Function and localization within rostral prefrontal cortex (area 10)

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We propose that rostral prefrontal cortex (PFC; approximating area 10) supports a cognitive system that facilitates either stimulus-oriented (SO) or stimulus-independent (SI) attending. SO attending is the behaviour required to concentrate on current sensory input, whereas SI attending is the mental processing that accompanies self-generated or self-maintained thought. Regions of medial area 10 support processes related to the former, whilst areas of lateral area 10 support processes that enable the latter. Three lines of evidence for this 'gateway hypothesis' are presented. First, we demonstrate the predicted patterns of activation in area 10 during the performance of new tests designed to stress the hypothetical function. Second, we demonstrate area 10 activations during the performance of established functions (prospective memory, context memory), which should hypothetically involve the proposed attentional system. Third, we examine predictions about behaviour–activation patterns within rostral PFC that follow from the hypothesis. We show with meta-analysis of neuroimaging investigations that these predictions are supported across a wide variety of tasks, thus establishing a general principle for functional imaging studies of this large brain region. We then show that while the gateway hypothesis accommodates a large range of findings relating to the functional organization of area 10 along a medial–lateral dimension, there are further principles relating to other dimensions and functions. In particular, there is a functional dissociation between the anterior medial area 10, which supports processes required for SO attending, and the caudal medial area 10, which supports processes relating to mentalizing.

Keywords: frontal lobes; executive function; BA 10; anterior prefrontal cortex; neuroimaging; neuropsychology

1. INTRODUCTION

Area 10 of the brain (also termed 'rostral prefrontal cortex (PFC)', 'anterior PFC' or 'frontopolar cortex') presents one of the most fascinating puzzles in cognitive neuroscience. There are many good reasons to suppose that it plays a critical part in the higher cognitive functions of humans yet, until very recently, virtually nothing was known about the mental processes that it might support.

The first reason for supposing that this region is important for human cognition is simply its size. It is a very large brain region in humans, covering at least 25–30 cubic cm (Christoff *et al.* 2001; Semendeferi *et al.* 2001). Indeed, it is the largest single architectonic region of the PFC (Christoff *et al.* 2001; Ongur *et al.* 2003). The second reason is that it is relatively larger in the human brain than in any other animal, including the great apes (Semendeferi *et al.* 2001; Holloway 2002). The third reason for supposing that area 10 supports cognition, which is both important and peculiar to humans, is its structure. It has a lower cell density in humans than that found in monkeys and apes. This has been interpreted as meaning that the

supragranular layers of area 10 in humans have more space available for connections with other higher-order association areas than in other animals (Semendeferi *et al.* 2001). Support from this view comes from findings that the number of dendritic spines per cell and the spine density are higher than in comparable cortical areas (Jacobs *et al.* 2001; Semendeferi *et al.* 2001). Furthermore, area 10 is also unusual in that it is the only PFC region that is almost exclusively connected to other supramodal areas within PFC and elsewhere (for a review, see Ramnani & Owen 2004). The fourth reason for supposing a role for this region in higher cognitive functions is that rostral PFC shows remarkably late developmental maturation. It is probably the last brain region to achieve myelination (Bonin 1950) and is one of the brain regions with the highest rates of brain growth between 5 and 11 years (Sowell *et al.* 2004). Indeed, reductions in grey matter density continue from adolescence to young adulthood (Sowell *et al.* 1999).

On these grounds, it is a reasonable hope that gaining an understanding of the role of this region in human cognition may provide a key to how the brain affects some of the behaviours peculiar to humans and, perhaps, thereby the symptoms that accompany its dysfunction (e.g. certain forms of psychological disorder).

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However, scientific evidence that might bear on the issue has only begun to emerge over the last 10 years or so. There are many reasons for this situation. For instance, the extreme difference in size and structure of this region in humans when compared with other animals limits the degree to which one might safely generalize from animal data to human experience. Furthermore, it is difficult to record from, and lesion, this region in non-human primates for practical anatomical considerations. Other cognitive neuroscience methods also face limitations. For instance, until very recently, the available electrophysiological methods have not had the required spatial resolution to collect data from different sub-regions within the frontal lobes. Transcranial magnetic stimulation studies of rostral PFC have also proved difficult for anatomical reasons (although these may not prove insurmountable).

Moreover, human lesion studies into the functions of this area have not, until very recently, been conducted. Partly, this has been due to the length of time it takes to collect sufficient data for this type of investigation (typically several years). But it is also because, traditionally, rostral PFC lesions have been considered neuropsychologically and neurologically 'silent'. In other words, they do not cause impairments easily elicited during the standard neurological or neuropsychological consultation. Thus, until very recently, virtually the only available evidence originated from the relatively new method of functional brain imaging.

Until the late 1990s, these neuroimaging findings were, however, largely restricted to the findings of rostral PFC haemodynamic changes associated with a particular cognitive function (e.g. episodic memory), rather than emanating from investigations that had the specific aim of discovering the functions of the brain region (but see, in particular, the studies by Kalina Christoff, Etienne Koechlin, and Raichle *et al.* 2001).

Unfortunately, these findings did not provide a firm basis for theorizing, since there seemed to be little obvious similarity between the paradigms that provoked area 10 activation. Indeed, area 10 activations could be found during the performance of just about any kind of task, ranging from the simplest (e.g. conditioning paradigms; Blaxton *et al.* 1996) to highly complex tests, involving memory and judgement (e.g. Koechlin *et al.* 1999; Burgess *et al.* 2001, 2003; Frith & Frith 2003) or problem solving (e.g. Christoff *et al.* 2001).

It was in this context that we started our research programme. It differed from most in that it had the specific aim of attempting to discover the cognitive functions of the brain area (BA) 10. This paper describes the stages that we have followed, and our conclusions at this early, but we hope promising, stage. We do not intend to provide an overview of the important work on this topic by our colleagues elsewhere. For this, the interested reader is referred to reviews by Grady (1999), Ramnani & Owen (2004), Burgess *et al.* (2005, 2006*b*) and Gilbert *et al.* (2006*c*).

2. STAGE 1: OBSERVATIONS OF EVERYDAY MULTITASKING PROBLEMS IN BRAIN-DAMAGED PATIENTS

The starting point for our investigations was a puzzling clinical observation that had been noted since the 1930s (e.g. Penfield & Evans 1935; see also Brickner 1936; Ackerly & Benton 1947). This was that some neurological patients show a marked behavioural disorganization in everyday life, despite little sign of impairment in intellect, memory, perception, motor and language skills—at least according to the evaluative methods available at the time.

It was not until 50 years later, however, that the full extent of this pattern became clear. Eslinger & Damasio (1985) described the case of EVR, who had undergone surgical removal of a large bilateral frontal meningioma. Premorbidly, EVR had been a trusted financial officer, a good father and a respected member of his community. But, following his operation, EVR lost his job, went bankrupt and divorced his wife. Extensive psychological evaluations found no deficit, however, and 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). Notably, Eslinger & Damasio (1985, p. 1737), however, report prospective memory (PM) problems in everyday life: '…it was as if he forgot to remember short- and intermediate-term goals…'.

Six years later, Shallice & Burgess (1991*a*) reported three cases with a similar profile in everyday life. None of them showed any significant impairment on formal tests of perception, language or intelligence. Moreover, two performed well on a variety of traditional tests of executive function. Shallice & Burgess (1991*a*,*b*) measured everyday life problems by inventing a real-life multitasking test carried out in a shopping precinct (the 'Multiple Errands Test'). Participants were required to complete a number of tasks, principally involving shopping in an unfamiliar shopping precinct, while following a set of rules (e.g. no shop should be entered other than to buy something). The tasks varied in terms of complexity (e.g. buy a small brown loaf versus discover the exchange rate of the Euro yesterday), and there were a number of 'hidden' problems in the tasks that had to be appreciated and the possible course of action evaluated (e.g. one item asked that participants write and send a postcard, yet they were given no pen and, although they could not use anything not bought on the street to help them, they were also told that they needed 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). All three of Shallice and Burgess's patients were significantly poorer than a group of age- and IQ-matched healthy controls on this test. The patients made a range of types of error, many of which could be interpreted as PM 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 bought at one visit; they did not complete the tasks that they had previously learnt that they needed to do; and they tended to forget to come over to the experimenter and tell them what
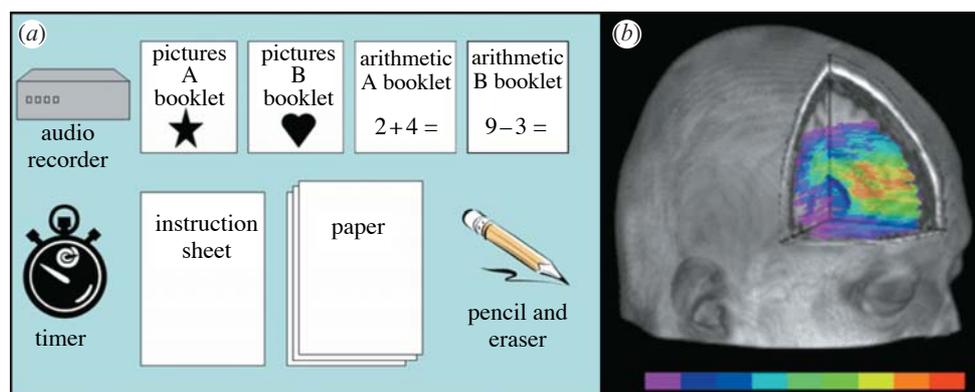
Figure 1. (*a*) Materials for the Modified Six Element Test (Burgess *et al.* 1996). Participants are given 10 minutes to complete at least some of each of the three subtasks, each divided into two parts (i.e. verbal dictation A and B, picture naming A and B, arithmetic A and B), but are not permitted to perform two subtasks of the same type straight after each other (e.g. arithmetic A then arithmetic B). (*b*) Lesion overlap figure from Burgess *et al.* (submitted *b*) for a group of right rostral PFC-damaged participants who made fewer task switches than other patients or healthy controls on a new version of the Six Element Test (right rostrals: mean voluntary task switches 3.0 (s.d. 2.1), other patients mean 6.3 (s.d. 4.0), $p < 0.005$).

they had bought when leaving a shop, which was a pre-learnt task rule. They also made a range of social behaviour errors (e.g. leaving a shop without paying, offering sexual favours in lieu of payment).

3. STAGE 2: DEVELOP 'MODELS' OF THE REAL WORLD WITH SIMPLER LABORATORY TASKS

Shallice & Burgess (1991*a*) also developed a laboratory task that aimed to mimic some of the critical demands of the multiple errands test, and thus serve as a 'model of the world' for experimental and assessment purposes. Termed the 'Six Element Test' (SET), this task required subjects to swap efficiently between three simple subtasks, each divided into two sections, while following some arbitrary rules (e.g. 'you cannot do part A of a subtask followed immediately by part B of the same subtask'; figure 1). Participants were given 15 minutes to perform the test, which was insufficient for all subtasks to be completed. There were no cues as to when to switch tasks, and although a clock was present it was covered so that checking it had to be a deliberate action. Despite their excellent general cognitive skills, all three cases reported by Shallice and Burgess performed these tasks below the 5% level when compared with the age- and IQ-matched controls.

However, it was not possible from these single case studies to determine the precise location of the lesion that caused this pattern of clinical impairment. Although all these people (and others with similar symptoms) were suffering from lesions affecting PFC, the lesions in each case were large, and invaded a number of prefrontal sub-regions (for brain scan results on these cases, see Shallice 2004; Burgess *et al.* 2005). It was not possible therefore with this small sample to ascertain the critical locus of damage. However, we now had a criterion laboratory measure that we could use for this purpose.

4. STAGE 3: ESTABLISH THE BRAIN REGIONS INVOLVED USING THE HUMAN GROUP LESION METHOD

Accordingly, Burgess *et al.* (2000) examined the performance of a series of 60 acute neurological patients (approx. three quarters of whom were suffering from brain tumours) and 60 age- and IQ-matched healthy controls on a multitasking test that shared similar principles with the SET. Called the 'Greenwich Test' this presented participants with three different simple tasks. They were told that they had 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 were four task-specific rules (e.g. 'in the 'Tangled Lines Test' you must not mark the paper other than to write your answers down').

It may be important to note that multitasking tests of this kind differ from most dual-task or task-switching paradigms in that: (i) only one subtask is attempted at any one time (unlike most dual-task paradigms) and (ii) switches of task have to be voluntarily initiated without the appearance of a cue (unlike most task-switching paradigms). In this way, tasks like the SET make strong demands upon PM abilities (i.e. the ability to remember to carry out an intended action after a delay).

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 the participants began the test, their ability to learn the task rules (by both spontaneous and cued recall) was measured. They were then asked how they intended to do the test, and a measure of the complexity and appropriateness of their plans was gained. This enabled us to look at whether their failures could be due to poor planning (e.g. Kliegel *et al.* 2000, 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 itself was calculated as the number of task switches minus the number of rule-breaks committed. After these stages were finished, subjects were asked to recollect their own actions by describing in detail what they had done and, finally, delayed memory for the task rules was examined.

We found that lesions in different brain regions were associated with impairment at these different stages in the multitasking procedure. Lesions in posterior medial brain regions, 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.* (2000) found that patients with left hemisphere rostral PFC lesions, when compared with patients with lesions elsewhere, showed a significant multitasking impairment, despite no significant impairment on remembering task rules. 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.

A subsequent study using a slightly modified form of the SET also showed that it is rostral PFC lesions that can lead to multitasking and PM problems in the context of preserved intellect and retrospective memory (Burgess *et al.* submitted *b*; reported in Burgess *et al.* 2005). In this study, a new version of the Burgess *et al.* (1996) SET was administered to 69 acute neurological patients with circumscribed focal lesions and to 60 healthy controls, using the administration framework of Burgess *et al.* (2000; see also Burgess 2000). 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 (figure 1). 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. Burgess *et al.* (in press *a*) argue that the hemispheric difference between these studies may reflect the differences between these two multitasking tests: the SET differs from the Greenwich Test in that the multitasking score reflects mainly voluntary time-based switching rather than rule-following. (For further discussion of this issue, see Burgess *et al.* in press *a,b*; Okuda *et al.* in press; for other relevant human lesion evidence, e.g. Goldstein *et al.* 1993; Burgess *et al.* 2000; Goel & Grafman 2000; Alexander *et al.* 2003; Bird *et al.* 2004; Picton *et al.* 2006.) Looking back from these group study results to previous case studies of patients with similar symptoms, revealed that all of them had rostral PFC involvement (e.g. Shallice & Burgess 1991*a,b*; Goldstein *et al.* 1993; Goel & Grafman 2000; see Burgess 2000 for details, and further cases).

5. STAGE 4: ESTABLISH THE RELATION BETWEEN ROSTRAL PFC AND THE HYPOTHETICAL SUB-FUNCTION USING NEUROIMAGING

Since the patients' problems on the multitasking tests could not be attributed to deficits in memory or planning, we hypothesized that deficits in PM were the core impairment in these people with rostral PFC lesions. If this were the case, then we might expect to see haemodynamic changes in this region when healthy people are performing PM tasks. And indeed, this seems to be the case. Burgess *et al.* (2001) showed, using positron emission tomography (PET), that regional cerebral blood flow (rCBF) increases in lateral BA 10 occur when people are performing a PM task, relative to when they are performing the ongoing task alone (see also Okuda *et al.* 1998). Importantly, these increases were just as large when participants were told that a PM cue might appear, but none actually did. Thus, we could conclude that at least some regions of lateral BA 10 are more involved with the maintenance of an intention rather than cue recognition or intention execution.

A second PET study confirmed this role for lateral BA 10 in PM conditions, and also showed that medial BA 10 is more active in ongoing conditions than PM ones (Burgess *et al.* 2003), i.e. the opposite pattern of results to that observed in lateral BA 10. Furthermore, medial BA 10 was also more active (compared with PM conditions) in a simple attentional baseline condition where the subject (S) just responded as fast as possible to any change in the display. These results raised the possibility that lateral and medial rostral PFC regions support a system that works in concert in PM situations, with a cost to environmental attending (one signature of which is anterior medial area 10 haemodynamic change) that accompanies the need to 'bear the PM intention in mind' (the signature of which is lateral area 10 activation.) (See e.g. Smith & Bayen (2004) for related views from experimental psychology.)

The two PET studies of Burgess *et al.* (2001, 2003) had used a 'multiple task averaging' experimental design. This is where one investigates haemodynamic changes across two or more tasks that putatively stress the process of interest (Shallice 1988), but where the other demands of the tasks are made quite different, for example, using spatial material for one and verbal for the other. Accordingly, Burgess *et al.* (2003) interpreted their results as suggesting that the functions supported by area 10 in PM are 'central' in the respect that they are material non-specific, and unrelated to the precise intention retrieval or cue recognition demands. Instead, Burgess and colleagues favoured an explanation in terms of one of the possibilities raised by Okuda *et al.* (1998), that the rostral PFC rCBF changes were related to the attentional demands made by having to 'bear in mind' an intention while performing an ongoing task.

We subsequently tested this hypothesis. Simons *et al.* (2006*b*) measured brain activity (using functional magnetic resonance imaging (fMRI) and a conjunction of two different PM tasks: 'words' and 'shapes') while manipulating the demands on either recognizing the appropriate context to act ('cue identification') or remembering the action to be performed ('intention retrieval'). A consistent pattern of haemodynamic changes was found in rostral PFC (BA 10) across both types of task and across both PM conditions (compared with the ongoing task alone). There was increased blood oxygen level-dependent (BOLD) signal in lateral BA 10, which was accompanied by

decreased BOLD signal in medial BA 10. Direct comparison of the 'high intention retrieval demand' with the 'high cue recognition demand' PM conditions also revealed greater BOLD signal in lateral area 10 regions bilaterally in the intention retrieval condition. These regions were somewhat more medial and caudal to those that showed activation common to both conditions. (For further investigations of the role of BA 10 in PM, see Burgess *et al.* in press *b*.)

6. STAGE 5: FORMULATE A HYPOTHESIS OF THE CRITICAL PROCESSING COMPONENT USING CONSTRAINTS FROM BOTH LESION AND NEUROIMAGING DATA

The studies described earlier suggested that the processes supported by rostral PFC are involved in PM and therefore multitasking. This is useful in understanding how the brain supports these 'functions' (i.e. behaviours understood in context of (i) a goal and (ii) a task analysis; see Burgess *et al.* 2006*a*,*b* for explanation). However, area 10 has been implicated as important in supporting many other functions, such as recollection or reflecting on mental states (see Grady 1999; Ramnani & Owen 2004; Gilbert *et al.* 2006*a*–*c* for review). It therefore seemed plausible that different subsections of area 10 support quite different functions. However, an account of this type raises two problems. The first is the possibility of infinite explanatory regress. Most functions will have sub-functions (or sub-operations) and the localization of each is likely at some level to be different. Moreover, one would be unlikely to discover processing common to many functions with this approach. The second problem is that starting with an assumption of strong modular functional specialization may leave the discovery of the relevant functions essentially to chance. Accordingly, in order to provoke new hypotheses, we proceeded on the basis of the simplifying assumption that BA 10 may support some critical processing component (or 'construct') which is shared by all the implicated functions (for definition of the terms function and construct in this context, see Burgess *et al.* 2006*a*).

The challenge was to find a function that fitted the myriad of observations from functional imaging and also those from the human lesion data. This was not straightforward, in particular because the findings from the two methods seemed to present a conundrum. This was that, based on the functional imaging findings of BA 10 activation in a wide range of tasks, an obvious suggestion might be that BA 10 supports some cognitive processing that is important to the performance of all of them. But if this were the case, then one would expect to see performance deficits across a correspondingly wide variety of tasks when this region is damaged in humans. However, this is not the case. As we have seen, neurological patients with rostral PFC lesions need not show impairments on tests of intelligence, clinical (retrospective) memory tests, language, perception and even tests of executive function such as the Wisconsin Card Sorting Test, FAS fluency, etc.

An appropriate account had to accommodate this apparent conundrum and also to be compatible with the other sets of constraints for theorizing presented by these different methods. Burgess *et al.* (2005) list the constraints we took as a starting position. There were seven constraints from human lesion studies and 17 from the functional imaging literature. Examples of the former were: 'rostral PFC lesions disproportionately impair performance in 'ill-structured' situations, in other words where the optimal way of behaving is not precisely signalled by the situation'; and 'rostral PFC lesions need not markedly impair performance on standard tests of intelligence, especially those that measure 'crystallized' intelligence, or those involving the use of over-learned procedures (e.g. arithmetic)'. Examples of the constraints for theorizing presented by the functional imaging literature were, for example, 'rostral PFC activation is not sensitive to the precise nature of stimuli, the nature of the intended action (in PM tasks) nor the precise response method, but is consistently implicated in tasks where one has to 'bear something in mind' while doing something else'.

The account that emerged as a potential solution was termed the 'gateway hypothesis' (Burgess *et al.* 2003, 2005, 2006*b*). This theory of the role of BA 10 in human cognition rests upon a distinction between stimulus-oriented (SO) and stimulus-independent (SI) attending (McGuire *et al.* 1996). SO attending refers to the attending behaviour that is required to concentrate on current sensory input. (Here, we make a distinction between 'attention' as a construct (i.e. a hypothetical processing resource that may operate across a range of operations or functions), and attending behaviour as a function or operation (function, directly observable behaviour; operation, mental experience) that may be indirectly inferred from observation; e.g. if presented with the sum $2+4$ and a person responds '6', one might infer that they have performed a calculation operation; see Burgess *et al.* 2006*a*,*b* for explanation.)

Examples of SO attending range from performance of vigilance tasks, to reading, watching the television, listening to a conversation and so forth. By contrast, SI attending is the attending behaviour required to effect either self-generated or self-maintained thought. Self-generated thought is cognition that goes beyond the overlearned associations or semantic memories provoked by currently available stimuli. In this respect, the concept shares similarities with that of *N*-order (i.e. second order, third order, etc.) representations used in experimental and developmental psychology and artificial intelligence. By contrast, self-maintained thought is where one deliberately maintains a representation in the absence of the stimuli that provoked it. It is the absence of the stimulus that provoked the representation that defines this operation as belonging to the class of 'SI' cognition. Examples of SI cognition therefore range from task-irrelevant thoughts such as mind-wandering or daydreaming, to goal-directed cognition such as that involved in making up a novel story, or maintaining a representation over a delay period, and so forth.

We assume that many mental experiences which occur over all but the briefest of durations will consist of combinations of SO and SI attending. Accordingly, for

empirical purposes, data relating to an SO or SI distinction might be thought of as existing along a continuum of relative proportions of variance. However, at the extremes at least, the distinction may be robust enough for empirical purposes. For instance, we describe four characteristics with which one can imbue a task that would increase the relative demand for SO attending, compared with a task that did not have these characteristics (Burgess *et al.* submitted *a*):

(i) Requires vigilance (e.g. attending in absence of stimulus or attentional capture).
(ii) Requires stimulus processing, i.e. awareness of stimulus characteristics (e.g. as required for conditional responding of the form 'if characteristic *X*, then respond *Y*').
(iii) The information required to respond appropriately is currently available. For instance, the task that presents subjects with maths problems of the form '4+2=' will be a purer measure of SO attending than one that requires comparing the sum of the currently presented numbers with the sum of two previously (but not currently) seen.
(iv) The operations involved prior to responding are automatic, well learnt or involve retrieval from semantic memory only (i.e. they are not novel).

Similarly, one might describe characteristics with which one might imbue a task which would increase the relative demand for SI attending, thus:

(i) The task encourages mind-wandering, for example, by being easy, monotonous, non-novel and repetitive.
(ii) All the information required to respond appropriately is not currently being presented, and:
  (a) The information that is required in order to respond appropriately is not well learnt or from semantic memory, but comes from a previously witnessed episode (e.g. as in a delay task).
  (b) The task requires the use of self-generated representations (e.g. novel problem solving, imagination).
  (c) The task requires working with representations that were self-generated on a previous occasion and have not been rehearsed in the meantime.

It is important to note that these are not the only characteristics one might outline. An everyday example to demonstrate the contrast between SO and SI modes of attending might be where one is trying to concentrate on a rather dull lecture (SO attending) versus imagining what one might do that evening after the lecture (SI attending). The gateway hypothesis proposes that rostral PFC in part supports a system which operates when one is required to maintain either mode of attending to an unusual degree or switch between them. More specifically, it proposes that medial rostral PFC plays a role in supporting SO attending, and lateral rostral PFC facilitates switching to, maintaining and voluntarily switching away from, SI cognition (figure 2).
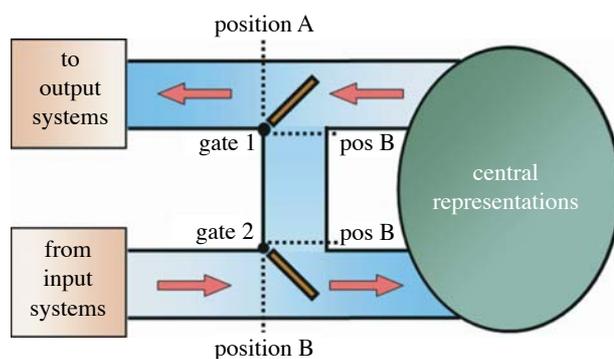
Figure 2. Stylized representation of the 'gateway hypothesis' of rostral prefrontal function. Rostral PFC regions are hypothesized to support a system that biases the flow of information between basic systems and central representations (i.e. equivalent to the adjustment of the position of the 'gates'). The gates are shown in the neutral position (equal to bias freely determined by context). If both gates are at position A, SI cognition is favoured. If both gates are at position B, full engagement with (external) stimuli is effected. Other combinations have further experiential correlates, especially when one considers dynamic, moment-by-moment switching. The operation of processes supported by lateral rostral PFC would correspond to the effecting of both gates to position A, with the operation of anterior medial rostral PFC regions effecting movement towards position B. However, this cartoon should not be taken too literally. The main purpose of the diagram is to emphasize how even a very simple switch system could effect a range of mental activity. Many other types of analogy could be used.

In this way, the cognitive system supported by rostral PFC was characterized as a 'gateway' between mental life and the external world. (For related accounts from neuroimaging, see McGuire *et al.* 1996; Christoff & Gabrieli 2000; Christoff *et al.* 2001, 2003, 2004; Pollmann 2001, 2004; Mason *et al.* 2007.) Within the information processing framework of Shallice & Burgess (1996), it is assumed that this attentional system lies between the contention scheduling (routine schema selection) and the other supervisory system modules (controlled processing), effecting bias between them (see also Shallice & Burgess 1991*b*, 1993)

This potential account, if true, might solve the apparent conflict between the imaging and lesion evidence since (i) the attentional 'gate' would operate in a wide variety of tasks, but not be critical to the performance of tasks that involve routine, informationally encapsulated processing resources or where attending is strongly driven by the environment, (ii) the difficulties that patients with rostral PFC damage experience (e.g. with multitasking and PM) are those that are particularly likely to require the operation of the attentional gate. This is because both multitasking tasks of the type investigated here (i.e. where one task is carried out while bearing in mind that one has to voluntarily switch to another soon) and also typical PM paradigms, both require active intention maintenance (SI cognition) while also engaging with external stimuli (SO attending) in performance of the ongoing task, or current subtask.

7. STAGE 6: TEST THE GATEWAY HYPOTHESIS

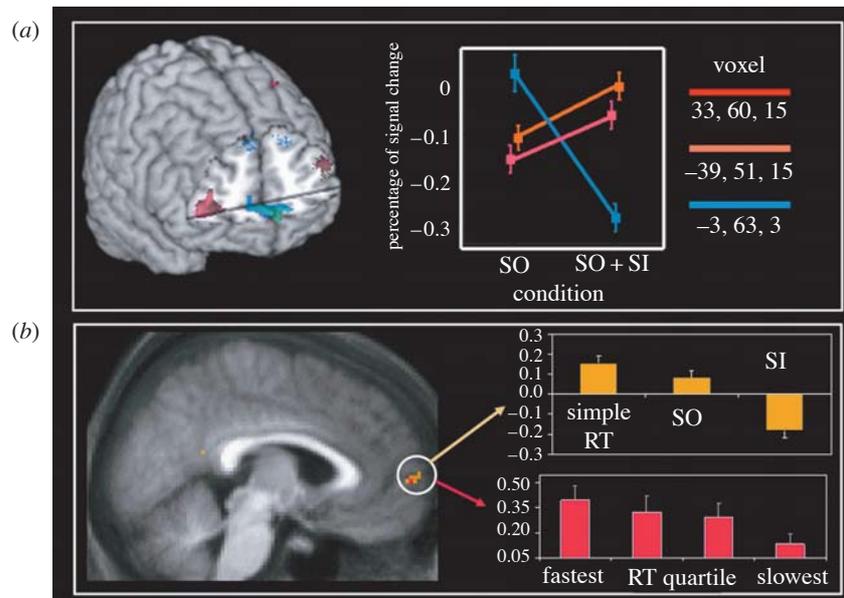The gateway hypothesis was then tested directly in three ways:

Figure 3. (*a*) Results from Burgess *et al.* (submitted *a*). Tasks requiring SO attending only are contrasted with tasks requiring SO attending plus SI attending (see text for details of the tasks). There is increased BOLD signal bilaterally in lateral area 10 in conditions requiring SI attending. Rostral medial area 10 shows the opposite pattern. The regions rendered on the brain (left) are colour coordinated to the graph (right). Coordinates are MNI. Bars are s.e.m. (*b*) Results from Gilbert *et al.* (2006*a*). Regions of activation revealed in the comparison of SO against SI conditions are shown in yellow. Regions where the BOLD signal correlated with reaction time in a separate simple-reaction time baseline condition are shown in red. This shows that BOLD signal in medial rostral PFC was greater on trials with relatively fast reaction times, ruling out an account of the role of this region in terms of task-unrelated thought during low-demand conditions (since this would be expected to compromise reaction time). (RT, reaction time.)

Stage 6(i). Development of direct indicators (i.e. tests) of the proposed function, and investigation of the involvement of area 10 in the performance of the tests using fMRI.

Stage 6(ii). Investigation with neuroimaging and lesion studies of specific functions (e.g. context memory), which should in theory make heavy demands upon this system.

Stage 6(iii). Meta-analyses of functional imaging studies to test the predictions that the theory would make about activation–behaviour associations.

We will consider these in turn.

(a) *Stage 6(i)*

Gilbert *et al.* (2005) invented three tasks that could be performed either using stimuli that were presented by visual display (i.e. requiring SO attending) or by performing the same tasks 'in one's head' only (i.e. SI attending). In the first 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. The second task required subjects either to navigate around the edge of a visually presented shape, or, when the shape was replaced by a 'thought bubble', to imagine the same shape and continue navigating as before. In the third task, in the SO condition, participants performed a classification task on sequential letters of the alphabet that were presented on a display. In the SI condition, they mentally continued the sequence and performed the same classification on each self-generated letter. 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 increased activity when participants 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 supported the hypothesis that rostral PFC is involved in selection between SO and SI attending, and suggested dissociable roles of medial and lateral rostral PFC in this selection process. It also showed that lateral BA 10 is activated at the point when one switches from performing a task in one's head to using displayed stimuli and vice versa.

A further fMRI study (Gilbert *et al.* 2006*a*) demonstrated performance-related activation (i.e. increased activation was associated with faster reaction times) in medial area 10 in simple reaction time conditions that did not require substantial stimulus processing (figure 3*b*). Thus, the characterization of medial rostral PFC as most active when an unusual degree of attention to external stimuli is required was supported. Moreover, unpublished data from this second experiment also showed that lateral rostral PFC is activated bilaterally during periods of extended SI cognition, and not only at the SI/SO switch points (SI–SO contrast: left hemisphere, -40, 36, 24, BA 9/46/10, $z = 4.28$, cluster size = 403 voxels; right hemisphere, 38,

44, 32, BA 9/46/10, $z = 4.43$, cluster size $= 643$ voxels; both $p < 0.001$ uncorrected; S. J. Gilbert 2006, personal communication).

However, there are different forms of both SO and SI attending. Therefore, we next considered whether we could see common BA 10 activations across the different forms, or whether rostral PFC seems to show regional specialization for the different types. Burgess *et al.* (submitted *a*) administered two quite different tasks, each of which consisted of four conditions, in an fMRI conjunction design. The conditions varied in the degree to which they made demands upon five attentional constructs, two of which were stimulus oriented (vigilance and stimulus attending) and three of which were stimulus independent in nature (mind-wandering, use of self-generated representations and maintenance over a delay). Regardless of task, conditions stressing both of the SO attentional forms activated similar regions of rostral medial area 10, and all three that stressed SI cognition activated similar regions of caudal lateral area 10. There was little evidence for further functional specialization within these regions. Figure 3*a* gives an example of these results, and shows the BOLD signal changes revealed by a contrast between tasks that required stimulus attending (e.g. deciding which of two numbers is the largest) and those that additionally required the use of self-generated representations (e.g. comparing the sum of two currently displayed numbers with the sum of two numbers seen on a previous trial).

(b) Stage 6(ii)

Another way to measure the utility of the gateway hypothesis using neuroimaging is to use it to predict which functions should activate area 10. Clearly, if the investigated function does not involve area 10, then the hypothesis is challenged. We chose a specific form of context memory as a prototype function. Context memory is, *prima facie*, a good candidate for the involvement of a mechanism that plays a role in the control of SI versus SO attending because the recollection of context requires the retrieval of information that goes beyond the associations immediately provoked by the current stimulus. We assume that when a trace is encoded, the strength of the links between elements will be indexed at least in part by what one was attending to at the time, which in turn is influenced by the nature of the task (see Burgess & Shallice 1996 for theoretical background). Thus, being required to recollect details that were part of the event but which were not central to it (or at least to what was attended, i.e. context details) will require the voluntary establishing of a partially new representation, i.e. SI cognition, and integration with the current perceived stimulus (requiring SO attending). Context memory paradigms should therefore be good examples of memory tasks that require switching between representations directly provoked by current stimuli (i.e. requiring SO attending) and those that are not currently perceived (i.e. SI attending).

Simons *et al.* (2005*a*) asked participants to make two different types of decision about words or famous faces that were presented either on the right or left of a display. They were then shown the words and faces again, while lying in an fMRI scanner, and were asked either which decision they had been required to make about the stimulus ('task memory'), or on which side of the screen the stimulus had appeared ('position memory'). Across both words and faces, activation in lateral rostral PFC regions occurred during both task and position memory conditions compared with a semantic classification baseline task. By contrast, medial BA 10 regions showed significantly increased BOLD signal during the task memory conditions compared with during the position memory ones. In a second study with a similar design (Simons *et al.* 2005*b*), we contrasted position memory with judging which of two previously presented and temporally distinct lists the stimuli belonged to ('list memory'). As with the previous experiment, both experimental conditions activated lateral rostral PFC relative to baseline. However, the aspects of left rostral PFC in both medial and lateral sub-regions additionally showed increased activation during the recollection of task compared with list. Furthermore, the time-courses of the activations in medial and lateral BA 10 were different, with lateral regions more active at the early stages, and medial regions more active at the later stages.

It would probably be premature to take a firm view of the significance of the finer points of these results; this awaits progress in our understanding both of the abilities that area 10 structures support, and of the processing demands made by context memory paradigms. However, it is quite clear from these two studies that: (i) recalling the contextual details is associated with very substantial haemodynamic changes in rostral PFC and (ii) there are lateral BA 10 regions that seem to be involved in context memory functions in a surprisingly non-specific way. In this way, the gateway hypothesis intersects with views of BA 10 involvement in memory retrieval (e.g. Lepage *et al.* 2000; Reynolds *et al.* 2006), which is one exemplar of operations whose signature is SI attending.

Remaining within the memory domain, a further prediction we made was that area 10 should be involved with distinguishing between perceived and imagined stimuli (Simons *et al.* 2006*a*). This is because imagining a stimulus is a cardinal form of SI thought, and therefore must be recalling that memory. However, processing a perceived stimulus in an experimental situation will of course be most effective if one is attending closely to the presented stimuli. Thus, the task will require considerable switching between SI and SO attending states. Accordingly, we showed participants well-known pair phrases (e.g. Romeo and Juliet; Laurel and Hardy) and they were asked to count the number of letters in the third word. This was called the 'perceive condition'. But on some trials the third word was replaced by a question mark (e.g. Romeo and ?), and on these trials, the subjects were required to imagine the word that completed the phrase and count its number of letters 'in their head'. Subsequently, the participants were presented with the first word from these phrases (e.g. 'Romeo') and required either to recall whether (i) the accompanying word had originally been perceived or imagined or (ii) the word-pair had been presented on the left or right side of the screen. We replicated our previous findings of lateral BA 10 activation in recalling which side of the

display the stimuli had appeared (versus baseline). However, we also found that on a subject-by-subject basis, people who showed least BOLD signal increase in a particular region of medial rostral PFC (MNI coordinates: $x=18$, $y=54$, $z=6$) tended to be those who made more errors in saying that they had actually witnessed a stimulus that they had in fact imagined (but not vice versa). It is probably too early to attempt a full explanation of these findings in information processing terms, since models of how people decide that they have imagined or perceived items are not sufficiently advanced. Moreover, there is always the possibility that the region of area 10 we identified in this study is not the same as those discussed earlier (it is, for instance, neither quite as medial nor as lateral as those discussed earlier). However, it does seem probable from these results that area 10 supports processing relevant to determining whether one has perceived or imagined an event. If this is the case, understanding the role this brain region is playing may help us to understand the genesis of disorders where mistaking imaginings for perceived stimuli is a key feature; for example, the hallucinations of schizophrenia. Indeed, when we examined the activation during this experiment in all three brain regions that Whalley *et al.* (2004) have argued show abnormalities in schizophrenia (sections of thalamus, cerebellum as well as the medial rostral PFC region examined here), we found significant BOLD signal increases in all three of these regions when people were engaged in discriminating between perceived and imagined items (relative to position memory).

(c) *Stage 6(iii)*

The third way in which we have tested the plausibility of the gateway hypothesis is to test a prediction that the theory would make about activation–behaviour associations using meta-analysis of functional imaging studies. If lateral area 10 plays some part in effecting tasks that require the various forms of SI cognition, as the gateway hypothesis proposes, then RTs to tasks that require attending to stimuli plus some form of stimulus-independent thought will be longer, typically, than to tasks that only require the stimulus attending component.

More specifically, we assume that the anterior medial rostral PFC is involved in simple attending to the outside world, and this can occur under even very low demand conditions (cf. Gilbert *et al.* 2006a). By 'low demand conditions', we mean those conditions that make few demands upon systems other than those involved in attending to the environment. In practice, this means that stimuli will tend to be familiar (and thus easily perceived and understood), conditional responding is either not required (e.g. simple RT paradigms) or taps an established S–R correspondence, and adequate performance of the task is within the capabilities of the individual. We also assume that lateral PFC is involved in SI cognition (e.g. attending to 'the thoughts in our head'; cf. Burgess *et al.* submitted *a,b*) as described earlier. If this is the case, then medial rostral PFC activations should tend to be associated with paradigms where RTs to the experimental condition are as fast, or faster than, whatever comparison task was used, while

lateral rostral activations should be associated with conditions where RTs were slower than in the comparison task. Perhaps the most obvious example comes from the field of PM. Performing an ongoing task while maintaining an intention, and checking for PM cues, is likely to result in slower RTs to stimuli than when one is performing the ongoing task alone. In this case, one would expect where the anterior medial area 10 activations were found, that they would be provoked mainly by the ongoing task alone, and where lateral activations are found they would be principally associated with the PM conditions. This is in fact the case (Burgess *et al.* 2001, 2003).

Accordingly, Gilbert *et al.* (2006b) analysed the RTs to paradigms from 104 PET/fMRI studies that had reported significant haemodynamic change in area 10. This yielded 133 independent contrasts. The tasks that had provoked these BA 10 activations came from a wide range of functions, e.g. memory, mentalizing, perception as well as tasks that involved multitask coordination (e.g. PM, task-switching, dual-task paradigms, etc.). Similarly, the tasks that had been used for comparison took many forms, and of course differed from study-to-study. But, if the gateway hypothesis holds, the precise form of neither the task under examination (e.g. memory, perception, etc.) that provoked the area 10 activation nor the comparison task (i.e. the task that had been used as a 'baseline' for the task that provoked the area 10 activation) should matter for these purposes. This is because all cognition consists of varying degrees of SO and SI cognition, so all tasks can be classified according to, for example, the proportion of variance (in BOLD signal change) one might attribute to one attending form or another. We assume that experiments where tasks have been compared that make similar demands upon SO or SI attending will have tended not to have yielded BA 10 activations. Hence, if we examine studies where BA 10 changes have been detected, and where the logic in the paragraph holds, there should be a medial–lateral BA 10 difference by RT.

As predicted by the gateway hypothesis, Gilbert *et al.* (2006a,b) did indeed find that RTs to tasks that had provoked lateral area 10 activations tended to be slower than RTs in whatever control task had been used. Furthermore, RTs to tasks that had provoked medial area 10 activations were as fast, or faster, than in the comparison task (figure 4a). This pattern occurred regardless of the type of task under study, and thus seems to be a general principle of area 10 neuroimaging findings.

8. FURTHER FUNCTIONAL SPECIALIZATION WITHIN AREA 10

Our studies strongly suggest that lateral and medial regions within BA 10 are differentially sensitive to the demands that tasks make upon SO and SI attending, and that this might provide a dimension along which the functional organization of rostral PFC might be understood (Koechlin *et al.* 2000). However, it does not provide, nor does it seek to be, a complete account of the relation between structure and function within rostral PFC.
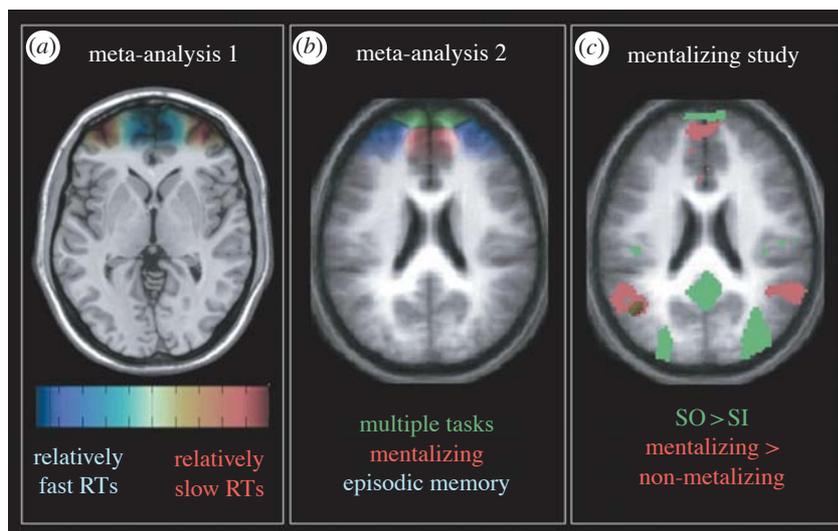
Figure 4. (*a*) Smoothed RT data from a meta-analysis of 104 functional neuroimaging studies reporting activation peaks in rostral PFC (Gilbert *et al.* 2006*b*). On average, contrasts producing activation peaks in regions coloured blue involved faster RTs in the experimental task than the control task against which it was compared. By contrast, those contrasts where the RTs in the experimental condition were slower than in the control condition tended to produce activation peaks in the regions marked in red. This pattern occurred regardless of the type of paradigm under use (e.g. episodic memory, mentalizing, etc.). (*b*) Results of a second meta-analysis of these 104 studies, which investigated the association between different types of task and the location of activation peaks within rostral PFC (Gilbert *et al.* 2006*c*). Note that the studies involving multiple-task coordination tended to yield activation peaks rostral to those involving mentalizing. (*c*) Results of an fMRI study that crossed the factors of attentional focus (SO versus SI) with mentalizing (mentalizing versus non-mentalizing judgments; Gilbert *et al.* submitted). The regions of activation in rostral PFC produced by the SO versus SI contrast were rostral to those produced by the mentalizing versus non-mentalizing contrast. In both (*b*) and (*c*), the results are plotted on an axial slice ($z = 24$) of the participants' mean normalized structural scan.

Most importantly, the account presented here does not preclude others. BA 10 is a very large brain region, with many connections to different brain regions. It is certainly possible that while we may have identified a particular function (e.g. attenuating SI versus SO attending), other sub-regions of rostral PFC may perform other unrelated functions. It might even be the case that the same brain regions as we have identified may perform different functions (e.g. by virtue of interactions with other brain regions).

Then, the gateway hypothesis as it currently stands deals only with the functional organization of BA 10 in respect of one spatial dimension: lateral versus medial. Yet, there is strong evidence from our own work and others that principles may emerge for functional organization along other dimensions (i.e. rostral–caudal, dorsal–ventral).

For instance, Gilbert *et al.* (2006*c*) investigated the location of activations within area 10 according to the type of task being used, with the neuroimaging database already described (see §7*c* earlier). The location in *X* and *Y* dimensions of area 10 activations were analysed across 133 contrasts found in the neuroimaging literature according to the type of task which provoked them. A classification algorithm was trained on half of the data and then tested on the other half to see if it could predict the task from the location of each activation peak. This algorithm is represented visually in figure 4*b*. Accuracy in the three main categories of task was 71% (chance: 33%; $p < 10^{-39}$). As shown in figure 4, episodic memory tasks were associated with lateral area 10 activations. More importantly, however, we found that mentalizing tasks tending to provoke activations within caudal

medial aspects of BA 10 (see also Frith & Frith 1999; Gusnard *et al.* 2001), but paradigms that required the coordination of two or more activities (dual task, PM, etc.) were associated with very rostral activations within area 10 (figure 4*b*).

In order to investigate this possible rostral–caudal localization distinction further, we conducted an fMRI study that crossed the factors of attentional focus (SO versus SI attending) and mentalizing (mentalizing versus non-mentalizing). Participants performed two of the three tasks investigated by Gilbert *et al.* (2005), which switched between SO and SI phases at unpredictable times. In 'mentalizing blocks', the participants were instructed that the experimenter was in control of the timing of these switches, and that they had to judge whether he had tried to be helpful or unhelpful in that block. In 'non-mentalizing blocks', the participants were instructed that the switches occurred at times randomly selected by a computer, and they were asked to judge whether these switches occurred more or less rapidly than average. In actuality, there was no difference between mentalizing and non-mentalizing blocks, but in post-experiment debriefing participants unanimously described inter-preting the timing of switches in the mentalizing blocks in terms of the mental state of the experimenter. For instance, one subject said 'I was thinking about whether you could see if I was stuck…and what was coming up on your screen so I did imagine what you were seeing sometimes during the experiment…I was more aware of the human element entering into the equation' (Gilbert *et al.* submitted).

The fMRI results were clear. Contrasting SO with SI phases revealed strong activity in the most rostral part of

medial PFC. This replicates the earlier finding of Gilbert *et al.* (2005). Moreover, the contrast of mentalizing with non-mentalizing blocks yielded activity in an adjacent caudal region of medial PFC, as predicted by the meta-analysis (Gilbert *et al.* 2006*c*). Most importantly, however, there was virtually no overlap between the brain regions activated in these two contrasts, and nor were there any regions showing a significant interaction between the mentalizing and attention factors (figure 4*c*). Thus, this study confirmed that dissociable, adjacent regions of medial rostral PFC are involved in (i) focusing attention on perceptual versus self-generated information or (ii) mentalizing. Taken with the result of the meta-analysis (figure 4*b*), these results suggest that it might be possible to establish a further principle of the functional organization of area 10 based around the rostral–caudal dimension.

9. CONCLUSION

This is an exciting time for scientists involved in trying to discover the functions of rostral PFC (BA 10). For many years, there was essentially little or no evidence that might speak to this issue. Then, the advent of functional neuroimaging placed the functions of this region at the heart of human cognition by demonstrating rostral PFC haemodynamic changes in a very wide range of tasks. However, the sheer volume and variety of these findings provided few constraints for theorizing. But, very recently, some principles have begun to emerge which suggest that achieving an understanding of the functional organization of this large, and uniquely human, brain region may not be an unrealistic aim. For instance, tasks that, in lay terms, require participants to 'bear something in mind while doing something else' very consistently provoke area 10 haemodynamic changes (e.g. Okuda *et al.* 1998, in press; Koechlin *et al.* 1999; Burgess *et al.* 2001, 2003), and these tasks also seem to be performed poorly by patients with damage to this brain region (e.g. Burgess *et al.* 2000). Yet, the functions of this region cannot be reduced to this function alone, since other consistent findings go far beyond this class of task. For instance, tasks that involve episodic recollection, 'mentalizing' and those that provoke mind-wandering are also accompanied by rostral PFC haemodynamic changes in a predictable fashion, as are simple tasks that involve making over-learned responses to environmental stimuli (e.g. Gilbert *et al.* 2005, 2006*a*. For review see Grady 1999; Ramnani & Owen 2004; Gilbert *et al.* 2006*b*,*c*). We have provided a framework that seeks to explain the multiplicity of these findings in a simple way, by invoking a construct that relies on the distinction between SO and SI attending. The experimental predictions that follow have been broadly confirmed in a series of experiments in our own laboratory, and we have also shown with meta-analysis that the hypothesis can explain important aspects of the findings from other laboratories, cutting across gross task characterizations. However, this gateway hypothesis, as it currently stands, seeks only to outline a principle for the functional organization of area 10 along a lateral–medial dimension. The most obvious next candidate discovery at this stage might be a

principle that relates to functional organization along a rostral–caudal dimension. Additionally, while we may have discovered one superordinate function of rostral PFC, this precludes neither the discovery of other functions that will provide conceptual challenge nor the possibility of functional specialization within sub-regions of area 10 that do not conform to the principle. In other words, in concentrating on discovering regions of area 10 which provide results that conform to the gateway hypothesis, we have not largely sought to discover those that might not. Nevertheless, we hope that the hypothesis we advance will prove a useful tool for investigation. Currently, it has three advantages over most other current accounts of the functions of this brain region. First, it is predicated on the results of both neuroimaging and human lesion data. This is particularly important, since the remarkably specific nature of the deficits shown by people with rostral PFC lesions provides a severe test of many other accounts that have emerged from neuroimaging data alone. Second, it provides a principle by which apparently similar activations (and their behavioural correlates) across tasks of different forms might be investigated. Third, it has received direct empirical examination. Clearly, however, we still have a great deal to learn. But, the special structure of rostral PFC in humans, its size, late development and links to the highest levels of human cognition, give hope that understanding how this fascinating brain region works may reveal key insights into the mental experiences and disorders that are peculiar to humans.

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