This manifested itself as tardiness and disorganisation, the severity of which ensured that despite their excellent intellect and memory, language and perceptual skills, none of the three people ever managed to make a return to work at the level they had enjoyed pre-morbidly.

Shallice and Burgess (1991) invented two new tests of multitasking to assess their problems. The first of these tests, called the “Multiple Errands Test” was a real-life multitasking test carried out in shopping precinct. Participants have to complete a number of tasks, principally involving shopping in an unfamiliar shopping precinct, whilst following a set of rules (e.g. no shop should be entered other than to buy something). The tasks vary in terms of complexity (e.g. buy a small brown loaf vs. discover the exchange rate of the Euro yesterday), and there are a number of “hidden” problems in the tasks that have to be appreciated and the possible course of action evaluated (e.g. one items asks that participants write and send a postcard, yet they are given no pen, and although they cannot use anything not bought on the street to help them, they are also told that need to spend as little money as possible). In this way, the task is quite “open-ended” or “ill-structured” (i.e. there are many possible courses of action, and it is up to the individual to determine for themselves which one they will choose).

The second task that Shallice & Burgess invented was a more controlled experimental task (the “Six Element Test”). This required subjects to swap efficiently between 3 simple subtasks, each divided into two sections within 15 minutes, whilst following some arbitrary rules (e.g. you cannot do part A of a subtask followed immediately by part B of the same subtask). There are no cues as to when to switch tasks, and although a clock is present, it is covered, so that checking it has to be a deliberate action. Thus this paradigm has a strong component of voluntary time-based task switching, i.e. one form of prospective memory.

Despite their 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. On the MET the subjects made a range of types of error, many of which could be interpreted as prospective memory failures. For instance they would find themselves having to go into the same shop more than once to buy items that could all have been be bought at one visit; not completing tasks that they had previously learnt that they needed to do; not remembering to come over to the experimenter and tell them what they had bought when leaving a shop (a pre-learnt task rule); or going outside the boundaries of the precinct (at the start of the test Ss are shown the boundaries and told not to cross them) (see Fig. 1). They also made a range of social rule-breaks (i.e. breaking social convention), such as leaving a shop without paying, or offering sexual favours in lieu of payment. Shallice and Burgess (1991) rather inelegantly termed this kind of behavioural disorganization in the context of preserved intellect and other cognitive functions the “Strategy Application Disorder”.

It was not possible on the basis of Shallice and Burgess’s data however to speculate on the anatomical localization of the lesion critical for this pattern of deficit, since the three patients had suffered large traumatic lesions. Two years later however, Goldstein et al. (1993) described a case which began to suggest a possible locus. This 51-year old right-handed man (GN) had undergone a left frontal lobectomy 2.5 years earlier following the discovery of a frontal lobe tumour (mixed astrocytoma-oligodendroglioma). A 5cm resection of left frontal lobe from the frontal pole was
undertaken. From the point of view of traditional neuropsychological tests, this surgery made little
difference to his cognitive abilities (e.g. WAIS-R 
VIQ 129, PIQ 111; story recall immediate 75- 
90th%ile, delayed 50-70th; Rey Osterreith delayed 
figure recall 80-90th%ile; Trail-making 70-75th% 
ile). However this did not reflect the change in 
his everyday competence. The patient had held a 
senior management position within an interna-
tional company, but two years after surgery he 
had to take medical retirement because of in-
creasing lethargy. He worked from home as a 
free-lance management consultant, but had diffi-
culty making decisions, culminating in his taking 
two weeks to decide which slides to use for a 
work presentation, but never actually reaching a 
decision. He also experienced anger control diffi-
culties.

Goldstein et al (1993) administered Shallice & 
Burgess’s (1991) Multiple Errands Test. GN made 
significantly more errors than controls, being less 
efficient (e.g. having to return to a shop), break-
ing tasks rules (e.g. using a stamp that another 
customer gave him), misinterpreting tasks (e.g. 
sticking the stamp on the wrong card), as well as 
 failing to complete some tasks altogether, report-
ing that he had known he had to do them but 
somehow “forgot” them. He also showed some 
“social rule” breaks. For instance, he had omitted 
to find out the price of tomatoes while earlier in

Fig. 1 Performance of a patient with rostral PFC damage on the Multiple Errands Test (Shallice and 
Burgess, 1991), and a typical control matched for age, sex, and estimated pre-morbid ability 
(NART). The patient took twice as long as the control yet failed to complete a number of tasks 
(the control completed them all). He also went out of bounds (boundary indicated by hatched 
line at end of street); entered shops more times than was needed; entered shops that were not 
necessary for the task, and made a number of task and social rule breaks. The patient was how-
ever able to repeat the task rules correctly both before and after the test.
the greengrocers, and realizing that he should not go back into the shop unless he was to buy something, he very conspicuously climbed onto the fruit display outside the shop and peered in the shop window.

This case, and others reported in the literature, show a remarkably similar pattern of neuropsychological test performance. Burgess (2000b) summarized the performance of 8 well-known cases: None of the cases had any language or visuoperceptual impairment and all scored within the superior range on tests of current intellectual functions. Four of the seven showed no impairment on any memory test. But most remarkably, two showed no impairment on a range of clinical executive function tests known to be sensitive to frontal lobe lesion. Moreover, no executive test has been failed by more than 2/8 cases. Most remarkably, two tasks have been administered to all the patients—the Wisconsin Card Sorting Test (WCST) and Verbal Fluency—and have been performed well by every case. This contrasts with the observation that all of the reported cases of “strategy application disorder” who have been given either the Multiple Errands or Six Element Tests have failed at least one of them.

**The components of multitasking**

Performance of the MET and SET described above requires “multitasking”. This is a behavioural-level description that has a precise meaning in cognitive neuroscience. Burgess (2000a, b) describes 8 features of a situation that requires multitasking, the first five of which are axiomatic, plus a further three (6-8) that are usually true of everyday life multitasking situations:

1. Many tasks: A number of discrete and different tasks have to be completed.
2. Interleaving required: Performance on these tasks needs to be dovetailed in order to be time-effective.
3. One task at a time: Due to either cognitive or physical constraints, only one task can be performed at any one time.
4. Delayed intentions: The times for returns to task are not signaled directly by the situation (i.e. requires prospective memory).
5. No immediate feedback: There is no moment-by-moment performance feedback of the sort that participants in many laboratory experiments will receive. Typically, failures are not signaled at the time they occur.
6. Interruptions and unexpected outcomes: Unforeseen interruptions, sometimes of high priority will occasionally occur, and things will not always go as planned.
7. Differing task characteristics: Tasks usually differ in terms of priority, difficulty and the length of time they will occupy.

Characteristics 3 and 4, and possibly also 6, 7 and 8 mean that “multitasking” may be different, at least in some regards, in the information processing demands it makes from “multiple-task performance” which is where someone is performing several tasks simultaneously (or dual-tasking where there are two tasks, e.g. Baddeley et al., 1997). Prototypical dual- or multiple-task situations are air traffic control, or operating a computer whilst talking to someone on a telephone. But there is little obvious prospective memory demand in e.g. dual-task situations since the retention interval over which an intention is to be maintained is typically so short. By contrast many real-life multitasking situations involve the co-ordination and dovetailing of many activities over longer time-scales (e.g. Alderman et al., 2003). These typically require one to perform one particular task at a time (e.g. writing a scientific paper) whilst bearing in mind that other unre-
lated tasks have to be performed before completion of this task (e.g. collect the car from the workshop at 1pm) and often having to periodically check the state of something else (e.g. has the expected e-mail arrived yet?). In other words, whilst multitasking and multiple-task situations share characteristics 1 and 2 above (plus in some situations 5), only multitasking has characteristics 3 and 4. It is these characteristics that necessitate the involvement of “prospective memory” or the carrying out of an intended action after a delay (e.g. Kvavilashvilli and Ellis, 1996), which is in this case a task switch.

**Investigations of the locus of the lesion which causes relatively isolated behavioural disorganization.**

There is now some evidence both that a prospective memory deficit, at least under some circumstances, is a key deficit in these cases, and there are some strong indications of where in the brain the critical locus of the lesion can be found. The largest human group lesion study to date in this area was published by Burgess et al. (2000), who 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 colour”) 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. 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”). This enabled us to look at whether their failures could be due to poor planning (see e.g. Kliegel et al., 2005). 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”).

A basic finding was that this sort of procedure is sensitive to a range of cognitive problems—despite no differences between the controls and patients on measures of pre-morbid (NART) or current fluid intelligence (Raven’s Advanced Progressive Matrices), the patients showed significant impairment on most of the variables (a similar finding is reported by Levine et al., 2000). At a more specific level however, lesions in different brain regions were associated with impairment at different stages in the multitasking procedure. Lesions to a large region of superior posterior medial cortex including the left posterior cingulate and forceps major gave deficits on all measures
except planning. Remembering task contingencies after a delay was also affected by lesions in the region of the anterior cingulate. Critically, however, Burgess et al found that patients with left hemisphere rostral PFC 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 ("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 did not do what they said that they intended to do.

This link between rostral PFC damage and the prospective memory component of multitasking accorded well with the lesion location of Goldstein et al’s (1993) previous single-case. Moreover, two of the original three patients reported by Shallice and Burgess (1991) also had lesions affecting the rostral parts of the left frontal lobe. However a specific problem is presented by other findings. Thus one of Shallice and Burgess’s (1991) cases had principally a right frontal lesion. Moreover Levine and colleagues (e.g. Levine et al., 1998; 1999; 2000) have repeatedly implicated right hemisphere lesions in poor performance on their multitasking test, the R-SAT. As Levine et al (2000) points out, these apparently conflicting results may be a result of the use of multitasking tests with differing characteristics: The Burgess et al (2000) study administered a test where the variable taken as the estimate of multitasking ability was based principally upon rule-following rather than task switching. But Levine’s task (R-SAT) is more similar to Shallice & Burgess’s original Six Element Test, in that the emphasis is upon voluntary time-based task switching rather than rule-following. So the lesion location differences could occur if task switching and rule-following are not equivalent in information-processing terms. This is certainly plausible with reference to the known characteristics of event- or time-based prospective memory (see e.g. Kvavilashvili and Ellis, 1996). Moreover, a recent group study of real-world multitasking in mixed aetiology neurological patients (Alderman et al., 2003) demonstrated a double-dissociation between rule-following and failures to initiate tasks. An alternative possibility however is that the difference between the findings of Levine’s group and Burgess’s may instead be due to the differing populations studied by them: Levine’s finding are based principally on traumatic brain injury, but the Burgess et al (2000) study used acute circumscribed lesions (principally tumours).

A resolution to this apparent paradox was provided by a recent human group lesion study by Burgess, Veitch and Costello (submitted; reported in Burgess et al (2006). In this study, a new version of the Burgess et al (1996) Six Element Test (SET) of multitasking was given to sixty-nine acute neurological patients with circumscribed focal lesions and sixty healthy, using the administration framework of Burgess et al (2000). The SET 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 attrib-
uted to deficits in general intellectual functioning, rule knowledge, planning, or retrospective memory (see Fig. 2).

Considering now the previous single case studies in the context of these group study findings, it is clear that there is a remarkably consistent finding of involvement of Area 10 in cases who have high-level disorganization in everyday life. For instance, in the 6 cases reviewed by Burgess (2000b) for whom good brain scan data was available, all of them had rostral PFC involvement of either the left or right hemispheres (or both). In addition to these cases, we might now also add the recent case of Bird et al (2004) who had suffered a rare form of stroke affecting the medial aspects of Area 10 bilaterally, and who failed the Six Element Test, despite passing some other executive tests (e.g. the WCST). It seems likely that prospective memory problems (and therefore multitasking ones) are just one indicator of the problems these unfortunate people experience.

**Convergent findings from neuroimaging.**

In our lab, we have been working in particular on one potential explanation of the puzzling phenomenon of the “strategy application syndrome”. The central idea is that rostral prefrontal cortex (PFC) plays a role in the goal-directed coordination of stimulus-independent (SI) and stimulus-oriented (SO) attending in situations where the established way of behaving would not achieve optimal outcome. Stimulus-oriented attending is the basic attentional mechanism required to attend closely to stimuli being experienced through the sensory organs (i.e. things that we can see, hear, etc.). Stimulus-independent attending is where one is concentrating instead on the “thoughts in one’s head”. The idea is that normally, there is continuous competition between SIT and SOT for activation of mental representations which is freely determined by the situation. For instance, SO attending is normally dominant
when a sudden unexpected stimulus “captures” attention; or an expected stimulus appears which is congruent with the current goal and which has a strong stimulus-response relation. By contrast, SI attending usually becomes dominant (i) in the absence of any external stimulus, (ii) when monotony has been achieved, (ii) when faced with a situation with no established way of behaving, (iii) cognitive capacity has been exceeded and the performance starts to break down, leading to errors and consequent rumina-
tive thoughts.

However, there are many occasions when one is required, for adequate performance, to alter the relative influence of these sources of activation. For instance one needs to bias towards SO attending if one wants to attend closely to something which is boring, or keep listening carefully for something. By contrast, one needs abnormal bias towards SI attending when one is actively maintaining an intention to do something at a future time, or is deliberately engaged in creative thought. Rostral PFC supports the cognitive processing which enables this unusual degree of bias, acting as a “gateway” between stimulus-oriented and stimulus-independent attending.

This hypothesis (known as the “gateway hypothesis”, see Burgess et al., 2005, 2006) explains the pattern of impairments seen by patients with damage to rostral PFC since (i) the attentional “gate” would expect to operate in a wide variety of tasks, but not be critical to performance tasks using routine, informationally encapsulated processing resources, such as those required for typical IQ tests; (ii) as noted above, patients with rostral PFC lesions typically show problems in dealing with “ill-structured” situations, but not with well-structured ones (Shallice and Burgess, 1991; Goel and Grafman, 2000) and Ill-structured situations are those likely to require the operation of the attentional system identified above, since they will involve the self-generation and prioriti-
ization of contingencies (SI attending required), and the verification of action outcome required in complex planning (SO attending required).

**Testing the Gateway Hypothesis**

Our first direct test of the gateway hypothesis involved contrasting the neural activation when people are performing tasks using stimuli presented on a display, with that when they are performing the same tasks “in their heads” (Gilbert, Frith and Burgess, 2005). Medial rostral PFC (Area 10) activation was found in the condition where people are using externally displayed stimuli (i.e. stimulus-oriented attending) compared with when they are doing the same task in the absence of relevant stimuli (stimulus-independent attending). Lateral BA 10 activation was also found at the points where Ss switched between either condition, regardless of the direc-
tion of the switch (i.e. SO->SI; SI->SO). Thus the existence of a central (Duncan & Owen, 2000) rostral mechanism which is responsive to differ-
ences in stimulus-independent and -oriented attending received support.

This study however left open the question of the degree of stimulus processing (i.e. any automatic cognitive processing provoked by a sti-
ulus, such as recognition, reading, etc.) required for the medial Area 10 activation. Accordingly the second study (Gilbert, Simons, Frith and Burgess, 2006) used fMRI to investigate 4 conditions, with a conjunction of two different tasks (i.e. results are only reported if they are true of more than one task which differ in their basic stimulus processing demands): Condition 1 required routine stimulus processing (SP) (e.g. simple arithmetic performed upon presented stimuli); Condition 2 required some degree of stimulus-independent thought (SIT) (e.g. mental arithmetic); Condition 3 combined conditions 1 and 2 (i.e. SP + SI attend-
Fig. 3  Panel A (upper) shows results from Gilbert, Simons, Frith and Burgess (2006). Medial Area 10 shows greatest activation in conditions requiring attending to currently perceived stimuli, and least activation in conditions requiring stimulus-independent thought. B. Attn = Basic RT baseline (no stimulus processing) ; SP = Stimulus Processing ; SIT = Stimulus-Independent Thought ; SIT + SP = combined condition (see text for details). Panel B shows data from Burgess, Dumontheil, Gilbert and Frith (submitted). There is a medial vs. lateral Area 10 activation BOLD signal dissociation between tasks requiring attending to perceived stimuli (Basic Attention) or to self-generated thoughts (SIT). The graph is colour-coded to the MRI. The region x condition interaction is significant (F (1,15) = 7.1, p < 0.001).

ing); and finally these was an basic attention (i.e. simple RT) control where no stimulus processing or SIT was required (see Fig. 3). The results showed highest activation in medial Area 10 in the baseline condition, and lowest in conditions requiring stimulus-independent thought, even if there was concomitant stimulus processing (see Fig. 3). Thus the situations where medial rostral PFC (principally BA 10) is most active are those with low stimulus processing demands. However, crucially for this issue, medial rostral PFC was also activated in an analysis of regions showing significant correlation between BOLD signal and trial-by-trial fluctuations in RT in the “Baseline” condition. The correlation was negative, i.e. greater activity in this region was associated with trials with faster RTs. This rules out a potential explanation in terms of stimulus-independent thought (e.g. “mind wandering”) during an easy task. (We have since replicated this finding; Burgess, Dumontheil et al., submitted.)

These two studies (Gilbert et al., 2005, 2006a) however involved only certain restricted forms of SO and SI attending. But there are many potential forms (see Burgess, Dumontheil et al., submitted). For instance, the gateway hypothesis predicts that rostral PFC may be involved in daydreaming or mind-wandering as well as in tasks
where one has to self-generate a novel representation (e.g. imagine something). Both forms of cognition are examples of thought that is (a) not provoked by currently experienced stimuli and (b) is novel in form, so should require to varying degrees the operation of processes supporting SI attending.

To test this hypothesis, Burgess, Dumontheil, Gilbert and Frith (submitted) administered two completely different tasks (“numbers” & “arrows”) under four conditions: (1) Simple RT attentional baseline (“press the left/right button on alternate trials as fast as you can each time a stimulus appears”); (2) Basic stimulus processing (e.g. “press the button on the side of the largest of two numbers”); (3) Stimulus-independent attending, which required processing self-generated information. For instance, in the latter condition of the numbers task, participants were asked if the sum of two numbers currently being presented to them was larger or smaller than the sum of the last two numbers presented; (4) A “working memory” condition.

The results of this study were exactly as predicted by the Gateway Hypothesis. Medial BA 10 was more active in condition 1 (basic attention to external stimuli, no stimulus processing) than in condition 3 (stimulus-independent attending), and an area of lateral rostral PFC showed the opposite pattern (see Fig. 3). We also replicated the previous significant negative correlation between BOLD signal increase and RT in low demand reaction time conditions.

**Evidence from other paradigms**

Of course, if rostral PFC supports as fundamental a cognitive system as is argued by the “gateway hypothesis”, one should find evidence of activation of this region across a wide range of tasks, not just those which are designed specifically to measure the hypothesis as described above. And this is indeed the case. Activations of area 10 can be found in neuroimaging studies of virtually any type of paradigm, from very simple conditioning ones to highly complex reasoning and memory tasks (for review see Grady, 1999; Ramnani and Owen, 2004; Burgess et al., 2005, 2006; Gilbert et al, 2006). Accordingly, we have also investigated the role of BA 10 in functions which putatively should involve the operation of a SI/SO attention “gateway”. In particular, we have investigated two such functions: “prospective memory” and “context memory”.

**Prospective memory**

Prospective memory (i.e. the creation, remembering and enactment of intended actions after a delay PM) should involve SI/SO attending biasing because in a typical PM paradigm one has to hold in mind an intention (SI attending) whilst also performing an ongoing task which requires attending to external stimuli (SO attending). Burgess, Quayle and Frith (2001) used PET to investigate regional cerebral blood flow changes in eight participants performing four different tasks, each under three conditions. The first condition (baseline) was subject-paced, and consisted of making judgements 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 PM 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” (PM) conditions in that they involved a delayed intention (see Burgess, Quayle and Frith for an outline of the further characteristics of PM 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 (B. A. 45/46) and right inferior parietal regions (B. A. 7, 19, 39, 40), precuneus, plus decreases in left fronto-temporal regions (B. A. 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 DLPFC. 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 recognising and responding to prospective memory cues.

However the brain region regarded as especially significant as regards intention maintenance was BA 10, on the grounds of two previous studies. In the first (Okuda et al., 1998) participants were taught a set of target nouns before scanning began. During scanning they were required to repeat verbally sets of five nouns that were presented to them. Occasionally one of these was one of the pre-learnt targets, and the participant was required to respond to them by tapping with their left hand. The contrast condition consisted of word string repetition alone. Okuda et al’s results implicated a number of frontal regions, including the right dorsolateral, ventrolateral (B. A. 8, 9, 47) and midline medial cortices (B. A. 8), and the anterior cingulate gyrus, plus the left parahippocampal gyrus. Most significantly however, they also implicated the left frontal pole (B. A. 10) in prospective memory.

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 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 prefrontal cortex (BA 10) relative to the baseline or ongoing task only conditions. However more lateral aspects of area 10 (plus the medio-dorsal 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 both the medial and lateral rostral regions showed (a) 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 favoured 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) whilst carrying out other operations on presented stimuli.

Most recently, this lab has further shown that
similar regions of BA 10 are activated regardless of the specific cue recognition or intention retrieval demands, although there appears to be other sub-regions of area 10 which are sensitive to such differences (Simons et al., 2006; see Fig. 4). We have also found differences in the regions of area 10 that are activated according to whether the prospective memory task is a time- or event-based paradigm (Okuda, Fujii, Ohtake, Tsukiura, Yamadori, Frith, & Burgess (in press); for review see Burgess et al., in press). Clearly we still have lot to learn. However the principle that area 10 is involved in some important way in prospective memory functions seems secure.

**Context memory**

Context memory (i.e. recalling details that were not central to an event when it occurred) should require stimulus-independent attending since it requires one to recall details that are not directly determined by the stimulus. Simons, Gilbert et al (2005) gave participants a study phase where cues indicated whether entertainment/politics or pleasant/unpleasant judgments were to be made on stimuli that were presented either on the left
or right of a display screen. These factors of task (i.e. the judgment one was asked to make) and position (L/R on the display) were crossed in the study design. In the test phase, participants were asked to recollecting either whether the previously presented stimulus had been presented on left or right of the screen, or whether an entertainment/politics or pleasant/unpleasant judgement had been carried out. We found a functional dissociation within anterior prefrontal cortex (principally Brodmann’s Area 10), with lateral regions associated with remembering either type of information (relative to baseline), and a medial anterior PFC region showing significantly greater activation during the “task memory” conditions. These results suggest different roles for lateral and medial anterior prefrontal cortex in context recollection, as predicted by the gateway hypothesis.

In a second fMRI study (Simons, Owen et al., 2005) the position judgement task was replaced with a temporal context task. In the study phase, two temporally-distinct lists of items were presented. In each list, participants were pseudo-randomly cued to make entertainment/politics or pleasant/unpleasant judgments about either words or faces. In the test phase, participants were cued to make context memory or baseline decisions about stimuli. In the context memory conditions, the decisions required recollection of whether stimuli had been studied in list 1 or list 2, or whether the entertainment/politics or pleasant/unpleasant task had been undertaken. There were also two baseline condition, one to control for basic spatial and motoric aspects of the task, and the other for the semantic judgment aspect. We found that area 10 was significantly more active when participants were recollecting the thoughts they had had about stimuli than when recollecting the time when the stimuli had been presented. Moreover, the regions activated were remarkably consistent with the first study (see Fig. 3).

Evidence from neuroimaging meta-analyses.

A third way in which we have tested the gateway hypothesis is to make predictions from it for behavior-activation relations and examine the evidence using meta-analysis. Gilbert, Spengler et al (2006) investigated the reaction times (RTs) to paradigms used in in 104 functional imaging papers (yielding 113 independent contrasts) which had reported Area 10 haemodynamic responses. If the gateway hypothesis is correct, since lateral rostral PFC activation is a precursor of stimulus-independent, self-generated cognition (i.e. that which utilizes second- or third-order representations; see Burgess et al., 2005 for further detail), RTs to tasks which activate this region should be longer than RTs to tasks which activate medial BA 10 regions, where responding is more “automatic” and “schema-driven” (Shallice, 1988). This effect should be true of all kinds of task, regardless of form.

The results did indeed confirm this prediction. Across all types of paradigm, regardless of their aim or form (e.g. memory, perceptual, motor, problem-solving; verbal, non-verbal, mixed etc.), we found that reaction times were significantly slower to paradigms which had provoked lateral BA 10 (than the contrast condition that had been used), and quicker for those which had provoked a medial BA 10 response. This result suggests an important general principle of rostral PFC function, since it occurred across any form of task (with the caveat that not all forms of task are used in functional imaging scanners), and provides a tight constraint for theorizing about the functions of this brain region. It also strongly supports previous suggestions of a medial/lateral functional distinction (see e.g. Koechlin et al., 2000; Burgess et al., 2003).
These results also show that regardless of which type of task is involved, haemodynamic change in this region is accompanied by a particular behavioral signature. However it would not be correct to infer therefore that there is no functional specialization within Area 10. This is demonstrated starkly by a very recent finding from this group. As an adjunct to the meta-analysis of imaging studies described above, we investigated the relation between activations in the different regions of Area 10 and the type of task that provoked the activation (Gilbert, Spengler, et al., 2006b). We found that there is good evidence for functional specialization within Area 10. Thus the haemodynamic changes provoked by dual- or multitasking paradigms tended to be located very rostrally within Area 10, and those provoked by mentalizing or episodic retrieval paradigms located, respectively, medially and caudally, and laterally.

**Conclusion**

Virtually nothing was known about the functions of rostral PFC until approximately 10 years ago. However the scientific progress since then has been remarkable. We now know (from functional neuroimaging) that area 10 supports cognitive processing which co-occurs with behaviour in a very wide variety of situations. This seems to put Area 10 at the very heart of human cognition, as might be suggested by the evidence from anatomical studies, which e.g. show how large this brain region is in humans. However the lesion evidence shows that rostral PFC lesions do not cause widespread deficits. Indeed, they typically leave intellect, straightforward memory functions (such as forced-choice recognition), visuo-spatial perception and many other cognitive abilities intact. Prima facie, these results from the two methods (imaging and neuropsychology) seem contradictory: if area 10 is involved in many functions, then why aren’t many functions impaired when this region is lesioned?

We have proposed a potential solution to this apparent conundrum. This is that rostral PFC plays a role in a mechanism which effect bias between attending, to a novel degree, to the outside world, or to our own thoughts. In this way, the mechanism is likened to a “gateway” between mental life and the external world. We have presented neuroimaging evidence which shows that area 10 is especially involved when performing tasks which are specifically designed to stress a hypothetical mechanism of this type. Moreover, activation of area 10 is also found in neuroimaging studies of behavioural functions which putatively should require this cognitive mechanism. Furthermore, we have shown from meta-analysis of area 10 activations that the predictions that this hypothesis makes are supported by the data across a wide variety of different paradigms.

However it is nevertheless clear that we are only at the very start of an understanding about the role that this large brain region plays in human cognition. For instance, our own research (and that of others) suggests that there is functional specialization within area 10. Specialization of this type presents an explanatory challenge to any account which describes the functions of a region in terms of a single mechanism. This challenge may not prove insurmountable. However, even if the “gateway hypothesis” does provide a broad approximation to an information processing-level explanation of the role of area 10, this does not exclude the possibility that there are other functions supported by it. Indeed, these may even be supported by the same regions as we have identified. Moreover, there may be other functions supported by sub-regions of area 10 other than those we have discovered. But it seems likely on the present evidence that gaining an understanding the role of rostral PFC in cogni-
tion may enable key insights into what is special about human thought, and provide information that is of direct clinical use in helping those who are unfortunate enough to suffer damage to this brain region.

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