ANTERIOR PREFRONTAL CORTEX: INSIGHTS INTO FUNCTION FROM ANATOMY AND NEUROIMAGING

Narender Ramnani and Adrian M. Owen‡*

The anterior prefrontal cortex (aPFC), or Brodmann area 10, is one of the least well understood regions of the human brain. Work with non-human primates has provided almost no indications as to the function of this area. In recent years, investigators have attempted to integrate findings from functional neuroimaging studies in humans to generate models that might describe the contribution that this area makes to cognition. In all cases, however, such explanations are either too tied to a given task to be plausible or too general to be theoretically useful. Here, we use an account that is consistent with the connectional and cellular anatomy of the aPFC to explain the key features of existing models within a common theoretical framework. The results indicate a specific role for this region in integrating the outcomes of two or more separate cognitive operations in the pursuit of a higher behavioural goal.

Although the importance of the prefrontal cortex (PFC) for higher-order cognitive functions is largely undisputed, it is unclear how (and whether) functions are divided within this region. Cytoarchitectonic subdivisions are thought to correspond well with functional boundaries, although there is little agreement about the functions of specific subregions (for review, see REF. 1). Human neuropsychological studies, lesion and electrophysiological studies in the monkey and, more recently, human functional neuroimaging studies have largely failed to map specific cognitive functions onto anatomical or cytoarchitectonic subdivisions of the PFC. For example, the dorsolateral frontal cortex (BRODMANN AREA (BA) 9/46) has been implicated in many cognitive functions, including holding spatial information 'on-line'[2–4], monitoring and manipulation within working memory[5,6], response selection[7], the implementation of strategies to facilitate memory[8], the organization of material before encoding[9] and the verification and evaluation of representations that have been retrieved from long-term memory[10,11]. The mid-ventrolateral frontal cortex (BA 47) has been specifically implicated in a similarly wide range of cognitive processes, including the selection, comparison and judgement of stimuli held in short-term and long-term memory[6], holding non-spatial information 'online'[2,12], task switching[13], reversal learning[14], stimulus selection[15], the specification of retrieval cues[10] and the 'elaboration encoding' of information into episodic memory[16,17]. Finally, the orbitofrontal cortex has been implicated in processes that involve the motivational or emotional value of incoming information, including the representation of primary (unlearned) reinforcers such as taste, smell and touch[18–20], the representation of learnt relationships between arbitrary neutral stimuli and rewards or punishments[21,22], and the integration of this information to guide response selection, suppression and decision making[23–26].

There is another frontal region for which there are few, if any, coherent theoretical accounts of function. BA 10, also known as the frontal pole or rostral frontal cortex, comprises the most anterior part of the frontal lobe (FIG. 1) and, despite much data from functional neuroimaging studies, has remained resistant to functional description. This is probably because the interpretation of functional neuroimaging studies

**Centre for fMRI of the Brain, Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK.*
‡MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge, CB1 3QB, UK.
Correspondence to A.M.O.
e-mail: adrian.owen@mrc-cbu.cam.ac.uk
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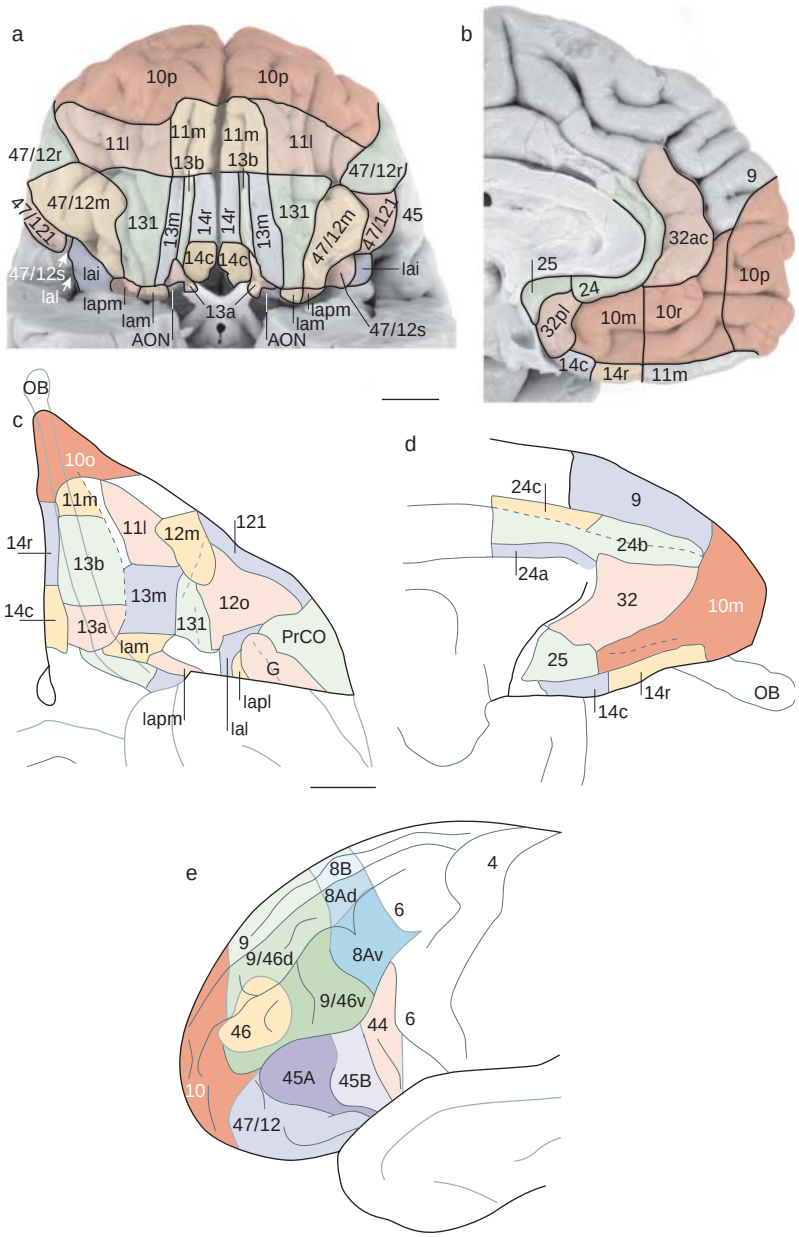


Figure 1 | **Brodmann area (BA) 10. a**–**d** | The location of cytoarchitectonic BA 10 (shaded in red) surface-rendered onto the orbital (**a**) and medial (**b**) surface of the human brain, and on the brain of the macaque monkey (**c** and **d**). The size of BA 10 (relative to other prefronal areas) seems to be significantly larger in the human brain than in the macaque monkey brain. Modified, with permission, from REF. 28 © John Wiley and Sons Inc. (2003). **e** | The location of BA 10 on the lateral convexity has been studied by Petrides and Pandya[106]. On the lateral convexity, area 10 incorporates the most anterior parts of the three frontal gyri. AON, anterior olfactory nucleus; G, gustatory cortex; OB; olfactory bulb; PrCO; precentral opercular area. Reproduced, with permission, from REF. 106 © Blackwell Publishing (1994).

relies heavily on investigations in non-human primates. To our knowledge, there are no studies in which the activity of frontopolar neurons in monkeys has been recorded, this area being difficult to access and study electrophysiologically in the macaque. In addition, essential neuroanatomical studies of the neuronal connections and cytoarchitecture of this region in non-human primates have become available only recently.

Here, we consider the existing accounts of aPFC function and evaluate each against a common set of criteria for relating structure to function. First, any useful theoretical account should generate testable hypotheses. In particular, converging evidence from studies of cortical activity using functional imaging and studies that use an intervention approach (such as lesions, transcranial magnetic stimulation or neuropsychology) is desirable. Second, any comprehensive functional theory of a particular brain region should specify the nature of the information being processed in that area, where it comes from and what is being done with it. Third, if localization of function is the aim, then the data that are used to relate structure to function must have some functional and anatomical specificity. This means that the level of functional description must accommodate the range of tasks that reliably recruit the aPFC, and the recruitment of that area alone should be the common link between those tasks. The recent functional neuroimaging literature is filled with proposals concerning specialization of function within the PFC, although in most cases these claims are based on a single observed association between a specific type of behaviour (or task) and activation in a particular brain region[27].

The anatomy of the aPFC

The Brodmann area that is most commonly associated with the most anterior region of the PFC is BA 10, which is conspicuously larger[28] and, importantly, comprises a significantly larger proportion of the cortex in humans than in other species[29]. However, the frontal pole and BA 10 are not synonymous. The most dorsal sector of the frontal pole includes BA 9 in non-human primates and probably also in the human brain[29]. Conversely, BA 10 extends beyond the frontal pole, particularly in 'higher' primate species[28]. The complexities of cross-species homology are highlighted by Brodmann's analysis of the comparative cytoarchitecture of the primate cerebral cortex[30]. He reports that the frontal pole in the monkey brain (*Ceropithicus*) is not occupied by BA 10 at all, but instead by BA 12. In this species, BA 10 occupies a region of the orbital cortex. Brodmann also argued that the frontal pole of *Ceropithicus* shares greater homology with human BA 11 in terms of cytoarchitecture. Others[28] have argued that BA 10 is so large in humans that it should be divided into three sub-areas. Only one of these occupies the frontal pole (area 10p), whereas the other two occupy most of the ventromedial PFC (10m and 10r). FIGURE 2 shows the relative sizes of human and macaque prefrontal areas on flattened representations of the cortex. Later studies have used more reliable methodologies to show that the relationship between the frontal pole and aPFC, while complex, is relatively consistent across species[29,31]. An important issue for the localization of activations in the PFC is the location of the borders between BA 10 and adjacent anatomical zones, particularly those on the lateral convexity. This issue poses particular difficulties when considering the functional neuroimaging literature, because no cytoarchitectonic information is available in scanned subjects and the cellular characteristics need to be approximated on the basis

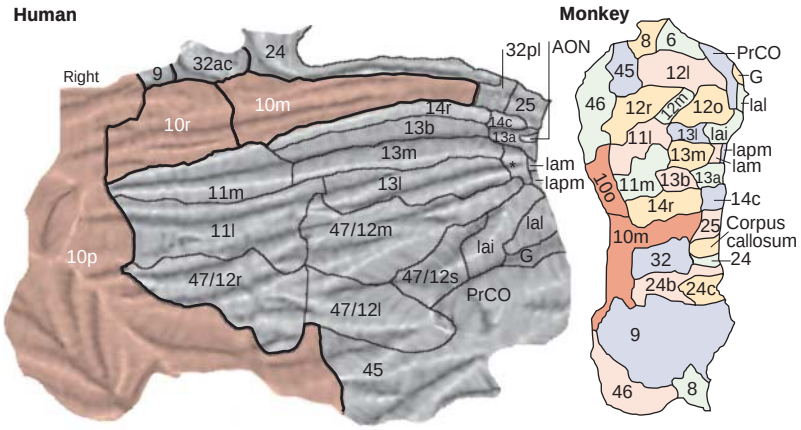


Figure 2 | **The right prefrontal cortex of in human (left) and macaque (right) brains represented as flattened surfaces.** These illustrate the considerably larger proportion of the surface area of prefrontal cortex occupied by area 10 in humans relative to macaque monkeys. AON, anterior olfactory nucleus; G, gustatory cortex; PrCO; precentral opercular area. Modified, with permission, from REF. 28 © John Wiley and Sons, Inc. (2003).

of gross morphology[1]. Studies agree that the cytoarchitectonic zone that occupies the anterior polar region of the frontal lobe is BA 10 (area 10p (REF. 28)). These studies also indicate that area 10 extends into the most anterior portions of the frontal gyri. So, a conservative estimate of the posterior border of area 10p on the lateral convexity would be the most anterior coronal plane in which the three frontal gyri are present. In this article, we refer to aPFC as the region within this boundary that is occupied by area 10p defined according to Ongur *et al.*[28].

One important distinguishing feature of the aPFC, even in comparison with other areas of supramodal (prefrontal) cortex, is that the number of dendritic spines per cell and the spine density are higher than in other comparable areas of the cortex, but the density of cell bodies is markedly lower[32]. This indicates that the computational properties of aPFC are more likely than those of comparable areas to involve the integration of inputs.

The primate cerebral cortex is hierarchically organized (BOX 1), with information becoming increasingly abstract as it is processed at higher points in the cortical hierarchy. At the apex of each information processing stream is a supramodal area (regions within the PFC and anterior temporal cortex) in which information is represented at its most abstract level[33]. The aPFC is unique in this respect: it seems not to be interconnected with 'downstream' areas in the way that other prefrontal areas are. Therefore, it is the only prefrontal region that is predominantly (and possibly exclusively) interconnected with supramodal cortex in the PFC[34–38], anterior temporal cortex[39,40] and cingulate cortex[37,38,41,42]. In addition, its projections are broadly reciprocal[43].

Current perspectives on aPFC function

Processing of internal states. Christoff and Gabrieli[44] suggested that human area 10 might be specialized "for the explicit processing of internal mental states and events — or introspective evaluation of one's own thoughts and feelings." Spontaneous mental activity, unrelated to the task at hand or the sensory environment, is often referred to as stimulus-independent thought, and is most likely to occur when the requirement to process information from external sources is low. Christoff and Gabrieli[44] propose that such unsupervised mental activity results in 'mind wandering' and could underlie the changes observed in the aPFC in studies in which the experimental requirements are insufficiently demanding to prevent such activity. This hypothesis concurs with the observation in functional neuroimaging experiments that anterior prefrontal regions, including BA 10, are disproportionately activated during the less demanding of two conditions, usually the baseline or rest condition[27,45]. Although 'mind wandering' is difficult to investigate, the idea that the aPFC is involved in the explicit processing of internal mental states and events generates testable hypotheses. In particular, tasks that require the generation and monitoring of internally generated responses should disproportionately activate the aPFC, and patients with damage to this region should have particular difficulty with problems of this type. An example is the TOWER OF LONDON TEST of planning[46], in which possible solutions must be internally generated and then accepted or rejected, before making a move. This test activates the aPFC, particularly when it emphasizes internalized, rather than explicit, problem-solving strategies[47]. Neurosurgical patients with damage to the frontal lobe are impaired at this task[46,48,49], although no study has looked specifically at patients with damage limited to the aPFC. This model also makes predictions about different types of memory task; in particular, recall tasks ('What is it that you remember?'), which emphasize self-generation, should involve aPFC more than recognition tasks ('Do you remember this?'). Christoff and Gabrieli[44] re-evaluated the episodic memory literature and found a higher incidence of aPFC activation in episodic recall tasks than in tasks that required only recognition. Again, although no studies have looked at patients with damage limited to aPFC, frontal-lobe damage, in general, disproportionately impairs recall relative to recognition memory[6,50].

Whereas the notion that the aPFC is crucial for the explicit processing of internal mental states and events generates testable hypotheses, our second criterion is less clearly met. The model does not specify where the 'internally generated' information comes from that is processed by aPFC (spontaneous thoughts, problem solutions and so on) and the processes that are carried out on that information (the model's functional specificity) are not sufficiently constrained to be falsifiable ('internally generated information is evaluated'[44]). With respect to anatomical specificity, it is also not clear whether activity observed in the aPFC can be reliably differentiated from that observed in the mid-dorsolateral frontal cortex (BA 9 and 46). For example[44], frontopolar activity has been observed in 13 out of 15 studies involving episodic memory tasks that require 'evaluation of self-generated material', but 11 of these cases also showed mid-dorsolateral activity. Similarly, in studies that involve problem solving, significant activity in the

BRODMANN AREA (BA). Korbinian Brodmann (1868–1918) was an anatomist who divided the cerebral cortex into numbered subdivisions on the basis of cell arrangements, types and staining properties (for example, the dorsolateral prefrontal cortex contains subdivisions, including BA 46, BA 9 and others). Modern derivatives of his maps are commonly used as the reference system for discussion of brain-imaging findings.

TOWER OF LONDON TEST A widely used neuropsychological test of planning and problem solving. Participants move a set of three balls between three rods (or 'pockets') to match a separate goal arrangement.

Box 1 | Information processing in hierarchical networks

Heirarchical organization seems to be a general principle of networks in the primate brain. Primary cortical areas lie at the foundations of these networks and are interconnected with supramodal areas of the prefrontal and anterior temporal cortex, through intermediate connections in unimodal and heteromodal areas[32]. The visual and motor systems are well understood examples. In the case of the visual system, information relayed to area V1 (primary visual cortex) cascades through a series of areas that elaborate and represent increasingly abstract aspects of visual stimuli (such as motion-sensitive and colour-sensitive areas[95]). These relay information to higher-order visual areas that represent visual information in terms of objects in temporal lobe circuitry (the ventral visual stream or 'what' pathway[96–98]). Finally, this information is relayed further to supramodal areas in the ventral prefrontal cortex (PFC), where it has been argued that object identity is represented in terms of its context[99]. Activity in Brodmann area (BA) 12/47, for example, is evoked when there are breaches of expectation during tasks that are concerned with visual attention[100]. The representation of rewards in the PFC is a special case of this general rule. Neurons in the orbitofrontal cortex can represent not just an object, but also its reward value and the degree to which it is expected in a given context[92,101]. In the case of the motor system, it has been argued that information cascades downwards from supramodal prefrontal areas to the primary motor cortex through a series of intermediate premotor areas. This cascade operates to convert relatively abstract goals in prefrontal areas into motor plans in the premotor system, and finally the more concrete representations of activity of specific motor units in the primary motor cortex[33]. The mid-portion of the sulcus principalis in the macaque monkey brain (BA 9/46) is the region of PFC that sends the strongest projections to the premotor system[102]. Cells in this area become active when the cognitive parameters of actions are manipulated (for example, the instruction to select an action from a number of alternatives[7,103]). The human homologue of this area is thought to lie in the mid-portion of the middle frontal gyrus[34], and is activated by similar tasks in functional imaging studies[7].

mid-dorsolateral frontal cortex is reported as often as activity in BA 10 (REF. 44). So, although the most anterior regions of the frontal lobe might be involved in the evaluation of internally generated information, they are probably not unique in this respect.

Memory retrieval models. A number of authors have suggested that the aPFC is involved in aspects of memory retrieval, including retrieval mode, success monitoring (or retrieval verification) and source memory. Although none of these ideas constitutes a functional model as such (they do not incorporate data on the aPFC outside the process under consideration), they are derived from a considerable data set and therefore require consideration. These various positions will be considered collectively and our assessment of each will be necessarily brief.

Tulving[51] proposed that a prerequisite for successful episodic retrieval is that the person doing the remembering is in the appropriate cognitive state, which he termed 'retrieval mode'. Retrieval mode is a tonically maintained state or 'set', which is entered into when episodic memory retrieval is necessary. Importantly, a stimulus event will be treated as an episodic retrieval cue only when an individual is in this state. On the basis of a series of positron emission tomography (PET) imaging studies[52–55], Tulving and colleagues[51] proposed that BA 10 in the right hemisphere is primarily responsible for retrieval mode. The retrieval mode hypothesis generates clear predictions: if the aPFC is activated by episodic memory retrieval, this activity should be invariant to both the nature of the task and the retrieval cue. Therefore, in experimental studies of episodic memory retrieval, the attentional set and the corresponding brain state will be established by the task instructions and maintained throughout the retrieval period. In addition, patients with damage to this area should be impaired regardless of the mechanism of retrieval (recall or recognition) and irrespective of whether retrieval cues are previously studied or non-studied items. Subsequent studies have provided mixed support for these hypotheses. Rugg *et al.*[11] showed that right prefrontal activity during episodic memory retrieval was greater during a cued recall task than during a recognition memory task. This result concurs with neuropsychological findings that patients with frontal-lobe damage are more impaired at recall than recognition[6]. The hypothesis that aPFC activity is insensitive to whether the retrieval cue is a studied or unstudied item has also been questioned[11,56]. Activity in the right aPFC was shown, in general, to increase with the proportion of studied relative to non-studied items presented at retrieval (although these findings have been challenged[57]). However, the hypothesis that the neural signature of retrieval mode should be sustained activity in the aPFC throughout retrieval has received some support. Velanova *et al.*[58] have shown temporally extended activity in the aPFC during controlled retrieval. They concluded that the aPFC is involved in forming and maintaining an attentional set, or task mode, that extends over several retrieval attempts.

With respect to our second criterion, the retrieval mode hypothesis has been computationally well-specified. For example, LePage *et al.*[59] defined retrieval mode as "A neurocognitive set, or state, in which one mentally holds in the background of focal attention a segment of one's personal past, treats incoming and on-line information as retrieval cues for particular events in the past, refrains from task-irrelevant processing and becomes consciously aware of the contents of successful ecphory [the cue-triggered retrieval of an episodic memory] should it occur as a successful event." However, where the information comes from, and what the aPFC does to that information, is vague beyond this general operational description. Regarding the third criterion, the retrieval mode hypothesis might be functionally too specific. Many tasks that do not require retrieval mode, or indeed any episodic retrieval, activate this region. For example, one review[60] found that the aPFC was routinely activated during episodic memory retrieval, working memory and 'miscellaneous tasks', leading the authors to conclude that "the critical processing demands [aPFC] subserves are most likely shared by a set of tasks extending beyond episodic retrieval."

Regarding anatomical specificity, retrieval-related activity has been observed in many brain regions other than PFC. For example, in experiments designed specifically to investigate retrieval mode, robust activity in multiple sites outside the aPFC was reported, including the anterior cingulate cortex, the frontal operculum/ventrolateral frontal cortex and a region of the right dorsolateral frontal cortex[59].

Theories of episodic memory retrieval often relate controlled retrieval processing to the recollection of contextual details surrounding a previous encounter with a stimulus[58]. Ranganath *et al.*[61] used functional magnetic resonance imaging (fMRI) to look at encoding and retrieval of pictures of objects. By having volunteers decide whether the identified pictures were bigger or smaller at retrieval than at encoding, the authors could ascertain whether activated regions were modulated by the specificity of the information to be retrieved. A region in the left aPFC was activated during retrieval, and activity increased as the retrieval of more perceptually detailed information was required. On this basis, they argued that the frontopolar cortex is important for source memory — memory not for the item, but for the context within which it was encoded.

A source memory view of aPFC function generates clear, testable hypotheses. Tasks that require source memory will activate aPFC whereas those that don't will not, and source memory tasks should be disproportionately impaired in patients with frontal-lobe damage. Although some studies of context (or source) memory have found more BA 10 activation for source than for item memory[62–66], others have not[16,67]. The neuropsychological literature is similarly equivocal; some studies find that patients with frontal-lobe damage are disproportionately impaired at tests of source memory[68], but others find no significant deficit[69].

With respect to the second of our criteria, there is no consensus regarding the nature of the information being processed by aPFC during source memory tasks. For example, Ranganath *et al.*[62] suggested that the aPFC "implements monitoring or evaluative processes that are engaged when one attempts to retrieve information from memory," and "was especially engaged during the evaluation of specific memory characteristics." On the other hand, Velanova *et al.*[58] conclude that frontopolar cortex "may contribute to gating processes in the cognitive domain, helping to maintain cognitive set during retrieval, particularly when a retrieval task requires that one constrain retrieval to a specific past context." The source memory account has functional specificity, but it cannot account for the repeated finding of activity in this region during tasks that seem not to require the retrieval of contextual memory (for review, see REF. 44). With respect to anatomical specificity, results are again mixed, although we know of no study where the aPFC has been activated in the absence of any other frontal region during a source memory task[58,62]. These findings indicate that models of episodic memory retrieval, including source memory, might be relevant to understanding the role of the aPFC in certain cognitive tasks, but are incomplete as a theoretical framework for understanding its functions.

Prospective memory. Although it is less a comprehensive model than an inferred association between function and anatomy, the aPFC has been proposed to be crucial for prospective memory[70]. Prospective memory allows an intended act to be carried out after a delay ('Remember to meet John at 5pm'). This framework was tested explicitly using PET. Four prospective memory tasks were given, each involving a different action (for example, respond in the direction indicated by an arrow). In certain trials (for example, when two arrows were the same colour) the volunteers were required to perform an additional act (such as pressing a buzzer), and remembering to do this was assumed to make demands on prospective memory. Regional blood flow increased bilaterally in the frontal pole during the task, indicating that this region is crucial for the maintenance of an intention. Because prospective memory has high functional specificity, this model makes clear predictions about the sorts of problems that should be encountered by patients with damage to the aPFC. Burgess *et al.*[71] described five frontal-lobe patients with some damage to aPFC. In all cases, their cognitive deficits included a failure to create and carry out intentions. The model also generates testable hypotheses about other types of task that should activate this area. For example, in one study volunteers heard a list of nouns and had to remember to tap a finger whenever they heard a previously learned target, a requirement that clearly involves prospective memory[72]. Frontopolar cortex was activated bilaterally. Unfortunately, there are also a number of studies that use prospective memory, but do not activate the aPFC. For example, in one such study, volunteers were asked to watch a series of numbers and to press a button whenever a pre-specified number appeared[73], a requirement that is functionally equivalent to that of the tasks used in REF. 70 and REF. 72.

This model does reasonably well with respect to our second criterion: the information stream in a typical prospective memory task has been well specified by Burgess *et al.*[60]. Situations that require prospective memory clearly involve a delay (from a few seconds to hours or days), an intended act ('to meet with John'), an ongoing task or set of tasks that occur during this delay period and are typically unrelated to the intended act or the retrieval context (thereby preventing continuous rehearsal) and a trigger to self-initiate the planned activity. According to Burgess *et al.*[70], the aPFC is involved in maintaining the intention, while additional processes required for the realization of that intention are carried out elsewhere in the brain.

Like the source memory account, a prospective memory view of aPFC is cognitively well-defined and cannot account for studies that have reported activity in this region during tasks that do not require prospective memory (for review, see REF. 44). With respect to anatomical specificity, the prospective memory model is also limited. In both of the imaging studies described above[70,72], frontopolar changes were accompanied by activity in the mid-dorsolateral frontal cortex, and in neither case was it possible to differentiate functionally between these two regions.

Branching and reallocation of attention. Koechlin *et al.*[74,75] have suggested that the frontopolar cortex mediates 'cognitive branching', or "The human ability to hold in mind goals while exploring and processing secondary goals, a process generally required in planning and

reasoning." This hypothesis was based on fMRI data that showed selective bilateral activity in aPFC when volunteers were required to keep in mind a main goal (a working memory task) while performing concurrent sub-goals (dual-task performance). Similar data led Braver and Bongiolatti[76] to describe the role of frontopolar cortex in cognitive branching as "subserving processes related to the management and monitoring of sub-goals while maintaining information in working memory". In that study, the crucial experimental condition required subjects to perform semantic classification as a sub-goal task while concurrently maintaining information in working memory and then combining the results of both sources of information to generate an appropriate response. So, according to this view, branching successively allocates processing resources between concurrent tasks, keeping relevant information in working memory to allow a return to a main task following the completion of a secondary task.

On the face of it, the branching hypothesis is readily testable, although the coordination and management of sub-goals is a requirement of many behavioural tasks including planning, problem solving, decision making and attentional set-shifting. In fact, almost all complex cognitive activities can be said to involve some form of branching, and even ostensibly simpler processes such as episodic memory retrieval can, and have, been recast in these terms[76]. In that sense, the functional specificity of the model is unclear because, whereas the cognitive processes in branching are clearly defined, they also occur in a wide variety of different tasks. However, many of these tasks do reliably and robustly activate aPFC. For example, the Tower of London planning task, which requires volunteers to integrate a number of sub-goals (moving balls around on pegs) with a main goal (reaching the problem solution), activates aPFC[47,77] and the task is sensitive to frontal-lobe damage[46,48].

Exactly what information is processed and where it comes from is not fully specified in the branching hypothesis. Koechlin *et al.*[74,75] focus on integration of task-switching and working memory processes, but as this is thought to occur when subjects are required to hold an ongoing task temporarily to complete an intermediate task, storage is also implied. Where the information that is integrated comes from and how it is combined and utilized is unclear. Braver and Bongiolatti[76] are similarly vague about the flow of information during cognitive branching, suggesting that aPFC activation "may reflect a specialized representational code that is used to actively maintain information in tasks that require sub-goal processing," and/or might be "recruited to provide storage of this information in a form that is more protected from interference," and/or "may be critically involved in the actual integration of the results of sub-goal processing with the information that had been actively maintained prior to the sub-goal task."

Relatively few studies, and none outside functional imaging, to our knowledge, have investigated branching specifically. Even so, the results are mixed with respect to anatomical specificity. For example, Koechlin *et al.*[74] found that cognitive branching activated only the aPFC bilaterally, whereas Braver and Bongiolatti[76] found that the aPFC was co-activated with several other regions, including the mid-dorsolateral frontal cortex.

Some aspects of the cognitive branching hypothesis are reminiscent of models of multi-tasking or 'multiple sub-goal scheduling' that have also implicated anterior regions of the PFC[71]. Multi-tasking or multiple-task situations typically require the allocation of attentional resources in the face of competing demands. Pollmann and colleagues[78,79] have suggested that the frontopolar cortex is involved in controlling 'attentional weight shifting'. The core feature of this view is that the most salient stimuli are often not the most relevant for a task and intentional selection is often required. Pollmann *et al.*[78] reported activity in the left lateral frontopolar cortex in trials where the relevant dimension changed relative to those where it stayed the same, and concluded that this region helps to control attentional reallocation after dimensional changes. In other studies, left frontopolar activity was associated with the deployment of attentional resources away from currently attended visual dimensions or spatial locations to a new dimension or location (for review, see REF. 79). However, such changes were observed only when subjects were not in a top-down controlled state of selective attention. So, activation of the left lateral frontopolar cortex seemed to be specific to stimulus-driven attentional shifts.

This model is easily testable, although as an account of aPFC function, it is perhaps too functionally specific; although it is true that the aPFC is activated during some tasks that require the relocation of attention, this does not account for its role in most cases where this region has been activated[44]. To our knowledge, this model has not been tested neuropsychologically, although attentional shifting deficits have been reported in patients with frontal-lobe damage[80,81]. However, these deficits are functionally specific and do not correlate well with other deficits in these patients, again indicating that attentional shifting is one aspect of, rather than an explanation for, frontal-lobe function. With respect to information flow, the model is well-specified conceptually, although whether the aPFC is involved in the monitoring of events that make the reallocation of attention necessary or in the initiation of these attentional shifts is unclear. Moreover, how this region interacts with other cortical and sub-cortical regions to control attentional reallocation is not specified. Finally, although the aPFC has been activated during several tasks that require the reallocation of attention, this region has not been shown to be unique in that respect[78].

Relational integration. An alternative hypothesis is that the aPFC is required for the explicit representation and manipulation of relational knowledge[82] and is essential for 'relational integration'; that is, the simultaneous consideration of multiple relations[83] (between objects or thoughts). The relational complexity of a reasoning task is assumed to increase with the number of relations that must be simultaneously considered to infer the required conclusion[84]. In one fMRI study, a problem-solving task based on RAVEN'S PROGRESSIVE MATRICES[85,86] was used to

compare problems that required analysis of the relations between multiple objects in two dimensions (for example, two aspects of shape), relations in one dimension (such as shape) or relations in zero dimensions (simple matching-to-sample). Comparing the first two conditions revealed frontopolar activity, which was taken to indicate a role for this region in the consideration of multidimensional relations[83]. In a similar experiment using Raven's progressive matrices, Kroger *et al.*[82] sought to decouple the effects of relational complexity from those of other factors that increase task difficulty. They found that reasoning problems that vary in the number of explicit relations that jointly determine the solution to a problem recruit a cortical network that includes the aPFC. In addition, the change in activity in this region as relational complexity increased was distinguishable from activity changes resulting from increases in (non-relational) task difficulty.

Relational complexity can be easily quantified, yielding testable hypotheses about expected activity in imaging studies and impairments in patients. Patients with frontal-lobe damage are significantly impaired in their ability to solve matrix problems that require the integration of multiple dimensions[87,88]. However, because this view is overly specific, it cannot account for many of the tasks that activate aPFC but that do not involve relational integration[44], nor for patients' deficits in such tasks. In addition, what information is integrated, where it comes from and what processes are carried out on it are not well specified. Finally, with respect to anatomical specificity, both of the studies described above found that increases in activity in the aPFC were accompanied by similar changes in the mid-dorsolateral frontal cortex. So, although the aPFC seems to be involved in tests that tap relational complexity, it is neither uniquely nor solely involved in such tasks.

Towards a common theoretical framework

In this review, we have considered a number of models that have attempted to describe the functions of the aPFC, largely on the basis of functional neuroimaging studies. In the introduction, we specified three criteria against which models of function should be judged. These were that they should (1) generate testable hypotheses, (2) specify where information comes from and how it is processed, and (3) be supported by data in a manner that is anatomically and functionally specific. With respect to the latter two criteria, many of these models fail to acknowledge a subtle but crucial distinction between ascribing a task-specific 'function' to an area (for example, source memory) and describing the information processing that is performed by that region. In terms of the functional architecture of the brain, 'task' and 'process' are rarely synonymous (several tasks can commonly recruit a given process for their successful completion). Although it can be argued that a specific kind of information processing is the function of an area, models that are based on tasks or even classes of task will inevitably have limited explanatory value outside the immediate cognitive domain of those tasks. This problem is illustrated by considering how different models have attempted to accommodate identical data sets into ostensibly unrelated theoretical frameworks. For example, in their discussion of the role of the aPFC in branching and sub-goal processing, Braver *et al.*[76] reconceptualize episodic retrieval in terms of monitoring sub-goals in working memory. Conversely, Christoff and Gabrieli[44], in their discussion of the importance of the aPFC in the processing of internal states, suggest that many episodic retrieval tasks can be thought of as requiring the evaluation of internally generated information. Finally, in their discussion of the role of BA 10 in relational integration, Kroger *et al.*[82] suggest that many episodic memory tasks involve "binding new information with existing knowledge into a meaningful and useful representation … potentially forming a complex relational structure." Given the prevailing emphasis on 'tasks' in defining the functions of the aPFC, it is perhaps unsurprising that there is considerable disparity between the various models. On the other hand, if one considers the type of information processing that aPFC might perform, a common thread emerges. The account that follows combines the core features of many of the models described above, but focuses on the common processes that are implied rather than the specific tasks that are employed. In doing so, it accommodates relevant findings from anatomical studies as well as much of the existing functional neuroimaging literature. We consider how it meets the three criteria defined earlier, and discuss the hypotheses that this account generates and how these hypotheses can be tested.

We propose that the aPFC is engaged when problems involve more than one discrete cognitive process: that is, when the application of one cognitive operation (such as a rule) on its own is not sufficient to solve the problem as a whole, and the integration of the results of two or more separate cognitive operations is required to fulfill the higher behavioural goal. Multiple, related cognitive operations can only be performed successfully if they are coordinated, and we speculate that the coordination of information processing and information transfer between multiple operations across supramodal cortex is an important aspect of aPFC function. One new and crucial aspect of this view is that it is consistent with the cellular and connectional properties of neurons in the primate aPFC. Earlier, we discussed evidence that the aPFC is interconnected exclusively with supramodal cortex. This connectional architecture indicates two general levels of information processing. First, when information is transmitted into supramodal cortex from areas outside it, it is represented at a more abstract level. Second, these representations form the inputs into the aPFC, where they are processed further. We also note that the cellular properties of neurons in the aPFC are better suited than those of other areas to integrate their inputs[32], and we speculate that this might allow the aPFC to integrate information from locations across supramodal cortex.

This account is also broadly consistent with much of the functional neuroimaging literature. As we have described, activity in aPFC is ubiquitous in many types of functional imaging study, making it difficult to specify the processes that activate this area on a task-by-task

RAVEN'S PROGRESSIVE MATRICES
A non-verbal test of inductive reasoning in which participants are required to discern the relationship between complex shapes, usually in more than one dimension.

basis. However, if we look for commonalities in the way that information is processed across these studies, it becomes clear that aPFC is almost always activated when the solutions of two or more discrete cognitive operations need to be integrated in the pursuit of a more general behavioural goal.

Perhaps the clearest examples come from studies that have investigated the cognitive control of action. Actions are often executed under the guidance of either a sensory cue or a rule (for example, a particular sequence of finger movements, or a sequence of timings). Several studies have manipulated both these factors so that timings and finger sequences are either under the guidance of a learned rule or under the guidance of a sensory cue[89,90]. In those experiments, the aPFC was activated when rules about timing and finger sequences were applied simultaneously to the same actions (so, the sensory cues are present, but not required). When one or the other (or neither) was rule-based, the aPFC was not significantly active. In fact, Ramnani and Passingham[89] showed that when one rule was overlearned (sequence) and the other was in the process of being learned (timing), there was a parametric increase in activity in this area. This indicates that the aPFC was engaged in the simultaneous representation of multiple rules to solve a motor control problem. In this example, the rules that are integrated to fulfill the higher goal are both from the motor domain. However, there are also examples from different domains. Rogers *et al.*[91] reported aPFC activation when a decision had to be made by resolving a choice between two independent probability judgements. Our account suggests that the aPFC should also be active when the rules that comprise a complex behavioural goal are themselves from different domains. Ramnani and Miall[92] found that the aPFC was specifically activated when subjects were required to apply two unrelated rules simultaneously: which action to perform on the basis of stimulus shape, and whether to expect a reward for correct performance on the basis of stimulus colour. In this case, the combination of the outcomes of a cognitive operation relating a stimulus attribute to an action and an unrelated operation relating an independent stimulus attribute to reward predicts activity in aPFC.

Despite the lack of coherence between other models of aPFC function, there are some parallels between specific models and our proposal. For example, Christoff and Gabrieli[44] proposed that the aPFC is specialized for the explicit processing of 'internal' information (including our own thoughts and feelings). By 'internal' they mean representations that are stimulus independent, and in this sense their account resonates with our view that the aPFC processes abstract information without reference to lower-order information (such as sensory input). However, unlike Christoff and Gabrieli[44], we would not predict that the consideration of internally generated information would always activate aPFC, particularly if a process or set of processes did not involve the simultaneous consideration of the outcomes of several independent cognitive operations. In fact, there are clear examples in the literature where the consideration of internally generated information does not activate aPFC[89,90].

There are also some parallels with models of memory. We suggest that source memory tasks activate aPFC because they require the simultaneous resolution of information about an item and about the context in which it was encoded. Successful performance is not possible with the resolution of only one or the other, as they are both required. Prospective memory tasks might activate this area for similar reasons: one rule ('meet John') has to be applied only in the context of another ('when it is 5pm'), and the processing streams that mediate these two aspects of behaviour undoubtedly proceed independently, but have to be brought together to fulfill the overall behavioural goal (remembering to meet John at 5pm). Concepts such as 'retrieval mode' and 'success monitoring' are also easily recast in these terms, requiring the integration of at least two distinct operations (for example, retrieval itself and a comparison between the retrieved item and either a stimulus or another internal representation).

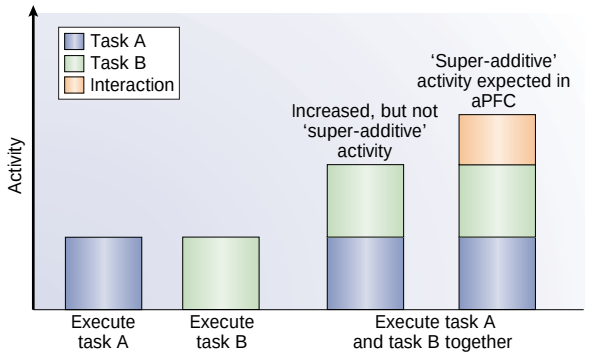
Models that emphasize the importance of 'branching' and the reallocation of attentional resources also have parallels with our account. Branching involves holding primary goals in mind in working memory while simultaneously exploring secondary goals. Although it is not explicitly stated in these models, branching occurs because the solution to the primary problem can be found only when the solution to the secondary one is found first. The solution to the first depends on the resolution of the second and is therefore entirely compatible with, but only a specific instance of, our account of aPFC function. Similarly, we take the view that the reallocation of attentional resources is a secondary effect of branching rather than an independent explanation for activity in the aPFC, because holding a primary problem online while exploring a second inevitably requires a shift of attention. In one recent study, sustained aPFC activity was observed when volunteers were required to switch between two tasks within a single block of trials, but not during single-task blocks[93]. The behavioural 'mixing cost' associated with the former condition indicates that the mixed blocks require the on-going consideration of the two tasks, whereas the single-task blocks allow attention to be allocated to one of the tasks rather than the other. Again, this resonates well with our view that aPFC activity occurs in situations that require the coordination of multiple related cognitive operations (in this case, two sub-tasks). Indeed, the authors conclude that their task requires that "the stimulus–response mappings for two different tasks have to be maintained simultaneously", that "attention toward the task cue must be maintained … in order to be sensitive to trials in which the cue indicates a task switch", and that "the task-set mappings have to be maintained in working memory, while attention is directed toward completing the various sub-goals", all of which imply the coordination of multiple cognitive operations.

'Relational integration' is perhaps the most closely related concept to our account, although again we believe that it represents a specific example of a more general requirement to combine and coordinate the outputs

Box 2 | Interactions in functional neuroimaging experiments: a hypothesis

We have argued that the anterior prefrontal cortex (aPFC) is engaged when successful task completion requires problem solving in two or more domains and during successful coordination of two or more cognitive operations. Crucially, it is the interaction of these solutions that allows task completion. So, it is not sufficient to show that activity in the aPFC occurs in the general context of problem solving. Nor would it be sufficient to demonstrate such activity in the presence of two unrelated problems. A stringent test of our hypothesis would be that we expect activity in the aPFC to reflect an interaction between two main effects of the same task. Although this criterion might not by itself be sufficient for testing our hypothesis, we consider it to be necessary and more stringent than the ones previously mentioned.

	Main effect B	Main effect B
Main effect A	A– B–	A– B+
Main effect A	A+ B–	A+ B+



In a typical factorial design experiment, the absence and presence of two main effects are independently manipulated (see table). Interactions reflect the information processing resources that are specifically devoted to the combining operations, over and above the main effects themselves. So, when all the rules that are required to solve a problem are available to subjects in a functional neuroimaging experiment, the 'super-additive' activity should exceed the sum of activities found when subjects solve one problem at a time (see figure). This might, for example, be achieved by manipulating the availability of information required to complete the task independently of sensory guidance, such that it can be completed using only abstract information in one condition (A+ B+). Some of the activity in this condition will be due to the additional processing demands of integrating the solutions to A and B, and this can be statistically partitioned by taking into account the main effects. So, Interaction effect = ([A– B–] + [A+ B+]) – ([A– B+] + [A+ B–]) (see table)

The anatomical component of our account emphasizes the combined use of inputs from supramodal cortex, so our proposal does not predict interaction effects in aPFC in all studies that test for interactions, but only those in which cognitive operations are combined where abstract information is represented. Note, for example, that Ramnani *et al.*[104] tested for activity related to the coordination of two over-practised and automatic motor tasks in a factorial design (finger movement and arm movement), but no interaction effects were seen in the prefrontal cortex. The figure shows a schematic diagram of expected changes in activity in voxels that do (fourth column) and do not (third column) demonstrate super-additive activity (interactions) in factorial experimental designs in functional neuroimaging experiments.

from multiple cognitive operations. In particular, relational integration requires the simultaneous consideration of multiple relations between objects or thoughts[83], Raven's matrices being the typical example. Such tasks can be solved only by considering multiple dimensions of a problem and abstracting a solution from their simultaneous consideration. As the literature review above demonstrates, there are many examples where aPFC has been activated but no 'relational integration' is required. We would argue, however, that in almost all cases, more than one cognitive operation has to be completed and the results combined to solve the problem. Moreover, several current models, such as relational integration and branching, do not accommodate one another except at this more general level of description. For example, branching does not involve the simultaneous consideration of relations, by definition, as one operation is held in check while another is completed. However, if one accepts the suggestion that aPFC is generally involved in integrating the outcomes of separate cognitive operations, then both relational integration and branching can easily be accommodated, as can the results of many studies outside these two models.

The main advantage of our account is that the level of explanation is neither specifically tied to a task or class of tasks, nor too general to be empirically testable. This account also seems to accommodate some of the core features of most of the models described above that otherwise present rather disparate views. One of our criteria was that models should specify the nature of the information processing that takes place in a given region. We have suggested that the aPFC receives its inputs from other areas of supramodal cortex where information from lower-order areas is abstracted. This abstract information forms the input into the aPFC. Another criterion is related to anatomical and functional specificity. We have made a clear case in favour of the view that the aPFC processes information by integrating the outcomes of two or more separate cognitive operations in the pursuit of a higher behavioural goal. But our primary criterion was that any reasonable model of BA 10 function should generate testable hypotheses. Our account does not make task-specific predictions, but instead makes predictions related to how the aPFC might process information across various tasks. Specifically, it suggests that activity in the aPFC will be evoked when the solution to an overall problem can be arrived at only by the simultaneous consideration of multiple sub-problems. In essence, this predicts that specific computational resources in the aPFC will be devoted to the integration of sub-problem solutions, over and above the processing that is required for the individual solutions themselves. This account can

be most easily realized in terms of the main effects and the interaction term of a factorial experimental design, where the solubility of each secondary problem can be independently manipulated as a main effect. Interactions allow us to examine how the activity related to one main effect is modulated by the context of another where specific information processing resources are dedicated to the modulation, over and above the processing of the main effects themselves. Experimental designs in functional neuroimaging experiments can statistically partition brain activity specific to the interactions between two or more main effects from the activity related to the main effects *per se* (BOX 2). In one of the conditions, where both problems become solvable, some of the activation can be ascribed to processing over and above the main effects. Our account predicts that this portion, the interaction effect, dedicated to the integrative processing of the two main effects, will be localized to the aPFC. Our hypothesis also specifically predicts, on the basis of the anatomical connections of the aPFC, that the main effects that yield this interaction should be tasks in which processing of abstract information is demanded. Recent evidence shows support for this view[90,92,94] but further studies are needed to test this possibility more robustly. We also suggest that a better understanding of the aPFC might be gained by investigating information flow through the networks of which it is a part, particularly in respect of the information flow from extra-supramodal to intra-supramodal areas during the processing of component problems, and from supramodal areas to anterior prefrontal areas when solutions from this first processing level are integrated to find a solution to the overall problem.

In summary, although recent studies have demonstrated that the aPFC is activated during many 'high-level' cognitive tasks, an adequate functional explanation for this ubiquitous involvement has remained elusive. We suggest that the coordination of information processing and information transfer between multiple cognitive operations within supramodal cortex is an important aspect of aPFC function. This explanation concurs with much of the functional neuroimaging literature, accommodating many of the key features of existing models into a common theoretical framework. Crucially, this framework is also entirely consistent with the connectional and cellular anatomy of the aPFC, which is the only prefrontal region that is predominantly interconnected with supramodal cortex.

1. Brett, M., Johnsrude, I. S. & Owen, A. M. The problem of functional localization in the human brain. *Nature Rev. Neurosci.* **3**, 243–249 (2002).
2. Goldman-Rakic, P. S. Working memory dysfunction in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* **6**, 348–357 (1994).
3. Jonides, J. *et al.* Spatial working memory in humans as revealed by PET. *Nature* **363**, 623–625 (1993).
4. Courtney, S. M., Petit, L., Haxby, J. V. & Ungerleider, L. G. The role of prefrontal cortex in working memory: examining the contents of consciousness. *Philos. Trans. R. Soc. Lond. B* **353**, 1819–1828 (1998).
5. Owen, A. M. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur. J. Neurosci.* **9**, 1329–1339 (1997).
6. Petrides, M. Frontal lobes and behaviour. *Curr. Opin. Neurobiol.* **4**, 207–211 (1994).
7. Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S. & Passingham, R. E. The prefrontal cortex: response selection or maintenance within working memory? *Science* **288**, 1656–1660 (2000).
8. Bor, D., Duncan, J., Wiseman, R. J. & Owen, A. M. Encoding strategies dissociate prefrontal activity from working memory demand. *Neuron* **37**, 361–367 (2003).
9. Fletcher, P. C., Shallice, T. & Dolan, R. J. The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain* **121**, 1239–1248 (1998).
10. Dobbins, I. G., Foley, H., Schacter, D. L. & Wagner, A. D. Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron* **35**, 989–996 (2002).
11. Rugg, M. D. *et al*. Neural correlates of memory retrieval during recognition memory and cued recall. *Neuroimage* **8**, 262–273 (1998).
12. Courtney, S. M., Ungerleider, L. G., Keil, K. & Haxby, J. V. Transient and sustained activity in a distributed neural system for human working memory. *Nature* **386**, 608–611 (1997).
13. Dove, A., Pollmann, S., Schubert, T., Wiggins, C. J. & von Cramon, D. Y. Prefrontal cortex activation in task switching: an event-related fMRI study. *Brain Res. Cogn. Brain Res.* **9**, 103–109 (2000).
14. Cools, R., Clark, L., Owen, A. M. & Robbins, T. W. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J. Neurosci.* **22**, 4563–4567 (2002).
15. Rushworth, M. F., Nixon, P. D., Eacott, M. J. & Passingham, R. E. Ventral prefrontal cortex is not essential for working memory. *J. Neurosci.* **17**, 4829–4838 (1997).
16. Henson, R. N., Shallice, T. & Dolan, R. J. Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain* **122**, 1367–1381 (1999).
17. Wagner, A. D. *et al.* Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science* **281**, 1188–1191 (1998).
18. Tataranni, P. A. *et al.* Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc. Natl Acad. Sci. USA* **96**, 4569–4574 (1999).
19. Gottfried, J. A., O'Doherty, J. & Dolan, R. J. Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. *J. Neurosci.* **22**, 10829–10837 (2002).
20. Rolls, E. T. The orbitofrontal cortex and reward. *Cereb. Cortex* **10**, 284–294 (2000).
21. Rolls, E. T., Critchley, H. D., Browning, A. & Hernadi, I. The neurophysiology of taste and olfaction in primates, and umami flavor. *Ann. NY Acad. Sci.* **855**, 426–437 (1998).
22. Tremblay, L. & Schultz, W. Relative reward preference in primate orbitofrontal cortex. *Nature* **398**, 704–708 (1999).
23. Roberts, A. C. & Wallis, J. D. Inhibitory control and affective processing in the prefrontal cortex: neuropsychological studies in the common marmoset. *Cereb. Cortex* **10**, 252–262 (2000).
24. Montague, P. R. & Berns, G. S. Neural economics and the biological substrates of valuation. *Neuron* **36**, 265–284 (2002).
25. Elliott, R., Friston, K. J. & Dolan, R. J. Dissociable neural responses in human reward systems. *J. Neurosci.* **20**, 6159–6165 (2000).
26. Dias, R., Robbins, T. W. & Roberts, A. C. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* **380**, 69–72 (1996).
27. Duncan, J. & Owen, A. M. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* **23**, 475–483 (2000).
28. Ongur, D., Ferry, A. T. & Price, J. L. Architectonic subdivision of the human orbital and medial prefrontal cortex. *J. Comp. Neurol.* **460**, 425–449 (2003).
This paper describes the cytoarchitecture of the medial and orbital PFC. The results are particularly striking because they indicate that BA 10 is larger than all other prefrontal areas in the human brain.
29. Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K. & van Hoesen, G. W. Prefrontal cortex in humans and apes: a comparative study of area 10. *Am. J. Phys. Anthropol.* **114**, 224–241 (2001).
This is the only anatomical study to comprehensively examine the comparative cytoarchitecture of BA 10 in the brains of several primate species, including humans.
30. Brodmann, K. *Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipien Dargestellt auf Grund des Zellenbaues* (Barth, Leipzig, Germany, 1909).
31. Petrides, M. & Pandya, D. N. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Eur. J. Neurosci.* **16**, 291–310 (2002).
32. Jacobs, B. *et al*. Regional dendritic and spine variation in human cerebral cortex: a quantitative golgi study. *Cereb. Cortex* **11**, 558–571 (2001).
33. Passingham, R. E. *The Frontal Lobes and Voluntary Action* (Oxford Univ. Press, Oxford, 1995).
34. Petrides, M. & Pandya, D. N. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur. J. Neurosci.* **11**, 1011–1036 (1999).
35. McGuire, P. K., Bates, J. F. & Goldman-Rakic, P. S. Interhemispheric integration: I. Symmetry and convergence of the corticocortical connections of the left and the right principal sulcus (PS) and the left and the right supplementary motor area (SMA) in the rhesus monkey. *Cereb. Cortex* **1**, 390–407 (1991).
36. Barbas, H. & Pandya, D. N. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J. Comp. Neurol.* **286**, 353–375 (1989).
37. Bachevalier, J., Meunier, M., Lu, M. X. & Ungerleider, L. G. Thalamic and temporal cortex input to medial prefrontal cortex in rhesus monkeys. *Exp. Brain Res.* **115**, 430–444 (1997).
38. Andersen, R. A., Asanuma, C. & Cowan, W. M. Callosal and prefrontal associational projecting cell populations in area 7A of the macaque monkey: a study using retrogradely transported fluorescent dyes. *J. Comp. Neurol.* **232**, 443–455 (1985).
39. Moran, M. A., Mufson, E. J. & Mesulam, M. M. Neural inputs into the temporopolar cortex of the rhesus monkey. *J. Comp. Neurol.* **256**, 88–103 (1987).
40. Amaral, D. G. & Price, J. L. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J. Comp. Neurol.* **230**, 465–496 (1984).
41. Morecraft, R. J. & Van Hoesen, G. W. Frontal granular cortex input to the cingulate (M3), supplementary (M2) and primary (M1) motor cortices in the rhesus monkey. *J. Comp. Neurol.* **337**, 669–689 (1993).
42. Arikuni, T., Sako, H. & Murata, A. Ipsilateral connections of the anterior cingulate cortex with the frontal and medial temporal cortices in the macaque monkey. *Neurosci. Res.* **21**, 19–39 (1994).
43. Passingham, R. E., Stephan, K. E. & Kotter, R. The anatomical basis of functional localization in the cortex. *Nature Rev. Neurosci.* **3**, 606–616 (2002).

44. Christoff, K. & Gabrieli, J. D. E. The frontopolar cortex and human cognition: evidence for a rostrocaudal heirarchical organisation within the human prefrontal cortex. *Psychobiology* **28**, 168–186 (2000).
In this comprehensive review of functional neuroimaging studies of reasoning and episodic memory, Christoff and Gabrieli set out their arguments that BA 10 might be specialized for the explicit processing of internal states.
45. Buckner, R. L., Raichle, M. E., Miezin, F. M. & Petersen, S. E. Functional anatomic studies of memory retrieval for auditory words and visual pictures. *J. Neurosci.* **16**, 6219–6235 (1996).
46. Shallice, T. Specific impairments of planning. *Philos. Trans. R Soc. Lond. B* **298**, 199–209 (1982).
47. Baker, S. C. *et al*. Neural systems engaged by planning: a PET study of the Tower of London task. *Neuropsychologia* **34**, 515–526 (1996).
48. Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E. & Robbins, T. W. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021–1034 (1990).
49. Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E. & Robbins, T. W. Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **33**, 1–24 (1995).
50. Lee, A. C., Robbins, T. W. & Owen, A. M. Episodic memory meets working memory in the frontal lobe: functional neuroimaging studies of encoding and retrieval. *Crit. Rev. Neurobiol.* **14**, 165–197 (2000).
51. Tulving, E. *Elements of Episodic Memory* (Clarendon, Oxford, 1983).
52. Cabeza, R. *et al*. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J. Neurosci.* **17**, 391–400 (1997).
53. Duzel, E. *et al*. Task-related and item-related brain processes of memory retrieval. *Proc. Natl Acad. Sci. USA* **96**, 1794–1799 (1999).
54. Kapur, S. *et al*. Functional role of the prefrontal cortex in retrieval of memories: a PET study. *Neuroreport* **6**, 1880–1884 (1995).
55. Nyberg, L. *et al*. Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* **7**, 249–252 (1995).
56. Rugg, M. D., Schloerscheidt, A. M., Doyle, M. C., Cox, C. J. & Patching, G. R. Event-related potentials and the recollection of associative information. *Brain Res. Cogn. Brain Res.* **4**, 297–304 (1996).
57. Wagner, A. D., Desmond, J. E., Glover, G. H. & Gabrieli, J. D. Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. *Brain* **121**, 1985–2002 (1998).
58. Velanova, K. *et al*. Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J. Neurosci.* **23**, 8460–8470 (2003).
59. Lepage, M., Ghaffar, O., Nyberg, L. & Tulving, E. Prefrontal cortex and episodic memory retrieval mode. *Proc. Natl Acad. Sci. USA* **97**, 506–511 (2000).
60. MacLeod, A. K., Buckner, R. L., Miezin, F. M., Petersen, S. E. & Raichle, M. E. Right anterior prefrontal cortex activation during semantic monitoring and working memory. *Neuroimage* **7**, 41–48 (1998).
61. Ranganath, C., Johnson, M. K. & D'Esposito, M. Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J. Neurosci.* **20**, RC108 (2000).
62. Ranganath, C. & Paller, K. A. Neural correlates of memory retrieval and evaluation. *Brain Res. Cogn. Brain Res.* **9**, 209–222 (2000).
63. Raye, C. L., Johnson, M. K., Mitchell, K. J., Nolde, S. F. & D'Esposito, M. fMRI investigations of left and right prefrontal contributions to episodic remembering. *Psychobiology* **28**, 197–206 (2000).
64. Ranganath, C. & Paller, K. A. Frontal brain activity during episodic and semantic retrieval: insights from event-related potentials. *J. Cogn. Neurosci.* **11**, 598–609 (1999).
65. Ranganath, C. & Paller, K. A. Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron* **22**, 605–613 (1999).
66. Nolde, S. F., Johnson, M. K. & D'Esposito, M. Left prefrontal activation during episodic remembering: an event-related fMRI study. *Neuroreport* **9**, 3509–3514 (1998).
67. Nyberg, L. *et al*. General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc. Natl Acad. Sci. USA* **93**, 11280–11285 (1996).
68. Janowsky, J. S., Shimamura, A. P. & Squire, L. R. Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia* **27**, 1043–1056 (1989).
69. Thaiss, L. & Petrides, M. Source versus content memory in patients with a unilateral frontal cortex or a temporal lobe excision. *Brain* **126**, 1112–1126 (2003).
70. Burgess, P. W., Quayle, A. & Frith, C. D. Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia* **39**, 545–555 (2001).
71. Burgess, P. W., Veitch, E., de Lacy Costello, A. & Shallice, T. The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia* **38**, 848–863 (2000).
72. Okuda, J. *et al*. Participation of the prefrontal cortices in prospective memory: evidence from a PET study in humans. *Neurosci. Lett.* **253**, 127–130 (1998).
73. Coull, J. T., Frith, C. D., Frackowiak, R. S. & Grasby, P. M. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. *Neuropsychologia* **34**, 1085–1095 (1996).
74. Koechlin, E., Basso, G., Pietrini, P., Panzer, S. & Grafman, J. The role of the anterior prefrontal cortex in human cognition. *Nature* **399**, 148–151 (1999).
We have suggested that the aPFC is required for integrating the outcomes of two or more separate cognitive processes. It is necessary to test for super-additive effects in functional neuroimaging studies to demonstrate a relationship between such a process and brain activity. Reference 74 elegantly demonstrates a highly specific super-additive effect in the aPFC when subjects held in mind goals while at the same time they processed secondary goals.
75. Koechlin, E., Corrado, G., Pietrini, P. & Grafman, J. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. *Proc. Natl Acad. Sci. USA* **97**, 7651–7656 (2000).
76. Braver, T. S. & Bongiolatti, S. R. The role of frontopolar cortex in subgoal processing during working memory. *Neuroimage* **15**, 523–536 (2002).
77. Owen, A. M., Doyon, J., Petrides, M. & Evans, A. C. Planning and spatial working memory: a positron emission tomography study in humans. *Eur. J. Neurosci.* **8**, 353–364 (1996).
78. Pollmann, S., Weidner, R., Muller, H. J. & von Cramon, D. Y. A fronto-posterior network involved in visual dimension changes. *J. Cogn. Neurosci.* **12**, 480–494 (2000).
79. Pollmann, S. Switching between dimensions, locations, and responses: the role of the left frontopolar cortex. *Neuroimage* **14**, S118–124 (2001).
80. Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J. & Robbins, T. W. Extradimensional versus intradimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalohippocampectomy in man. *Neuropsychologia* **29**, 993–1006 (1991).
81. Owen, A. M. *et al*. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* **116**, 1159–1175 (1993).
82. Kroger, J. K. *et al*. Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. *Cereb. Cortex* **12**, 477–485 (2002).
83. Christoff, K. *et al*. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. *Neuroimage* **14**, 1136–1149 (2001).
84. Robin, N. & Holyoak, K. J. in *The Cognitive Neurosciences* (ed. Gazzaniga, M. S.) 987–997 (MIT Press, Cambridge, Massachusetts, 1995).
85. Raven, J. C. Standardization of progressive matrices. *Br. J. Med. Psychol.* **19**, 137–170 (1938, 1941).
86. Carpenter, P. A., Just, M. A. & Shell, P. What one intelligence test measures: a theoretical account of the processing in the Raven Progressive Matrices Test. *Psychol. Rev.* **97**, 404–431 (1990).
87. Waltz, J. A. *et al*. A system for relational reasoning in human prefrontal cortex. *Psychol. Sci.* **10**, 119–125 (1999).
88. Duncan, J., Burgess, P. & Emslie, H. Fluid intelligence after frontal lobe lesions. *Neuropsychologia* **33**, 261–268 (1995).
89. Ramnani, N. & Passingham, R.-E. Changes in the human brain during rhythm learning. *J. Cogn. Neurosci.* **13**, 1–15 (2001).
90. Sakai, K., Ramnani, N. & Passingham, R. E. Learning of sequences of finger movements and timing: frontal lobe and action-oriented representation. *J. Neurophysiol.* **88**, 2035–2046 (2002).
91. Rogers, R. D. *et al*. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J. Neurosci.* **19**, 9029–9038 (1999).
92. Ramnani, N. & Miall, C. Instructed delay activity in the human prefrontal cortex is modulated by monetary reward expectation. *Cereb. Cortex* **13**, 318–327 (2003).
93. Braver, T. S., Reynolds, J. R. & Donaldson, D. I. Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron* **39**, 713–726 (2003).
94. Ramnani, N. & Passingham, R. E. Changes in the human brain during rhythm learning. *J. Cogn. Neurosci.* **13**, 952–966 (2001).
95. Zeki, S. & Shipp, S. The functional logic of cortical connections. *Nature* **335**, 311–317 (1988).
96. Ungerleider, L. G. & Mishkin, M. in *Analysis of Visual Behavior* (ed. Mansfield, R. J. W.) 549–586 (MIT Press, Cambridge, Massachusetts, 1982).
97. Haxby, J. V. *et al*. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc. Natl Acad. Sci. USA* **88**, 1621–1625 (1991).
98. Ettlinger, G. 'Object vision' and 'spatial vision': the neuropsychological evidence for the distinction. *Cortex* **26**, 319–341 (1990).
99. Passingham, R. E. & Toni, I. Contrasting the dorsal and ventral visual systems: guidance of movement versus decision making. *Neuroimage* **14**, S125–131 (2001).
100. Nobre, A. C., Coull, J. T., Frith, C. D. & Mesulam, M. M. Orbitofrontal cortex is activated during breaches of expectation in tasks of visual attention. *Nature Neurosci.* **2**, 11–12 (1999).
101. Schultz, W., Tremblay, L. & Hollerman, J. R. Reward processing in primate orbitofrontal cortex and basal ganglia. *Cereb. Cortex* **10**, 272–284 (2000).
102. Lu, T., Preston J. B. & Strick P. L. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J. Comp. Neurol.* **341**, 375–392 (1994).
103. Hadland, K. A., Rushworth, M. F., Passingham, R. E., Jahanshahi, M. & Rothwell, J. C. Interference with performance of a response selection task that has no working memory component: an rTMS comparison of the dorsolateral prefrontal and medial frontal cortex. *J. Cogn. Neurosci.* **13**, 1097–1108 (2001).
104. Ramnani, N., Toni, I., Passingham, R. E. & Haggard, P. The cerebellum and parietal cortex play a specific role in coordination: a PET study. *Neuroimage* **14**, 899–911 (2001).
105. Sarkissov, S. A., Filimonoff, I. N., Kononowa, E. P., Preoprashenskaja, I. S. & Kukuew, L. A. *Atlas of the Cytoarchitectonics of the Human Cerebral Cortex* (Medgiz, Moscow, 1955).
106. Petrides, M. & Pandya, D. N. in *Handbook of Neuropsychology*, Vol. 9 (ed. Grafman, J.) 17–58 (Elsevier, Amsterdam, 1994).

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Competing interests statement

The authors declare that they have no competing financial interests.

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