

Title: Managing competing goals – a key role for the frontopolar cortex

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Abstract

Many elements of advanced cognition and behavior set humans apart from other animals including language, judgment and reasoning. But, what is special about the human brain that gives rise to these abilities? Might the foremost part of prefrontal cortex (frontopolar cortex), which has significantly enlarged in human evolution relative to other animals, be important, especially since in primates it contains a unique cytoarchitectural field, area 10? Now the first studies of frontopolar cortex function in monkeys have provided critical new insights about its precise function in monitoring the significance of current and alternative goals. In human evolution, the frontopolar cortex may have acquired a further role in allowing monitoring the significance of multiple goals in parallel, and switching between them. We will argue that many other forms of uniquely human behavior may benefit from this cognitive ability mediated by the frontopolar cortex.

Humans clearly stand apart from other animals in their ability to engage in complex, organised, goal-directed behaviors, and some of our advanced cognitive abilities may be uniquely human (for example language, judgment, long-term planning and reasoning). Although it is clearly tempting to speculate that there might be some underlying anatomical basis supporting these cognitive functions that separate us from other animals, relatively few morphological differences have so far been identified that distinguish our brains from those of non-human primates. One notable exception is that in the primate evolutionary lineages leading to humans, the anterior parts of the frontal lobes (referred to as prefrontal cortex) have expanded in volume relative to posterior cortical regions¹. Moreover, in primates the foremost part of prefrontal cortex (the frontopolar cortex) contains a cortical area, commonly referred to as ‘cytoarchitectonic area 10’, which is of special interest. Area 10 is not only exclusive to primates, but also differs markedly even between the brains of our closest relatives, non-human primates, and humans¹ (Fig. 1a). Area 10 is not only proportionally larger in volume relative to the rest of the brain in humans than in apes, but its neurons are more widely spaced, allowing more room for intra and inter-area connectivity¹. A higher-order role in cognition²⁻⁷ is certainly suggested by the neuroanatomical features of area 10, including its unusual pattern of afferent connections, the vast majority of which originate from multimodal and high-order association areas (Fig. 1b)⁸⁻¹¹, which is unlike the case for other prefrontal areas. Area 10 also shows late postnatal maturation, suggesting that its neurons undergo extensive experience-dependent structural changes that could be essential for development of higher cognitive functions¹²⁻¹⁶. For the purposes of this review, we will consider our region of interest, the frontopolar cortex, as overlapping primarily with cytoarchitectural area 10p (area 10 polar) of the nomenclature proposed by Ongur and collaborators¹⁷.

The frontopolar cortex is further unique in that, unlike other prefrontal subregions, we do not have decades of research involving circumscribed animal lesion studies revealing functions that necessarily depend upon it, nor do we have numerous cellular activity recording studies

revealing underlying neuronal mechanisms operating in the frontopolar cortex and mediating specific cognitive processes²⁻³. However, now that the first animal models of area 10 have emerged¹⁸⁻²⁴, it is timely and important to assess the critical new insights these behavioral-lesion and neuronal recording studies reveal about its precise function. In particular, the first ever circumscribed behavioral-lesion studies of the frontopolar cortex in monkeys reveal a distinct pattern of spared, impaired, and in some cases enhanced cognitive abilities²³⁻²⁴.

Specifying the contribution of the frontopolar cortex to cognition is important not only for understanding the mechanistic basis of higher order cognitive functions in primates (including possibly some unique forms of intelligent human behavior), but also because this knowledge may help us to understand some of the underlying causes of the behavioral deficits associated with a range of neuropsychiatric disorders linked to disturbed prefrontal interactions. This article will review the extent to which a wide range of influential hypotheses of human frontopolar cortex function, largely based on human neuroimaging, are supported by new studies in animal models, which address causality to a degree rarely possible by human neuropsychology. This will be followed by our outlining how a particular set of recent studies combining human neuroimaging and computational modelling has provided a synergistic view with these recent animal studies, while also revealing new insights about specific features of the human frontopolar cortex. We conclude that a key specialisation of primate frontopolar cortex is in managing competing goals, in part by keeping track of the significance of current and alternative goals, and therefore enabling switching away from ongoing behavior. We theorise that in human evolution, the frontopolar cortex has acquired additional, but related roles, in allowing monitoring of the significance of several competing goals in parallel, and in switching between them. In particular, we propose that these new functions are linked to a lateral subdivision of cytoarchitectural area 10 (Fig. 1), which some data suggests might have no clear monkey counterpart²⁵. We propose that a range of unique human behaviors relate to this underlying advance in cognition mediated by the frontopolar cortex.

Pursuing goals in changing environments

In a complex and changing environment, the validity of tasks or goals might change in terms of their associated reward and cost, and we often face the necessity to make a strategic decision to adaptively shift between these goals. Imagine you are employed in a university but receive a job offer from a different institution. The decision to cease exploiting the current source of income and shift to explore another would require assessing different aspects of cost and benefit of these alternative opportunities based on your internal goals and plans (Fig. 2). Adjusting the tendency for exploitation versus exploration is likely to be a fundamental aspect of foraging behavior, to increase the chances of success and survival in long-term. Humans are not the only species that face such a dilemma in a changing environment. Other species might also face the necessity to cease exploiting a current source of reward, and explore other resources, to increase the chance of their survival and reproduction. Such a decision entails assessment of the value (cost and benefit) of current and alternative reward resources and associated goals for the individual, and also for the group, in socially advanced species (Fig. 2). A distributed neural network involving prefrontal and medial frontal cortices regulates the use of cognitive resources to optimize exploitation of current reward resources, while minimizing the associated cost. This is referred to as executive control of goal directed behavior²⁶. Our main thesis is that recent studies in monkeys and humans suggest that the most rostral part of the prefrontal cortex (frontopolar cortex) plays a crucial role in adjusting the tendency for exploitation, versus exploration of other alternative resources, by assessing the value of alternative tasks/goals and re-distribution of our cognitive resources. Before reviewing evidence for this proposed model, we will review previous models of frontopolar cortex function in a goal-directed behavior.

Previous models of human frontopolar cortex function

Human non-invasive neuroimaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have correlated activity in the

frontopolar cortex with participant performance in a diverse range of cognitive tasks and experimental paradigms²⁻⁷. Although many influential ideas about frontopolar cortex function in higher-order cognition have emerged from this correlational evidence (as reviewed below), no consensus has yet been attained. Neuropsychological examination of patients with lesions involving the frontopolar cortex has also so far proved limited insight, due to the fact that selective and bilateral damage to the frontopolar cortex is very rare. Nonetheless, we know that lesions involving this region do not impair overall intelligence, language ability, or basic sensory and motor abilities^{2-3, 27-28}. Similarly, these patients do not exhibit deficits in standard neuropsychological tests or in the performance of executive control tasks, which are sensitive to lesions in more posterior or medial regions of the prefrontal cortex^{2-3, 27-28}. Patients with frontopolar cortex lesions do however show some profound impairment in managing their daily life, particularly in dealing with open-ended, novel, or changing situations^{2-3, 27-28}. As we argue below, new findings in monkeys and humans, combined with pioneering electrophysiological results, have allowed a revised interpretation of the results of previous imaging and neuropsychological studies, leading to new understanding of the unique role for the frontopolar cortex in executive control of goal-directed behavior.

Gateway hypothesis

One cognitive ability assumed to be central to human mental processing is the ability to control the extent to which we attend to stimuli and events in the external environment, or to self-generated or maintained representations (i.e. the 'thoughts in our head'). The influential 'gateway hypothesis' maintains that the frontopolar cortex is positioned at the heart of such a mechanism, thus controlling transitioning between aptly named stimulus-oriented (SO) and stimulus-independent (SI) modes of attention^{3, 29-31}. This model is supported by imaging studies that showed that sustained attention in either mode, or a transition between these two modes, correlate with frontopolar cortex activation. Moreover, the model proposes that medial and

lateral subdivisions of the frontopolar cortex support SO and SI attention, respectively^{3, 29-31}.

Although it is intuitive that the frontopolar cortex may have subdivisions, as its connections vary with location⁸⁻⁹, it is unclear how SO and SI modes of attention relate to anatomically-defined subregions. In addition, other areas, including those in the lateral prefrontal cortex, show similar SO/SI associated changes in activation, leaving open the question of which distinct cognitive processing operates specifically in the frontopolar cortex. Although deficits in multi-tasking and prospective memory in patients with frontopolar cortex damage have been considered to support the gateway hypothesis³, the fact that patients with frontopolar cortex damage do not show impairment in many other tasks that require a transition between SO and SI attention does not support this hypothesis^{2-3, 32}.

Mind wandering and self-referential mental processes

Another arguably unique human cognitive ability that the frontopolar cortex has been closely implicated in is the processing self-referential knowledge, including knowledge of self, knowledge of the internal mental world³³⁻³⁴, and evaluation of self-generated information³⁵. When imaging studies compared activation between rest and task performance conditions, it was shown that several brain areas, including the frontopolar cortex, exhibit a higher level of activation during a rest period or during tasks with minimal cognitive demands^{2, 33-34}. Therefore, the frontopolar cortex has been associated with mind-wandering and engagement in aforementioned processes. However, this hypothesis remains poorly predictive without further specification of the cognitive processing that depends on the frontopolar cortex, and poses difficulties in explaining activation of this area in various cognitively challenging tasks^{2, 4-7}.

Integration of the outcome of multiple cognitive processes

Many advanced cognitive abilities depend on integration of highly processed information that emerges from processing in distributed neural networks involving different brain regions.

Due to its robust connections to supra-modal areas, the frontopolar cortex has been proposed to sit atop a hierarchy of frontal brain regions, and to facilitate the transfer of highly processed information between discrete operational units located elsewhere, to enable goals that cannot be achieved by individual operations². This model suggests that the frontopolar cortex plays a unique role in integrating the outcome of separate cognitive operations, mediated by other cortical areas². The model is not supported by observations that many tasks that do depend on integrating outcomes of multiple cognitive processes are not impaired either in patients³ (or, as we will see later, monkeys²⁴⁻²⁵) with frontopolar cortex lesions.

Mnemonic functions

Various mnemonic processes support advanced human cognitive abilities. The most prominent mnemonic function associated with the human frontopolar cortex is episodic memory³⁶⁻³⁷. Activation of the frontopolar cortex has been reported during various tasks involving retrieval of episodic memory³⁶⁻³⁷. The frontopolar cortex is also activated in prospective memory, which refers to the ability to maintain an intention to act in a certain way in mind, usually after a delay filled with an unrelated ongoing task^{3, 38-41}. Lesions including but not limited to the frontopolar cortex have also been reported to lead to impairment in prospective memory in humans^{3, 42}. Notably, however, it is time-based (not event-based) prospective memory that is associated with the frontopolar cortex in voxel-based lesion analyses⁴¹, and a key element of such memory may be the relative value of two alternative tasks (which changes continually over time as the time for the prospective action approaches). As we will see, the monkey lesion work discussed later in this review points to general impairments in exploring the value of a broad range of alternatives²³.

There is a long history of association of prefrontal cortex with working memory (i.e. online maintenance of task-relevant information)^{26, 43-46}. Activation of the frontopolar cortex has

also been observed in tasks requiring working memory, leading to the suggestion that the dorsolateral prefrontal and frontopolar cortices form a hierarchical system that is specialized for the evaluation, monitoring, and manipulation of information held in working memory⁴⁶⁻⁴⁸. Specifically, the dorsolateral prefrontal cortex has been seen as supporting the processing of externally generated information, whereas the frontopolar cortex would hold internally generated information in memory⁴⁷⁻⁴⁸. Although activation of the frontopolar cortex in these and other mnemonic tasks indicates that this region might play a role in organizing the retrieval, maintenance and processing of information, the exact function of the frontopolar cortex in such diverse mnemonic processes remains unknown. As we will see, the monkey lesion work discussed later in this review reveals an absence of general impairments in working memory and retrieval of contextual information, but points instead to specific deficits in rapid learning about novel alternatives that impinge upon performance across a range of diverse learning and memory tasks²³⁻²⁴.

Analogical, relational, transitive and abstract reasoning

Analogical reasoning⁴⁹ and relational integration^{2, 35, 50} are clearly higher-order cognitive processes (though not necessarily uniquely human) that depend on the construction of mental representations to facilitate comparisons and judge similarities between episodes, to enhance learning and make inferential judgements⁵¹. Reasoning by transitive inference also requires the integration of multiple relations to reach a conclusion^{1, 51-52}. Activation of the frontopolar cortex has been reported in the context of many tasks that require such abstract reasoning^{2, 35, 50-52} and a recent study also suggests that patients with lesions extending to the frontopolar cortex show deficits in tests which require analogical reasoning⁵³. Overall, these studies have suggested that the frontopolar cortex is involved when the processing and integration of abstract information guides decision-making and creativity, and supports emotional, affective and social cognitive functions^{2, 35, 50-53}. A hierarchical anterior-posterior organization in the frontal cortex has also

been proposed based on the level of abstractness of representation upon which control is exerted^{6-7, 54-55} or on the level of actions selected¹¹, with the frontopolar cortex processing the highest level of abstraction and pre-motor cortex dealing with representation of concrete events or actions. Some investigators have suggested an important role for the frontopolar cortex in other kinds of abstract reasoning including theory of mind, deception^{56, 57} and moral judgement⁵⁸. However, in these cases activations were not specific to the frontopolar cortex, being also seen in other prefrontal and parietal areas⁵⁹⁻⁶¹.

Establishing task set and preparation for upcoming task demands

The phrase ‘task set’ is used to refer to a configuration of cognitive processes that is actively maintained for subsequent task performance, and this capability has also long been linked to prefrontal cortex. However, the frontopolar cortex in particular has been proposed to be involved in establishing task sets or shifting between them⁶². In one fMRI study, frontopolar (but not dorsolateral prefrontal) activity was more strongly correlated with different posterior regions depending upon the rule the participants intended to apply after a delay⁶². In patients with rostral prefrontal lesions, scanned for fMRI, it was found that the set-related delay-period activity of posterior areas (involved in each task performance) was not affected, but that the functional connectivity (a measure of synchronous activity implying interaction) between these areas was significantly attenuated³². These patients showed behavioral deficits when the task shifted, but performed significantly better than the controls when the task stayed the same³² (see later for details of related kinds of improved performance in monkeys with frontopolar cortex lesions). This finding was interpreted as the result of patients following a default state/strategy when the task remains stable³²; alternatively, the frontopolar cortex may support the maintenance of the alternative set in a state of readiness, and therefore facilitate transition between the sets without the necessity for re-establishing it⁶³.

Exploratory decision-making

Optimum decision-making in uncertain environments requires balancing the conflicting demands of gathering and exploiting information. An influential study highlighted the role of the frontopolar cortex in resolving this explore/exploit dilemma in a simulated gambling task⁶⁴, and implicated the frontopolar cortex more generally in such higher-order executive control processes. Specifically, the frontopolar cortex and intraparietal sulcus were together more active during exploratory behavior, whereas regions of striatum and ventromedial prefrontal cortex were associated with exploitative behavior. The results suggest a highly interactive model of action selection under uncertainty that at least implicates the frontopolar cortex in switching between exploratory and exploitative modes⁶⁴. The animal work reviewed later extends this idea of frontopolar cortex involvement to broader kinds of exploratory behavior.

Planning

Planning is an important aspect of human cognition and imaging studies have revealed an activation change in the frontopolar cortex in the context of planning tasks, such as the Tower of London Test (see glossary). This led to the hypothesis that the frontopolar cortex plays a crucial role in planning⁶⁵⁻⁶⁶. However, these activations were not specific to this region and patients with frontopolar cortex lesions did not show deficits in performing the Tower of London test²⁷; similarly, neuronal activity related to multi-step planning is also observed outside the frontopolar cortex in monkeys⁶⁷.

Cognitive branching or multi-tasking

Achieving goals in many tasks might require holding information of a pending task in short-term memory while alternative (sub-) tasks are being completed. This allows the individual to monitor and resume the main task after completing the alternative tasks. This cognitive ability

has been considered as cognitive branching or multi-tasking^{4-6, 68}. Some of the aforementioned cognitive abilities such as planning, analogical and abstract reasoning and problem solving usually involve cognitive branching, and an influential hypothesis that emerged from human imaging and computational studies suggested that the frontopolar cortex plays an essential role in cognitive branching⁴⁻⁶. Cognitive branching enables multi-tasking, which is conceptually different from dual-task performance. In dual-task performance, the subject switches back and forth between different tasks according to the stimuli presented, without requiring the information of one task to be held in memory while performing another task. Bilateral activation of the frontopolar cortex has been observed in branching, but not in dual-task conditions⁴⁻⁶. As only the branching condition requires the additional process of retaining information about the main task while performing another task, it has been proposed that the cognitive branching function is specific to the frontopolar cortex⁴⁻⁶. Neuropsychological examination of patients with lesions confirmed that the number of errors in the branching condition, but not in the dual-task condition, is proportional to the involvement of the frontopolar cortex^{28, 68}. Further supporting evidence has also come from a subsequent fMRI study in which participants recurrently chose between alternative courses of action based on their expectations of a reward (which was probabilistically changing, and consequently uncertain)⁶⁹. Frontopolar cortex activations signalled that the reward-based evidence had accumulated in favour of the best unchosen course of action during the performance of the chosen course of action⁶⁹. This led to the suggestion that the frontopolar cortex encodes the reward-based advantage of the unchosen, pending option, and that when this advantage becomes positive, the frontopolar cortex recruits posterior frontal and parietal regions to implement the behavioral shift between the two options⁶⁹. Finally, frontopolar activations associated with cognitive branching appears to be located in the lateral sector (Fig. 1), which seems to have no functional equivalent in monkeys^{5, 25}. This suggests that unlike humans, monkeys should have difficulties in properly performing cognitive branching between tasks.

The macaque frontopolar cortex

Neuronal activity

To our knowledge there has been no study in which neuronal activity was recorded in the human frontopolar cortex. The first publications reporting the results of recordings in the frontopolar cortex of monkeys have recently emerged¹⁸⁻²¹, and their findings proved to be remarkably unlike those of recordings in neighbouring prefrontal and medial frontal regions (the dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices)²¹. According to these reports, neuronal activity in the frontopolar cortex is only modulated around the time a reward is delivered, when this resulted from a successful self-generated (as opposed to directly cued) decision. By contrast, recordings in adjacent areas have shown that neurons encode a much wider range of parameters that may support the motivational and higher-order cognitive aspects of a task^{20-21, 43-45, 70-80}, including working memory^{26, 43-44, 46, 76-77, 79-80}, prediction error⁸², actions⁷⁴, value⁷⁵, risk^{78, 82}, outcomes^{26, 78}, rules (Fig. 3a) and strategies^{26, 43, 79-80}, and numerosity⁸¹ among others.

The frontopolar cortex neuronal activity was recorded while monkeys performed a task in which cues instructed either a “stay” or “shift” decision¹⁹⁻²¹. Stay cues required a saccade in the same direction as that chosen on the preceding trial, whereas shift cues required a saccade in the alternative direction. Thus, the monkeys had to remember the direction of the saccade performed in the previous trial, and select the next target according to the presented (stay or shift) cue. This cue was either visual, in some test blocks, or a pattern of delivery of fluid drops to the mouth, in others. A fluid reward (feedback) was given for all correct responses. The main finding was that neuronal activity was only modulated around the feedback period, and only reflected the action (saccade direction) performed in that trial (Fig. 3b)¹⁹⁻²¹. The conclusion that the activity was bound to the feedback was based on the fact that modulation in activity persisted during the feedback period, even when this was delayed. Intriguingly, the neuronal activity did not encode

the short-term memory of the preceding action, the cued strategy (which was necessary for the task performance), the anticipated or delivered reward, or the preparation and execution of action¹⁹⁻²¹. Hence, the task-relevant activity of frontopolar cortex neurons is indeed quite distinct from those reported for other frontal areas. These findings were interpreted by the authors as reflecting a crucial role in a feedback-based learning process¹⁹⁻²¹. However, these kinds of neural signals appear to already be present in other prefrontal and medial frontal areas, albeit, as mentioned above, embedded in a much richer context^{21, 26, 43, 70, 72-73, 80} (Fig. 3a). Consequently, the distinctive information conveyed by neuronal activity in the frontopolar cortex remains unclear. An alternative view of the electrophysiological results, which will be discussed in the following sections, is that the modulation of frontopolar cortex cell activity confined around the feedback encoded the reward obtained from a successful decision in the current task. Such information might reflect the overall relevance of performing the current task and facilitate monitoring the opportunity to stay vs. to switch away from the current task⁴ (Fig. 2).

Behavioral consequences of lesions

Only two studies to date have examined the behavioral consequences of bilateral selective frontopolar cortex lesions²³⁻²⁴. In one of these studies²⁴, the monkeys performed a computerized analogue of the Wisconsin Card Sort Test (WCST) (Fig. 3a), which provides a measure of cognitive flexibility in learning, and switching between abstract rules (i.e. matching-by-colour or matching-by-shape). In contrast to the previously reported consequences of lesions in the dorsolateral prefrontal, orbitofrontal, or anterior cingulate cortices⁸³, frontopolar cortex lesions did not impair basic perceptual-motor functions or the ability of the animals to adapt to rule changes in the WCST²⁴ (Fig. 4). The absence of impairment in behavioral measures related to the working memory of rules, selective attention to the current rule, inhibition of a previously relevant rule, or assessment of the behavioral outcome to shift between abstract rules (to detect and adapt to unannounced rule changes) (Table 1), together demonstrated a functional

dissociation between the frontopolar cortex and these other prefrontal and medial frontal cortical areas²⁴ (Fig. 4).

The monkeys were also tested in another version of the task, in which the level of conflict between rules changed trial-by-trial. Conflict cost^{24, 45, 71, 80} (adverse effects of conflict on performance in the current trial; see glossary) was unimpaired in frontal pole-lesioned monkeys, but conflict adaptation^{25, 45, 71, 80} (conflict-induced improved performance in the following trial; see glossary) was significantly augmented. This was a distinctive behavioral alteration in frontal pole-lesioned monkeys because lesions in dorsolateral prefrontal cortex or orbitofrontal cortex cause a reduction in conflict adaptation, whereas lesions in the cingulate cortex (anterior or posterior) have no significant effect^{24, 45, 71, 80}. The better-than-control conflict adaptation indicated that the context-dependent allocation of cognitive resources to resolve the conflict was enhanced in frontal pole-lesioned monkeys. These findings led to the hypothesis that the frontopolar cortex is involved in redistributing cognitive resources away from the current task, towards alternative targets for attention²⁴.

To test this hypothesis, the monkeys were trained to perform another version (WCST-interruption), in which intentional attempts were made to distract the animals from WCST trials. When performance with one rule reached the shift-criterion, instead of a rule-shift being implemented, they had to perform two trials of an unrelated task (face-detection task) before returning to the WCST (still using the same rule). Whereas the performance of control monkeys on this first trial after returning from the interruption dropped to the chance level, the frontal pole-lesioned monkeys still performed significantly better than the controls. The result first shows that monkeys were unable to properly perform the cognitive branching between the two tasks. Second, the diverting (albeit significant) task presumably triggered the control monkeys' propensity to explore the significance of the new task, consequently interfering with the maintenance of the currently relevant rule over the interruption. The propensity to explore

alternative goals when switching away from the on-going task was likely diminished in lesioned animals²⁴. The hypothesis links the frontopolar cortex to redistributing cognitive resources over alternative goals, when the current goal is deemed no more relevant. The hypothesis further predicts that monkeys with frontopolar cortex lesions would be less concerned with any events that bring into question the relevance of ongoing behavior in general. To test this, in another version of the WCST, a free reward (a reward given to the animal without the necessity to perform a task) was given, during the inter-trial interval, after the monkeys reached the shift criterion. Again, the performance of the control animals dropped to the level of chance in the first subsequent trial, whereas that of the frontal pole-lesioned monkeys did not²⁴. Thus, monkeys with lesions within frontopolar cortex remained focused on the main task, accounting for their superior performance. By contrast, control monkeys appeared to judge the free reward as altering the relevance of the current behavior, thereby prompting the exploration of alternative behavioral options²⁴.

In the second of the frontopolar cortex lesion studies²³, the monkeys performed a series of learning and memory tasks (Table 1), the results of which confirmed that frontopolar cortex lesions do not impair standard object working memory tasks (i.e. matching or non-matching to sample) or standard stimulus-reward associative learning tasks (i.e. concurrent object discrimination learning). However, the frontal pole lesioned animals were impaired (compared to control animals) in the rapid learning about the relative value of alternatives, in three different tasks. Firstly, in a standard concurrent object-in-scene learning task, the frontal pole lesioned animals were observed to have a highly specific deficit in rapid one-trial learning. That is, they did not show the normal marked level of improvement in performance accuracy from the first run through a set of novel problems (in which their first choice was a self-generated 'guess'), to the second run (in which normal control animals show a distinct one-trial learning effect). This highly specific deficit is not seen after lesions to other prefrontal regions, thereby further

distinguishing the frontopolar cortex from those areas. That the same pattern of deficit specific to rapid early learning about novel alternatives was also observed in a very simple successive single problem learning task²³ denies the importance of scene and/or context based learning for frontopolar cortex function. These selective deficits in one-shot learning after frontopolar lesions are consistent with the results described in the preceding section on WCST tasks in that they may similarly reflect impaired consideration of alternative behavioral options; this is because in these one-shot learning tasks, the learning rate of the monkeys (that are evidently not perfect learners from their learning rate curves²³) are presumably enhanced if animals learn not only about the value of the chosen stimulus in each trial but also about the inferred relative value of the unchosen stimulus. This benefit in rapid acquisition diminishes with problem repeats, as then slower, frontopolar independent²³ learning by repeated reinforcement comes to predominate. Hence frontopolar cortex may therefore provide primates with a mechanism for rapid learning when faced with novel alternatives. Taken together with a significant deficit in rapid learning of new rules after frontopolar cortex lesions, the findings instead point to a general deficit in exploring novel behavioral options in the early stages of learning²²⁻²³, as previously observed in humans³. In summary, these findings (Table 1) across both studies indicate that the frontopolar cortex plays a general and crucial role in favoring the exploration of the value of alternative behavioral options²³⁻²⁴.

Frontopolar cortex function in monkeys

The aforementioned frontopolar cortex lesion studies together suggest the hypothesis (Fig. 5) that, while neurons in prefrontal areas are generally interacting with each other in order to maximise the value or benefit that can be derived from a current task or goal, those in the frontopolar cortex instead may be monitoring the environment for indications that potential alternative goals may be more advantageous, and as such may come to trigger disengagement in favour of a new task or goal (Fig. 2) when switch conditions are favourable²³⁻²⁴. Hence this

model also proposes a balance between ‘exploitatory’ drive from other frontal areas, which allocate attentional and control resources in service of the current task or goal, and an ‘exploratory’ drive from the frontopolar cortex, which allows redistributing these resources^{23-24, 64} (Figs. 2 and 5). Based on activation pattern of frontopolar cortex in imaging studies, other investigators have also suggested that the left lateral human frontopolar cortex is involved in the stimulus-driven allocation of attentional resources, away from a currently attended visual dimension or spatial location, to a new dimension or location⁸⁴⁻⁸⁵.

At first glance, the better-than-control performance observed in monkeys²⁴ (and humans³²) with frontopolar cortex lesions might appear counterintuitive. However, in real-life environments, which may be uncertain, changing and open-ended, focusing exclusively on optimal performances in an ongoing task may be detrimental. In such environments, the relevance of tasks or goals may be subject to change according to new external contingencies. For example, imagine a monkey engaged in grooming her young; it would be maladaptive to allocate all attentional resources to this task at the expense of potentially missing cues to predators, food or social opportunities²⁴. Thus, evolutionary pressure may have favoured the development of an additional system centred on the frontopolar cortex to redistribute and limit allocation of attentional/control resources to a single endeavour²³⁻²⁴ (Figs. 2 and 5). Such a strategic balance between exploitation and exploration may be a fundamental aspect of adaptive behavior, particularly in socially advanced species^{6, 46, 86-87}.

Insights into human frontopolar function

What can be learned about human frontopolar cortex function from monkey studies? Interspecies comparisons are often delicate. This is particularly true in the case of the anterior prefrontal cortex, for which there is evidence of anatomical differences between monkeys and humans^{1, 25}.

Nevertheless, some reasonable inferences can be made from monkey studies about human frontopolar cortex function.

First, the monkey studies found that, unlike the multifaceted neuronal representations in posterior prefrontal and medial frontal regions, frontal pole cell activity appears to be unrelated to the prospective memory of cued upcoming actions, the retrospective memory of previously performed actions, or the formation and shift between cognitive sets, even though all these components were required in the tasks the animals performed. Moreover, lesions in monkeys have revealed that, in contrast to posterior lesions, those in the frontopolar cortex induce no significant impairments in working memory of task rules, selective attention to ongoing task rules, inhibition of previously relevant rules, or the assessment of behavioral outcomes to detect and adapt to unpredictable rule changes. Furthermore, frontopolar cortex lesions induce no impairments in the ability to concurrently consider several different attributes of stimuli, or to implement well-learned complex rules. We may then reasonably infer that, if these cognitive processes are independent of the integrity of the frontopolar cortex in monkeys, the human frontopolar cortex is unlikely to specifically subserve these processes. Consequently, these findings provide little support for models which assume that the human frontopolar cortex has an essential role in mnemonic and particularly working memory functions, in establishing and shifting between cognitive sets, or in relational integration or integration of the outcome of multiple cognitive processes.

Second, studies in monkeys support the idea that the function of the frontopolar cortex is to redistribute the allocation of attentional and executive resources away from a default behavioral strategy, which is driving ongoing behavior. This function is likely to be inherited in the human frontopolar cortex. This may explain the critical involvement of the human frontopolar cortex in cognitive abilities such as mind-wandering, planning, abstract reasoning,

multitasking and cognitive branching, which require switching away from an ongoing behavioral option, considering multiple behavioral options or exploring new ones.

Third, a striking finding was that frontal pole-lesioned macaques perform better than controls when returning to an interrupted task, after being diverted by behaviorally meaningful events (rewards) or the execution of a secondary task²⁴. Interestingly, this behavioral paradigm involves cognitive branching (Table 1), and suggests that, unlike humans, monkeys have difficulty properly performing true cognitive branching. While the finding reveals a critical role of the macaque frontopolar cortex in redistributing cognitive resources, and exploring options beyond the ongoing behavioral strategy²⁴, it suggests that normal monkeys are unable to hold relevant information, and resume the task after completing or exploring other options. This is in contrast with human cognition, where branching is an inherent aspect of goal-directed behavior. Cognitive branching in humans is specifically associated with activation of a region in the lateral frontopolar cortex (Fig. 1a), which appears not to exist in monkeys²⁵. In contrast to monkeys, lateral frontopolar lesions in humans do impair their efficient performance in cognitive branching²⁸. Thus, lesion studies in monkeys, human imaging and comparative-anatomical studies provide convergent evidence that a higher capability for cognitive branching may have emerged in human evolution associated with the enlargement and development of the lateral frontopolar cortex^{1, 5-6}.

Human frontopolar cortex function

Recent studies combining computational modelling, behavioral tests and fMRI experiments have proposed a model that describes arbitration processes between exploitation and exploration behaviors (Figs. 2 and 6), and formalizes aspects of the evolution of the frontal pole function from monkeys to humans^{5-6, 87}. This model distinguishes two arbitration systems:

- A basic system that monitors online the relevance (“absolute reliability”, in the model terminology) of the ongoing behavioral strategy (i.e. the “actor”), and triggers undirected exploration when this strategy is deemed irrelevant. Relevance is inferred from the predictability of action outcomes and the occurrence of contextual cues. Undirected exploration is conceived as the emergence of a new cognitive set that serves as the actor. This is initially built from long-term memory of previously learned, contextually relevant strategies, and subsequently adjusted to external contingencies. The relevance of this cognitive set is monitored online and may eventually be consolidated in long-term memory, when it is deemed relevant.
- An add-on system that further monitors online the relevance of a few alternative behavioral strategies. These strategies were previously used as relevant actor strategies, but subsequently deemed irrelevant. Critically, this system allows one of these alternative strategies to replace the current actor strategy when the latter is deemed irrelevant (by the basic system) and the former is deemed as relevant again (by the add-on system) (Fig. 6). The add-on system thus enables directed exploration, i.e. the ability to keep track, test several behavioral hypotheses simultaneously, and as a special case, to perform cognitive branching.

Unlike other computationally meaningful adaptive behavior models, the model integrating the two systems accounts for human sequential choices in uncertain, changing, recurrent or open-ended environments^{4-6, 87-88}. Furthermore, fMRI studies in humans reveal that monitoring the relevance of strategies based on the predictability of action outcomes is associated with anterior prefrontal activations, with medial ones involved in monitoring the actor strategy and lateral ones in monitoring alternative strategies⁵⁻⁶. Intriguingly, this latter activation is located in the frontopolar cortex region previously identified as subserving cognitive branching⁴⁻⁶, which may have no homolog in monkeys²⁵. Consistent with these findings, there is convergent evidence from functional and morphometric MRI, as well as transcranial magnetic

stimulation studies⁸⁹⁻⁹⁰, that human subjective reports about their confidence in chosen actions is associated with anterior prefrontal function. Moreover, single cell activity recorded in the monkey frontopolar cortex following action choices and preceding positive outcomes¹⁹⁻²¹ also suggests that the frontopolar cortex monitors the relevance of the actor strategy⁴ and supports human confidence judgments regarding current behavior. These results, together with those of macaque studies reviewed above, thus suggest that the monkey frontopolar cortex subserves the basic system that monitors the relevance of the current behavioral strategy and arbitrates between exploiting this strategy and undirected exploration of alternative ones. The human lateral frontopolar cortex further features a new functional region that may support, through interaction with other regions, the add-on system that enables directed exploration of concurrent alternative strategies^{5-6, 87}. If this is the case then this function may explain the activation of the lateral frontopolar cortex in the various cognitive paradigms reviewed above, such as exploration, cognitive branching, abstract reasoning and problem-solving.

Conclusions and future directions

We propose that there is a balance between an ‘exploitatory’ drive from the posterior parts of the prefrontal cortex, which allocates cognitive resources to an ongoing task, and an ‘exploratory’ drive from the frontopolar cortex, which promotes the redistribution of such resources away from the current task, when other potential goals might appear behaviorally more relevant as a result of changes in the environment (Figs. 5 and 6). Modulating the balance between exploratory and exploitatory drives is a shared cognitive challenge for human and non-human primates, and is a core function in the regulation of foraging and appetitive behavior with direct relevance to survival and fitness (Fig. 2). However, the volume of the frontopolar cortex in humans surpasses that of the corresponding areas in monkeys (Fig. 1a)^{1, 17, 92-93}, likely enabling unique cognitive functions that are inaccessible to non-human primates but might nonetheless be underscored by the frontal pole’s contribution to the management of competing goals. Indeed, the frontopolar

cortex has already been previously linked with several arguably uniquely human forms of intelligent behavior, yet this new view that the frontopolar cortex supports the management of competing goals may offer a unique unifying perspective. For example, reasoning requires mental consideration of competing abstract thoughts and projections. Even episodic memory and its associated introspection and “mental time travel”⁸⁶ are now defined specifically with respect to future planning the enhancement of which may involve representing and simulating/considering imagined future alternatives in order to plan most effectively. Whether or not the human frontopolar cortex contains a subregion that has no analogue in monkeys, as indicated by imaging studies²⁵, is also highly intriguing, but ultimately requires further confirmation through studies that do not confound state (resting versus anaesthetized) across species, as is currently the case, and that ideally compare functional connectivity during the performance of similar cognitive tasks.

We argue that understanding the role of the frontopolar cortex in non-human primates provides key insight into fundamental aspects of primate cognition. The exploratory role of the frontopolar cortex in monkeys may have been preserved in humans but may also have evolved to acquire additional cognitive capacities for the directed exploration of concurrent alternative strategies (Figs. 2, 5-6). Our model stresses interactions between the frontopolar cortex and posterior cortical areas (Fig. 2). Recent studies indicate that alterations in frontopolar cortical activation are associated with functional impairment in neuropsychiatric disorders⁹⁴. Testing the role of the frontopolar cortex in humans and monkeys using similar cognitive tasks while recording from multiple interacting areas, in both the presence and absence of interventions using newly developed techniques⁹⁵⁻⁹⁶, will likely herald important future insights regarding how neuropsychiatric diseases like schizophrenia, bipolar disorder and obsessive compulsive disorder⁹⁷⁻⁹⁹ and related behavioral deficits stem from dysfunctional interacting frontal regions

The complexity of a changing environment, particularly for species with advanced social behavior, is likely to have led to strong evolutionary pressure for the development of an alternative neural system for the disengagement and redistribution of executive control between potential options and goals. This in turn might have led to the emergence of high-level cognitive abilities that underlies advanced intelligence and the creativity of the human mind.

Figure legends

Figure 1. Neuroanatomy of the frontopolar cortex

(a) Extent of the frontopolar cortex (cytoarchitectural area 10p), is shown in lateral (left) and medial (right) views of the right hemisphere in three species of simian primate. Pictures are shown according to the same scale (top centre = 1cm). These brain models generated with the software CARET (Computerized Anatomical Reconstruction and Editing Toolkit, RRID:nif-0000-00279)^{17, 100}. The extent of area 10 is highlighted in red. In the human brain the yellow region indicates the lateral subdivision of the frontopolar cortex, which is hypothesised to have subserved functions of which monkeys are less capable^{4, 25}. This comparison illustrates the fact that the frontopolar cortex becomes larger not only in absolute terms, but also in relative terms, as a function of brain size¹. (b) Main sources of cortico-cortical afferent connections to the non-human primate frontopolar cortex, here illustrated in a macaque brain. All major direct synaptic projections to the frontopolar cortex originate in high-order association areas⁸⁻¹⁰. Abbreviations on the panels: dlppfc: dorsolateral prefrontal cortex; vlppfc: ventral-lateral prefrontal cortex; sts: superior temporal sulcus; stg: superior temporal gyrus; tp: temporal pole; acc: anterior cingulate cortex; mpfc: medial prefrontal cortex; ofc: orbitofrontal cortex; pcc: posterior cingulate cortex; rsc: retrosplenial cortex; phc: parahippocampal cortex.

Figure 2. Adaptive goal-directed behavior requires a balance between exploitation of the current goal and the tendency to shift into an alternative goal.

Pursuing the current goal requires participation and coordination of multiple cognitive functions, such as implementing strategy/rule, representing spatio-temporal contingencies (task context), action selection, mnemonic functions, assessing behavioural outcome, reward prediction/risk, and task-related emotional and motivational regulations to accomplish a task. An executive control network including dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) supports these cognitive processes. The frontopolar cortex

does not necessarily participate in execution of well-learned tasks but instead, collects highly processed information regarding the value (cost and benefit) of the current and alternative tasks/goals to adjust a balance between the tendency for exploitation of the current task and the drive for exploring alternative reward sources or goals in the environment. Monkeys and humans might share the overall organization and the neural substrate of such adaptive goal-directed behavior, however human brain might have acquired additional capacities to assess multiple goals and direct the exploratory shift toward the most advantageous one.

Figure 3. Neuronal activity in posterior and anterior prefrontal cortex of the macaque monkey.

(a) The monkeys performed a computerized version of the Wisconsin Card Sorting Test (WCST) (upper panel). In each trial, a Start-cue was shown and if the monkey pushed a bar, a fixation period and then a sample appeared at the centre of a touchscreen. If the monkeys kept pressing the bar and maintained eye fixation, three test items appeared surrounding the sample and the monkeys had to touch one of the test items that matched the sample by colour or shape. Cells in lateral and orbital regions of prefrontal cortex conveyed information about the details of the task while the monkeys were performing the WCST. Activities of two example cells, which were recorded in orbitofrontal cortex (OFC cell) and dorsolateral prefrontal cortex (DLPFC cell), are shown. The orbitofrontal cell (Left and middle panels) showed anticipatory activity before reward delivery and then a strong increase in activity after the arrival of the reward. However, the orbitofrontal cell did not respond to the free reward (a reward which was given randomly without performing the matching task), indicating that this cell responded to the reward only when it resulted from a correct decision. The response to the reward was also dependent on the level of conflict that the monkey experienced in the course of achieving the reward, and this was seen only when the shape matching rule was used. The neuronal activity of a dorsolateral prefrontal cortex neuron (right panel) was modulated by the matching rule during Sample

presentation period. The peri-stimulus time histogram shows the mean activity when the colour- or shape-matching rule was applied in correct trials. These findings indicate that DLPFC and OFC cells represent rules/strategies and convey detailed information about feedback within the task context. Adapted from Mansouri et al.^{43, 70}.

(b) The monkeys performed a strategy task (upper panel) in which a ‘strategy cue’ indicated whether the monkey should ‘stay’ with the previously made saccade or ‘shift’ to the alternative saccade direction. Strategy cues could be either visual objects or the presence/absence of a reward at the beginning of each trial. The neuronal activity of a frontopolar cortex cell was not modulated by the strategy cues or the actual strategy taken by the monkey or the memory of the previous action, but was modulated after a saccade around the feedback time. Adapted from Tsujimoto et al.²⁰.

Figure 4. Behavioral consequence of selective and bilateral lesions within the frontopolar cortex

In the Wisconsin Card Sorting Test (WCST) subjects should match visual items based on color- or shape-matching rules. The relevant rule is frequently changed without any notice and the subjects should find the rule and its changes by trial and error. The number of rule-shifts in a daily session indicates the ability of monkeys to adapt to unannounced rule-shifts in the WCST. Panel **a** shows the number of post-lesion rule-shifts as a percentage of the pre-lesion level in different groups of monkeys. A value of 100 on vertical axis would mean that there was no change in the number of rule shifts from the pre- to post-operative testing. The control group refers to the monkeys without any lesion. Lesions within the dorsolateral prefrontal, anterior cingulate and orbitofrontal cortices (DLPFC, ACC, OFC) impaired the ability to adapt to rule-shifts; however, lesions of the frontopolar cortex (FPC) or posterior cingulate cortex (PCC) had no significant effect, indicating a dissociation of function between the frontopolar cortex and the posterior parts of the prefrontal cortex (DLPFC, ACC and OFC). The schematic diagrams on the

right show the intended lesion extent (grey) on different aspects of the frontopolar cortex (upper row) and in other lesion groups (lower row). Adapted from Mansouri et al.²⁴.

Figure 5: Functional model of the frontopolar cortex in monkeys

We propose that the frontopolar cortex (area 10 cortex depicted in red color) and posterior parts of the prefrontal cortex (including dorsolateral and ventrolateral prefrontal cortices, orbitofrontal cortex, area 8 within the periarculate region and the anterior cingulate cortex) have complementary but dissociable roles in adjusting the distribution of cognitive control. In this model, there is a balance between the “exploitation” drive from the posterior parts of the prefrontal cortex and “exploratory” drive from the frontopolar cortex that limits the focus on the current task and redistributes some cognitive resources to other potential goals. To redistribute cognitive resources for the exploration of other potential tasks and goals, the frontopolar cortex may construct and monitor an estimated value for the relevance of the current behavioral strategy based on posterior prefrontal representations that control this strategy and trigger exploration when the strategy is deemed irrelevant. The figure is adapted from Mansouri et al.²⁴.

Figure 6: Functional model of the frontopolar cortex in humans

We propose that the monkey FPC function has further evolved in humans through the development of a lateral frontopolar cortex sector. Accordingly, the monkey frontopolar cortex function, mainly involved in monitoring the relevance of the current task/goal and regulating the redistribution of cognitive resources away from this task/goal according to changes in internal and external contingencies, and referred to as undirected exploration, is inherited in the medial sector of human frontopolar cortex (red). The lateral sector of human frontopolar cortex (yellow) is associated with the development of more elaborated exploration function, referred to as directed exploration, monitoring the relevance of a few alternative tasks/goals and the opportunity to redistribute cognitive resources towards one of these. As in monkeys, the

posterior prefrontal cortex (blue) mainly serves to control the execution of the current task/goal according to the context in which the subject is acting (exploitation).

Table 1: Impaired and intact cognitive functions after selective bilateral lesions within frontopolar cortex in monkeys.

Glossary:

fMRI: Functional Magnetic Resonance Imaging is a neuroimaging technique that measures local changes in blood flow to assess the activation change in brain regions in relation to cognitive processes.

Theory of mind: Cognitive abilities that allow one to infer someone else's beliefs, intents, desires and feelings.

Episodic memory: A memory of events enriched by contextual information such as the associated emotion, place and time.

Working memory: A process of short-term storage of information to support ongoing or upcoming actions.

Analogical reasoning: A process of reasoning based on comparison between objects, events or models to help in understanding, learning and decision making.

Transitive inference: A process of reasoning based on relative relation between objects or events to help in understanding, learning and decision making.

Tower of London Test: A cognitive test of planning in which participants must plan the order of balls on a peg based on a given template.

Conflict cost: When competition or conflict arises between behavioral choices in experimental tasks, performance is adversely affected in terms of speed and accuracy. This is referred to as the 'conflict cost'.

Conflict adaptation: Refers to the behavioral effects of conflict that affect performance in the subsequent trial, where they are manifested as a behavioral improvement if the subject is faced with conflict again.

Transcranial Magnetic Stimulation: Is a brain stimulation technique in which magnetic field is used to transiently stimulate neurons.

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TOC summary

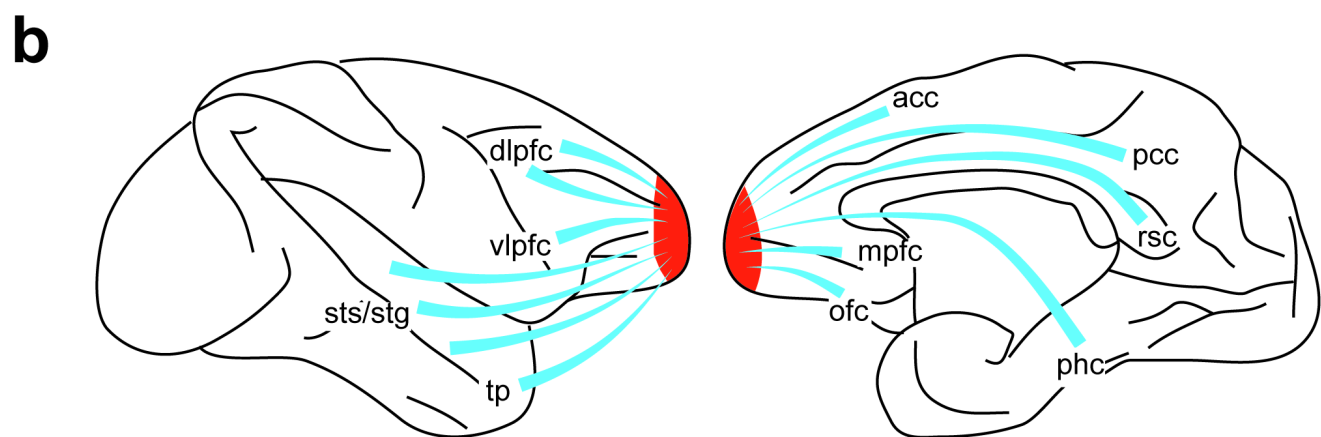
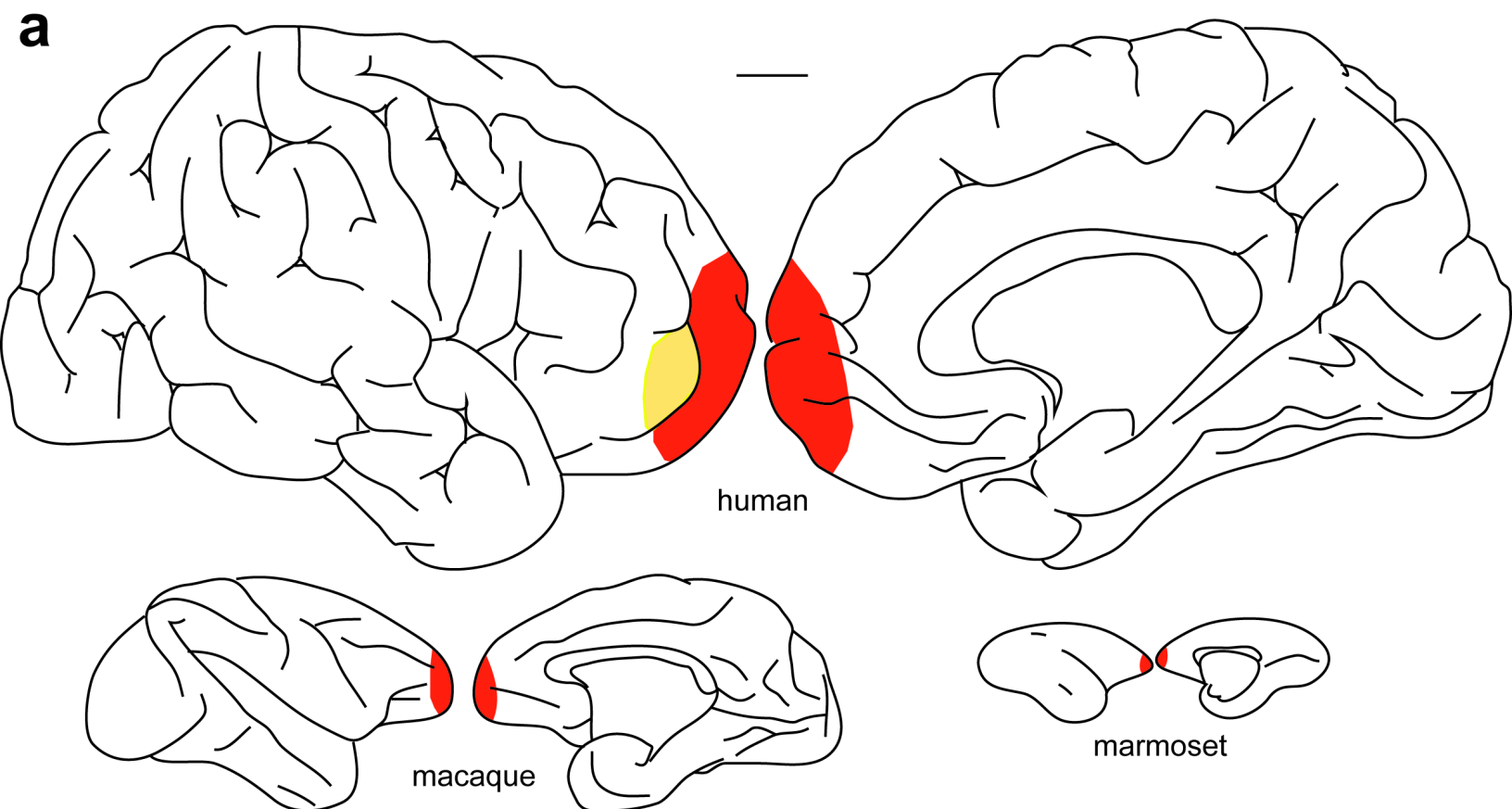
Only primates possess ‘cytoarchitectonic area 10’ in anterior prefrontal cortex and its function is unknown. In this review, Mansouri and colleagues argue that area 10 monitors the relative significance of current behavior, a function extending in humans to multiple concurrent goals.

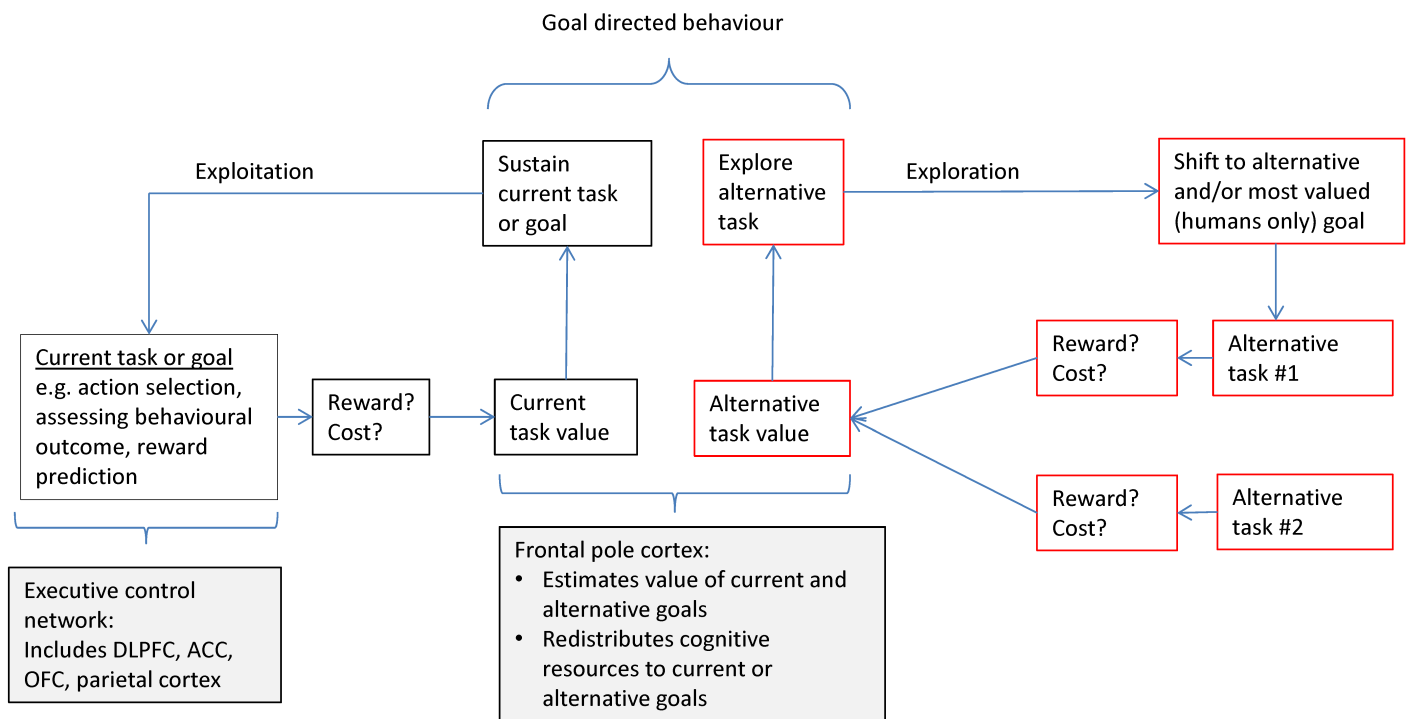
On-line summary

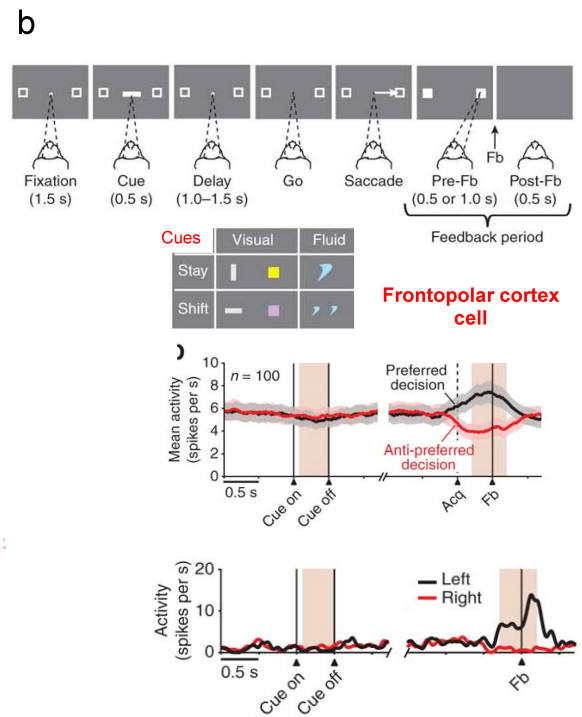
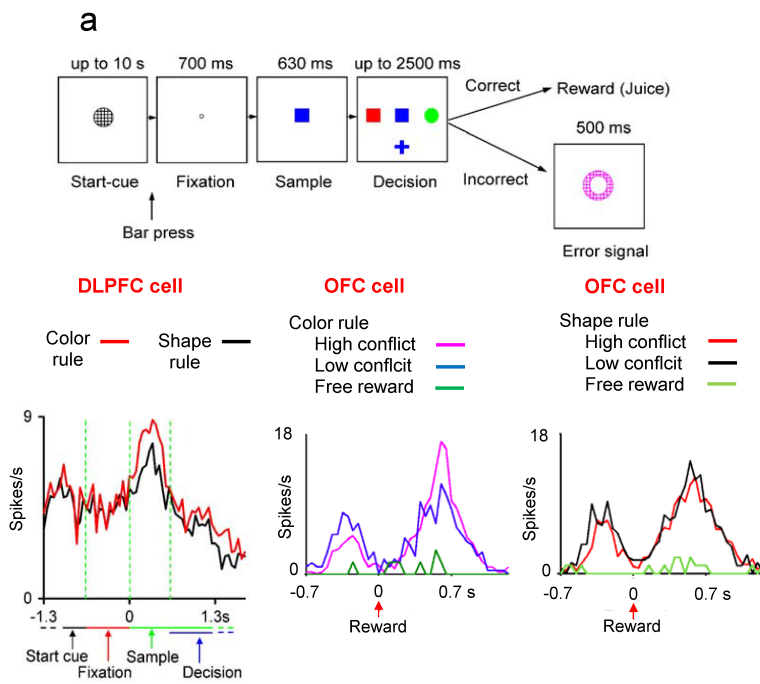
- In primates, the foremost part of prefrontal cortex (the frontopolar cortex) contains cortical ‘area 10’ that is of special interest because it is exclusive to primates, it is proportionally larger in humans than in apes, has a pattern of anatomical connections that suggest area 10 sits atop a prefrontal hierarchy.
- We review the most influential theories of frontopolar function based upon human neuroimaging and neuropsychological investigations and conclude its crucial contribution to cognition has not yet been specified.
- Importantly, we review the first ever circumscribed behavioral-lesion studies of the frontopolar cortex in monkeys which reveal a distinct pattern of spared, impaired, and in some cases enhanced cognitive abilities.
- Considering all these animal experiments, we conclude that a key specialization of primate frontopolar cortex is in managing competing goals, in part by keeping track of the significance of current and alternative goals, and therefore enabling switching away from ongoing behavior.
- A particular set of recent studies in humans combining human neuroimaging and computational modeling has provided a synergistic view with these recent animal studies, while also revealing new insights about specific features of the human frontopolar cortex

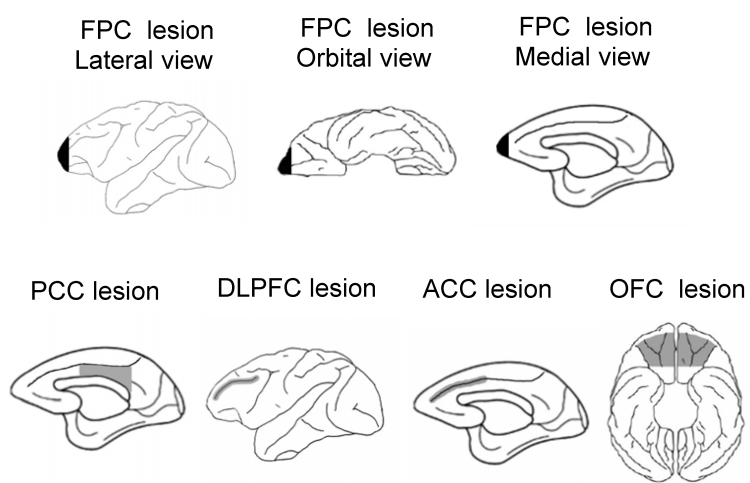
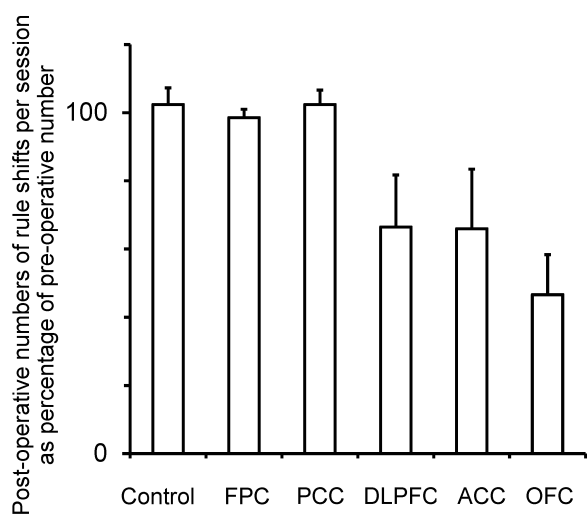
which we argue has acquired additional, but related roles, in allowing monitoring of the significance of several competing goals in parallel, and in switching between them.

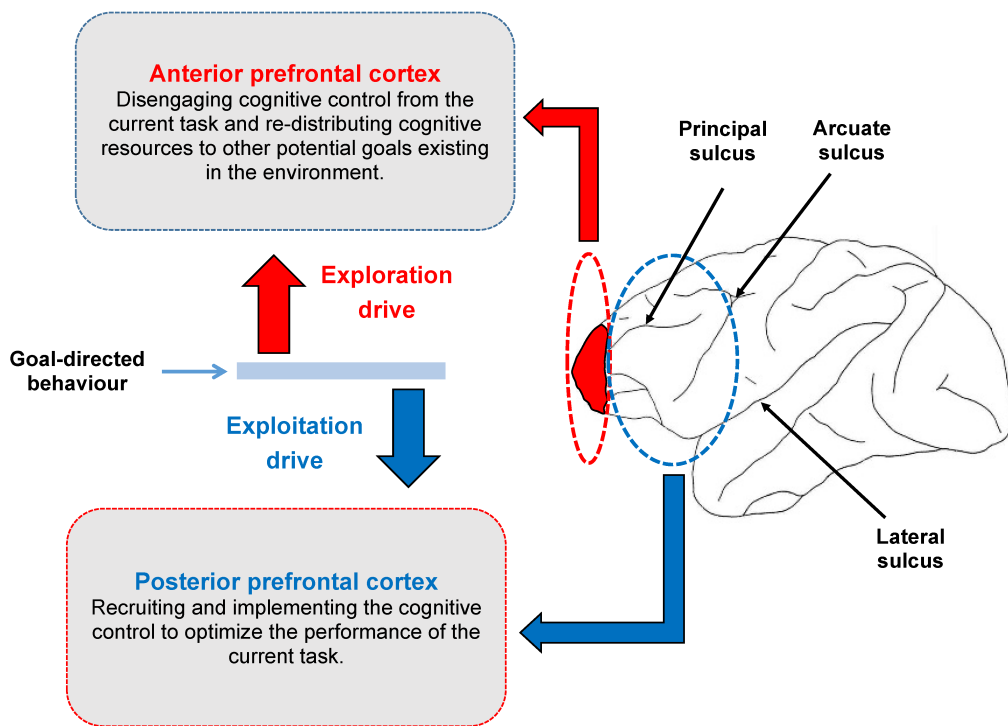
- We consider whether these new functions may be linked to a lateral subdivision of cytoarchitectural area 10 which some data suggests might have no clear monkey counterpart but if this is the case then this function may explain the activation of the lateral frontopolar cortex in several key cognitive paradigms we reviewed, such as exploration, cognitive branching, abstract reasoning and problem-solving.

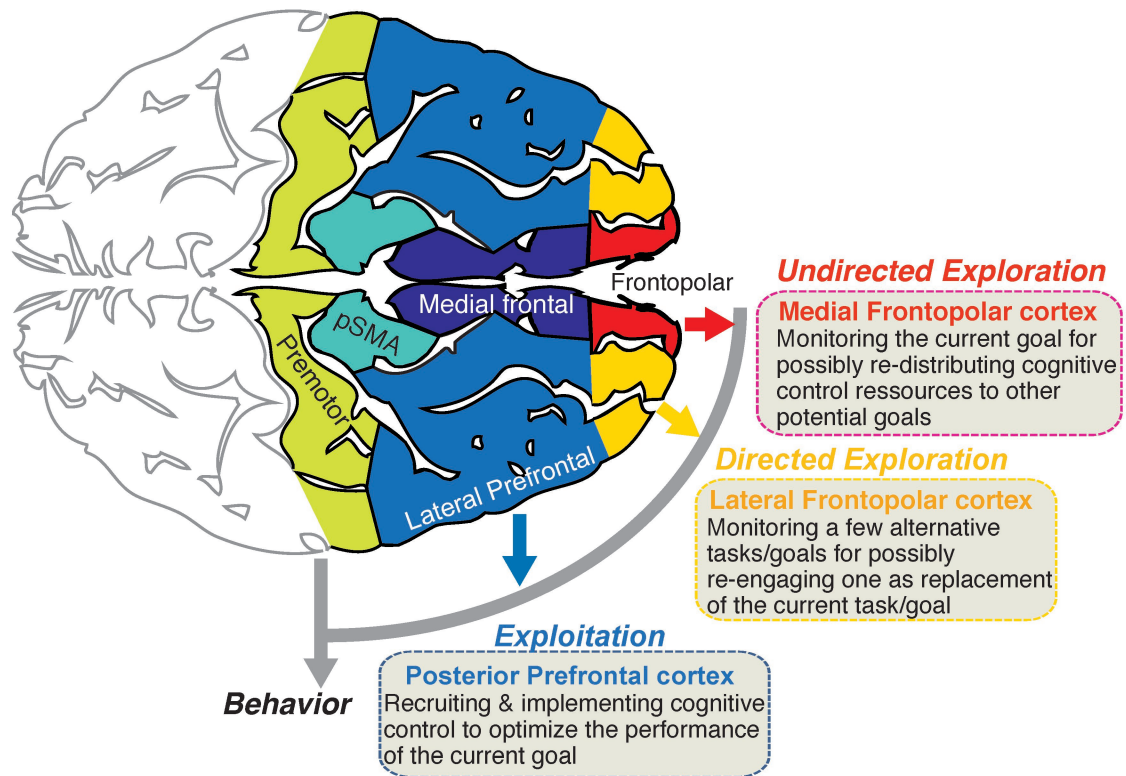












Task	Effect of frontal pole lesion	Lesion-induced behavioural change	Key involved cognitive processes
1. Object-in-scene learning	Yes	1-trial learning impaired.	Rapid reinforcement based learning.
2. Concurrent object discrimination learning	No	None	Slow gradual reinforcement based learning.
3. Successive single problem learning	Yes	1-trial learning impaired.	Rapid reinforcement based learning.
4. Standard WCST	No	None	Rapid switching between well-established abstract rules.
5. WCST-conflict	Yes	Conflict-induced behavioral adaptation enhanced.	Resolving conflict between well-established behavioral rules. Conflict-induced behavioral adjustment.
6. WCST-interruption	Yes	Animals remember the rule after the interrupt better than controls	Maintaining information of a pending task while an alternative task is performed for successful resumption of the pending task.
7. WCST-free reward	Yes	Animals remember the rule after the distracting free-reward better than controls	Remaining focused on maintaining information of the on-going task despite extra-task salient events.
8. Delayed matching-to-sample (DMS)	No	None	Working memory for stimulus
9. Delayed non-matching-to-sample (DNMS)	No	None	Working memory for stimulus
10. Learning new abstract rule ('smaller-than')	Yes	FPC lesioned animals fail to learn the new rule in the first three days.	Learning new rules.
11. Applying two rules ('smaller-than' and 'same identity' at the same time)	No	None	Applying two abstract rules at the same time; combining the result of multiple cognitive operations.

Footnote: The first column from left indicates the cognitive task. The second column indicates the presence (yes) or absence (none) of significant behavioral effects of lesion. The lesion-induced behavioral change in each task are described in the third column. The fourth column explains the key involved cognitive processes. Adapted from Boschini et al.²³ and Mansouri et al.²⁴.