Symposium

What Does the Frontopolar Cortex Contribute to Goal-Directed Cognition and Action?

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Understanding the unique functions of different subregions of primate prefrontal cortex has been a longstanding goal in cognitive neuroscience. Yet, the anatomy and function of one of its largest subregions (the frontopolar cortex) remain enigmatic and underspecified. Our Society for Neuroscience minisymposium *Primate Frontopolar Cortex: From Circuits to Complex Behaviors* will comprise a range of new anatomic and functional approaches that have helped to clarify the basic circuit anatomy of the frontal pole, its functional involvement during performance of cognitively demanding behavioral paradigms in monkeys and humans, and its clinical potential as a target for noninvasive brain stimulation in patients with brain disorders. This review consolidates knowledge about the anatomy and connectivity of frontopolar cortex and provides an integrative summary of its function in primates. We aim to answer the question: what, if anything, does frontopolar cortex contribute to goal-directed cognition and action?

Key words: **Area 10; frontal pole; nonhuman primates; decision-making; explore/exploit; cognitive control**

Introduction

Frontopolar cortex (FPC), commonly referred to as Area 10 in monkeys and humans, represents the apex of the primate granular prefrontal cortex. Yet, our understanding of FPC anatomy and function has lagged behind other prefrontal subregions for several reasons. Neural activity in FPC does not seem particularly driven by external cues (Tsujimoto et al., 2010), human brain lesions are rarely confined to FPC (Koechlin and Hyafil, 2007; Badre, 2008), FPC is difficult to access for neurophysiological recordings in monkeys (Mitz et al., 2009), and FPC is difficult to modulate using transcranial stimulation in humans. Meanwhile, comparative anatomic analyses have revealed that Area 10 is among the largest cytoarchitectonically defined regions of the human prefrontal cortex (Ongür et al., 2003). Human FPC is relatively larger compared with other apes (Semendeferi et al., 2001), suggesting that a better understanding of FPC anatomy and function is key for unlocking mysteries of complex cognitive functions that are uniquely specialized in humans relative to other primates.

A primer on the neuroanatomy of the FPC

Before we can answer questions about the function of the FPC, we should first understand its makeup. Most of what is known about the neuroanatomy of FPC is focused on cytoarchitectonics (Walker, 1940; Barbas and Pandya, 1989; Preuss and Goldman-Rakic, 1991) and anatomic tracing of connections between FPC and other brain regions using autoradiographic (Petrides and Pandya, 2007) or retrograde tracers (Barbas and Pandya, 1989; Preuss and Goldman-Rakic, 1991; Petrides et al., 2012; Markov et al., 2014).

In primates, the frontal pole of the granular PFC is characterized by a well-defined layer IV and is populated by small- to medium-size pyramidal neurons. In rhesus macaques (Dombrowski et al., 2001), the overall neuronal density of FPC is higher than in agranular or dysgranular regions of the frontal lobe (e.g., orbitofrontal or cingulate cortex) but does not differ from other granular subdivisions of prefrontal cortex (e.g., Area 46), although neuronal density in layer IV is higher in Area 10m than in Area 9 (Dombrowski et al., 2001). Myelination of FPC is sparse relative to adjacent Areas 9 and 8 of granular PFC, but myelination is still greater in the frontal pole compared with more caudal, dorsolateral prefrontal areas (Preuss and Goldman-Rakic, 1991). Medial frontopolar (Area 10m) cortex also contains fewer parvalbumin- and calbindin-immunoreactive neurons

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relative to other frontal lobe regions, especially Area 14 in orbitofrontal cortex and Area 46 in PFC (Dombrowski et al., 2001). Dopamine receptor expression and dopaminergic innervation of the frontal pole is poor relative to other granular prefrontal regions (Berger et al., 1988; Williams and Goldman-Rakic, 1993). Dopaminergic fibers innervating FPC also exhibit laminar innervation patterns distinct from more caudal prefrontal regions (Williams and Goldman-Rakic, 1993). This contrasts with low but similar cholinergic innervation of FPC and prefrontal areas (Lewis, 1991). In humans, FPC pyramidal neurons have a higher number and density of dendritic spines compared with neurons in orbitofrontal cortex (Jacobs et al., 2001), and there is a greater horizontal distance between neuronal cell bodies in layer III of FPC compared with apes. This has led to speculation, in humans at least, that the frontal pole has an enhanced capacity for neural integration (Tsujimoto et al., 2011), but direct tests of this hypothesis are lacking. Although brief, this synopsis represents the current state of knowledge regarding the cytoarchitecture, molecular, and cellular diversity within the FPC. While it is settled that Area 10 is a distinct cytoarchitectonic region in multiple species of primates (Preuss and Goldman-Rakic, 1991; Tsujimoto et al., 2011; Petrides et al., 2012), there remains an immediate need to use additional neuroanatomical and transcriptomics approaches (Bakken et al., 2021; Scala et al., 2021) to establish a more comprehensive catalog of the neural elements in FPC and that distinguish it from other frontal lobe regions.

An ongoing debate surrounds how to best subdivide the FPC, recognizing its expansion in humans relative to nonhuman primates. Cytoarchitectonic analyses have not yielded a clear answer, so a common approach is to delineate subregions based on their anatomic connections. Across primates, FPC can be subdivided into at least two subdivisions: a lateral subdivision that is forward of the principal sulcus on the surface of the frontal cortex and a medial subdivision that encompasses the medial wall anterior to the cingulate gyrus. A third orbital subdivision is also evident in humans (Liu et al., 2013; Orr et al., 2015). Retrograde tract-tracing studies in both macaques and marmosets find that the most robust connections of the medial and lateral subdivisions of the FPC are intrinsic, emanating from adjacent areas of Area 10 (Barbas et al., 1999; Petrides et al., 2012). The next strongest set of inputs to the FPC come from adjacent dorsolateral prefrontal (Area 9) and orbitofrontal (Areas 11,12, and 14) cortex.

The FPC receives input via the cingulate and uncinate fasciculi, as well as the extreme capsule (Petrides and Pandya, 2007). Anterior cingulate cortex (ACC) inputs to the frontal pole form large, asymmetric connections with the spines of excitatory neurons, whereas ACC inputs to dorsolateral prefrontal cortex (dlPFC) mainly target inhibitory interneurons (Medalla and Barbas, 2010). These synaptic specializations suggest that ACC can enhance inhibition in dlPFC and strengthen excitation in FPC, which may help direct attention to new tasks while temporarily holding in memory another task (Medalla and Barbas, 2010). Ablation lesions of the FPC in macaques have also been shown to profoundly impact the functional connectivity of FPC with posterior cingulate cortex (Ainsworth et al., 2022). Outside of the frontal lobe, corticocortical connections of the FPC emanate mainly from auditory and polysensory regions of the superior temporal sulcus (Medalla and Barbas, 2010, 2014).

Retrograde tracers injected into the frontal pole of marmosets (Burman et al., 2011a) and macaques (Porrino et al., 1981) have also established that a sparse projection exists from the magnocellular division of the basal and accessory basal nuclei of the amygdala to the frontal pole. Probabilistic tractography studies in humans have also detected amygdala inputs to FPC (Orr et al., 2015). Using complementary anatomic tracing techniques (Barbas and Pandya, 1989; Petrides and Pandya, 2007; Markov et al., 2014), outputs from the FPC to other brain regions largely match the pattern of its inputs, consistent with probabilistic tractography and resting-state fMRI assessments of frontal pole connectivity in humans (Liu et al., 2013) and macaques (Yacoub et al., 2020; Ainsworth et al., 2022). However, connections from FPC to the striatum are not matched by a direct input. In macaques, anterograde tracers injected into the ventral aspect of the lateral and medial subdivisions of FPC label connections that terminate along the rostrocaudal extent of the medial edge of caudate nucleus bordering the lateral ventricle (Ferry et al., 2000; Petrides and Pandya, 2007). Projections from FPC have also been shown to terminate in the rostroventral portion of the putamen (Petrides and Pandya, 2007). These projections overlap the projection zones of many other prefrontal regions (Averbeck et al., 2014), particularly orbitofrontal cortex, implicating cross links between striatal inputs from the frontal pole, and other cortical areas might be another means of influencing cognition and action.

The lateral and medial subdivisions of the frontal pole are reciprocally connected to the dlPFC (Barbas et al., 1999; Petrides and Pandya, 2007; Markov et al., 2014; Orr et al., 2015). Using methods to trace the efferent and afferent connectivity of FPC in macaques, projections from the frontal pole to dlPFC are clustered throughout Area 46 (Petrides and Pandya, 2007), whereas dlPFC inputs to the FPC mainly originate from the rostral and dorsal sector of Area 46 (Barbas et al., 1999). It has been noted that these connections are less prominent in the marmoset (Burman et al., 2011b). One additional feature that clearly differentiates FPC from other granular PFC regions, particularly Areas 9/46, is the lack of connectivity between Area 10 and parietal cortex, which is observed in marmosets (Burman et al., 2011b), macaques (Petrides and Pandya, 2007; Sallet et al., 2013), and humans (Orr et al., 2015). This is in stark contrast to dense reciprocal connectivity between the dlPFC and the parietal cortex. One exception is anterolateral FPC in humans, which exhibits unique resting-state functional connectivity with lateral intraparietal cortex (Sallet et al., 2013; Neubert et al., 2014). Because this connectivity profile bears more resemblance to resting-state functional connectivity profiles of Area 46 in macaques, an otherwise untested functional homology has been proposed between Area 46 in macaques and anterolateral FPC in humans.

While pathway tracing and neuroimaging studies in nonhuman primates and humans have characterized the key corticocortical and subcortical connections of the FPC, an important next step to take is developing a more detailed understanding of how connections between the frontal pole and other brain regions are structured and impact neural function. Consider the density of the connections between the FPC and two hubs of the motivational brain, the ACC and amygdala. The dense reciprocal connectivity between the ACC and FPC compared with the sparse connectivity between the amygdala and FPC suggests that these distinct circuits might contribute differently in goal-directed action and cognition. For example, we know from neuroimaging studies that the ACC and the amygdala exhibit differential encoding of key value computations that are also encoded in FPC and that enable flexible reinforcement learning and decision-making (Hogeveen et al., 2022). An open question that we will address in our symposium (see talk by Medalla at Neuroscience 2022) is how the

synaptic structure and specialization of FPC influence the cognitive computations and operations it supports. Future work focusing on the molecular and proteomic profiles of FPC neurons and their connections will pave the way in thinking about the FPC as part of a broader neural network enabling goal-directed exploratory behaviors and help unravel the role of specific cell types in future oriented goal-directed cognition and action.

Consequences of FPC lesions in humans and monkeys

What are the functional contributions of FPC to goal-directed cognition and action? At first glance, evidence from humans and monkeys with FPC lesions seems to provide a relatively straightforward answer: not much. Human patients with FPC lesions demonstrate typical performance on IQ tests, and on many gold-standard neuropsychology tasks sensitive to frontal lobe damage (Shallice and Burgess, 1991; Goel and Grafman, 2000; Uretzky and Gilboa, 2010). Similarly, monkeys with FPC lesions are able to flexibly respond to rule reversals during the Wisconsin Card Sorting Test (WCST), a critical assay of cognitive flexibility that is often impaired following damage to more caudal prefrontal regions (Mansouri et al., 2015). Looking closer, despite reasonably intact general cognitive functioning, patients with FPC lesions demonstrate disorganized behavior that can significantly disrupt functional outcomes in everyday life (Eslinger and Damasio, 1985; Shallice and Burgess, 1991). These patients also demonstrate clear deficits on complex, nonstandard neuropsychological tasks that require abstract reasoning, problem-solving, or multitasking/cognitive branching (Dreher et al., 2008; Roca et al., 2010). Similarly, monkeys with ablation lesions of FPC, despite generally intact WCST performance, demonstrate specific aberrations in their ability to explore the value of alternative goals to adjust future redistribution of executive control resources (Mansouri et al., 2015). FPC-lesioned monkeys also show deficits in rapid learning, possibly because of impaired exploration of interactions between objects and events (Boschin et al., 2015). Primate lesion studies therefore indicate that FPC's functional contributions to goal-directed cognition and action are complex and nuanced. Neuroimaging and neurophysiology experiments in non–brain-injured subjects will therefore be critical for further evaluating hypotheses regarding the content and timing of FPC function in primates.

Noninvasive and invasive recordings of FPC function

Human FPC has been implicated across a wide range of cognitive tasks using fMRI. Task-related changes in FPC activation occur during analogical reasoning (Green et al., 2006), prospection (Burgess et al., 2003), cognitive branching/multitasking (Koechlin et al., 1999; Braver and Bongiolatti, 2002), value-based decision-making (Daw et al., 2006; Boorman et al., 2009, 2011; Domenech and Koechlin, 2015; Hogeveen et al., 2022), and metacognition (Mazor et al., 2020, 2022; Soutschek et al., 2021). This has led to several integrative perspectives on putative FPC function in humans (Ramnani and Owen, 2004; Burgess et al., 2007; Koechlin and Hyafil, 2007; Badre, 2008; Botvinick, 2008; Badre and D'Esposito, 2009; Badre and Nee, 2018; Badre and Desrochers, 2019). Across these perspectives, FPC is thought to be involved in tasks that require the control of cognition and action in response to two or more competing goals that are organized either hierarchically (e.g., multitasking studies involving a superordinate goal above multiple competing subgoals) (Braver and Bongiolatti, 2002), or in time (e.g., as in complex sequential performance tasks) (Desrochers et al., 2015). Sequence monitoring studies have been especially consistent in revealing a role for parametric changes in the BOLD response of lateral FPC (i.e., "ramping") during the control of temporally extended behaviors that integrate task-relevant motivational signals (Desrochers et al., 2019; McKim and Desrochers, 2022). At the network level, learning hierarchical task structures to support cognitive control likely involves changes in connectivity between FPC and medial temporal or subcortical regions (van Holstein et al., 2018; Theves et al., 2021). Despite having a reasonable understanding of the genre of hierarchical and sequential control tasks that recruit primate FPC, there is little current understanding of the specific neuronal computations that take place in this region, and when those computations are implemented relative to ongoing goal-directed cognition and action.

The first electrophysiological recordings from primate FPC during a strategic decision-making task revealed a fantastically simple neural coding scheme in this region: task-related FPC neurons encoded goals at the time of feedback and nothing else (Tsujimoto et al., 2010). Specifically, the decision-making task used by Tsujimoto et al. (2010) comprised monkeys seeing a cue indicating their upcoming goal is either the same or shifted relative to the previous trial. Then, after a delay period, they executed a saccade that was either to the same target or the alternative target compared with the previous trial, respectively. Task-related FPC neurons were identified that were goal-selective (i.e., encoded one target or the other), and activity differences between these goal-selective neurons were only distinguishable at the moment of feedback (i.e., after the goal had been achieved). Tsujimoto et al. (2010) integrated these findings with the existing literature on human and monkey FPC to suggest that this region plays a role in a distinct form of credit-assignment they termed "retrospective monitoring." In this view, FPC neurons merge current schematic or "synthetic" goals (i.e., not directly related to a cue or sensory event, but derived from abstract knowledge of the task structure) with a memory for the previous goal, and evaluate each goal based on specific behavioral outcomes. This retrospective monitoring mechanism would enable humans and other primates to manage hierarchical or sequential control tasks, by providing critical feedforward inputs to other, more caudal prefrontal subregions that implement the "in-the-moment" control of cognition and action (Tsujimoto et al., 2011).

This role of FPC in retrospective monitoring may explain its involvement in managing competing goals during value-based decision-making. A compelling series of studies on the neural correlates of counterfactual choice option encoding suggested the FPC is particularly sensitive to the value of unchosen/alternative options during decision-making, updating this signal at the time of feedback based on counterfactual prediction errors (Boorman et al., 2009; Boorman et al., 2011). An FPC representation of the value of counterfactual options would be critical for enabling primates to engage in highly sophisticated decision policies, which can temporarily defer an overarching value maximization goal while exploring alternatives in the immediate term. This function of FPC is readily apparent as participants attempt to maximize immediate- and future-expected value during explore-exploit decision-making. Explore-exploit decisions refer to the ubiquitous trade-off humans and other animals face when deciding whether to explore a novel option with an unknown value (i.e., providing the opportunity to discover a new favorite) or exploit a familiar choice option where the immediate expected value is known. In such situations, FPC encodes when exploration is most beneficial to maximize

relative future value (see Hogeveen talk at Neuroscience 2022) and minimize uncertainty in the task set (Badre et al., 2012). The FPC might be involved in adjusting the balance between exploitation and exploration of alternative goals and therefore support cognitive flexibility and foraging behavior in a changing environment (Mansouri et al., 2017). A causal role of human FPC in exploration has been evidenced by studies using noninvasive brain stimulation (Beharelle et al., 2015; Zajkowski et al., 2017). In monkeys, explore-exploit goals are decodable from caudal prefrontal neurons close to the time of choice, whereas more rostral neurons encode those goals closer to the time of feedback (Tang et al., 2022). The percentage of neurons that encode goals to explore or exploit also follows a caudo-rostral organization in lateral PFC. Dense encoding of goal information is observed in caudal subregions, whereas more rostral subregions demonstrate sparse encoding (Tang et al., 2022). Sparse encoding of goal information at the time of feedback in FPC is congruent with the idea that this region encodes abstract information that can be used flexibly to optimize goal-directed cognition and action (Botvinick, 2008).

Flexible goal encoding in FPC is further evidenced by this region's involvement in WCST performance in monkeys. In the standard WCST, monkeys learn to select the appropriate rule (match shape vs match color) through trial-and-error learning, and the rule is reversed once the monkey reaches a prespecified performance criterion. Monkeys with focal FPC lesions perform indistinguishably to controls with respect to the number of successful reversals made during a task run of this standard WCST but demonstrate increased conflict-induced behavioral adjustments in a conflict-modulated version of the WCST [i.e., heightened levels of conflict adaptation, which might indicate tendency for exploitation of the current task (resolving the conflict) in the absence of exploratory drive in frontopolar-lesioned monkeys] (Mansouri et al., 2015). Recent computational modeling and electrophysiological recordings collected during a version of the standard WCST task in monkeys suggest that the animals weigh the potential value of exploiting the current rule versus exploring the counterfactual rule to flexibly adapt behavior on each trial, and that these rules can be decoded from FPC neuronal signals in the γ frequency range at distinct times relative to other prefrontal subregions (see Ainsworth and Galeazzi talks at Neuroscience 2022). Collectively, across counterfactual choice, explore-exploit, and WCST paradigms, the FPC computes the value of competing goals at the time of outcome to shape abstract policies that guide future goal-directed cognition and action (see Mansouri talk at Neuroscience 2022) (Mansouri et al., 2017).

Clinical significance of FPC neuromodulation

Aberrant FPC function has been observed in a number of clinical groups. For example, FPC is involved in abstract goal-directed emotion regulation following treatment for post-traumatic stress disorder (Fonzo et al., 2017), demonstrates atypical corticocortical connectivity in patients with treatment-resistant major depression (Fettes et al., 2018), and has recently been identified as a central node in a brain network causally related to substance addiction (Joutsa et al., 2022). While further neurocomputational work is needed to understand the role of FPC across these distinct brain disorders, each of them likely involves a disruption in the flexible control of cognition and action according to hierarchically or sequentially organized goals. Accordingly, FPC is a vital target for neuromodulatory treatment with transcranial magnetic stimulation (TMS) with transdiagnostic clinical relevance (see Hanlon talk at Neuroscience 2022) (Hanlon et al., 2019). This is a particularly exciting approach in light of recent studies suggesting that the network-level effects of FPC neuromodulation with TMS extend to motivational brain regions, including the striatum (van Holstein et al., 2018). As a caveat, FPC neuromodulation with TMS can often induce modest or null behavioral effects on tasks requiring hierarchical cognitive control (e.g., van Holstein et al., 2018; Nee, 2021). Therefore, additional studies testing "online" stimulation (i.e., TMS delivered during task performance) (Silvanto et al., 2008) and/or higher TMS doses (McCalley et al., 2021) are vital to help to optimize the parameter space for future FPC neuromodulation trials.

Forward progress on the forward frontal fields

Why has our understanding of FPC anatomy and function lagged behind other subregions of PFC, and how can we advance current understanding of the most forward prefrontal subregion? In nonhuman primate work, the dominant approach has been to examine task-related neuronal spikes in FPC from individual circuits or neurons, which may not be the relevant module for understanding FPC. Instead, FPC might utilize sparse, abstract representations that necessitate population-level neural encoding analyses using technologies that enable simultaneous recordings of neural ensembles, or whole-brain noninvasive imaging approaches (e.g. fMRI). But historically in cognitive neuroscience, we have relied on standardized tasks that are built on a foundation of interrogating frontal lobe function broadly, using simple psychological subtraction logic to assay the neural correlates of working memory load (e.g., 2 vs 0 back), response inhibition (e.g., stop vs go), set-shifting (e.g., stay versus shift), etc. Given that these conventional contrasts often fail to identify task-related changes in FPC, there is a need for novel tasks that probe goal-directed cognitions and actions that rely on estimation of nonobservable future states, as in hierarchical or sequential cognitive control tasks (Badre and Nee, 2018; Badre and Desrochers, 2019), or when one is required to maintain information about alternative choices during motivated decision-making (Boorman et al., 2009; Mansouri et al., 2017; Hogeveen et al., 2022). In parallel, these tasks should be designed alongside new and innovative computational model-based approaches for quantifying latent neuronal signals (Vyas et al., 2020; Ebitz and Hayden 2021) that may more closely reflect the information encoded in FPC, rather than correlating neuronal responses with conventional neuropsychological behavioral assays (e.g., reaction time, accuracy, and d'). These efforts, paired with more modern approaches to interrogating the basic neurobiology of this distinct cytoarchitectonic region, across primate species, should fast-forward our knowledge of how the apex of the forward frontal fields (Wise, 2008) contributes to goal-directed cognition and action.

References

Ainsworth M, Wu Z, Browncross H, Mitchell AS, Bell AH, Buckley MJ (2022) Frontopolar cortex shapes brain network structure across prefrontal and posterior cingulate cortex. Prog Neurobiol 217:102314.

Averbeck BB, Lehman J, Jacobson M, Haber SN (2014) Estimates of projection overlap and zones of convergence within frontal-striatal circuits. J Neurosci 34:9497–9505.

Badre D (2008) Cognitive control, hierarchy, and the rostro–caudal organization of the frontal lobes. Trends Cogn Sci 12:193–200.

Badre D, D'Esposito M (2009) Is the rostro-caudal axis of the frontal lobe hierarchical? Nat Rev Neurosci 10:659–669.

Badre D, Desrochers TM (2019) Hierarchical cognitive control and the frontal lobes. Handb Clin Neurol 163:165–177.

Badre D, Nee DE (2018) Frontal cortex and the hierarchical control of behavior. Trends Cogn Sci 22:170–188.
Badre D, Doll BB, Long NM, Frank MJ (2012) Rostrolateral prefrontal cortex and individual differences in uncertainty-driven exploration. Neuron 73:595–607.
Bakken TE, et al. (2021) Comparative cellular analysis of motor cortex in human, marmoset and mouse. Nature 598:111–119.
Barbas H, Pandya DN (1989) Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol 286:111–119.
Barbas H, Ghashghaei H, Dombrowski SM, Rempel-Clower NL (1999) Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. J Comp Neurol 410:343–367.
Beharelle AR, Polanía R, Hare TA, Ruff CC (2015) Transcranial stimulation over frontopolar cortex elucidates the choice attributes and neural mechanisms used to resolve exploration–exploitation trade-offs. J Neurosci 35:14544–14556.
Berger B, Trottier S, Verney C, Gaspar P, Alvarez C (1988) Regional and laminar distribution of the dopamine and serotonin innervation in the macaque cerebral cortex: a radioautographic study. J Comp Neurol 273:99–119.
Boorman ED, Behrens TE, Woolrich MW, Rushworth MF (2009) How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. Neuron 62:733–743.
Boorman ED, Behrens TE, Rushworth MF (2011) Counterfactual choice and learning in a neural network centered on human lateral frontopolar cortex. PLoS Biol 9:e1001093.
Boschin EA, Piekema C, Buckley MJ (2015) Essential functions of primate frontopolar cortex in cognition. Proc Natl Acad Sci USA 112:E1020–E1027.
Botvinick MM (2008) Hierarchical models of behavior and prefrontal function. Trends Cogn Sci 12:201–208.
Braver TS, Bongiolatti SR (2002) The role of frontopolar cortex in subgoal processing during working memory. Neuroimage 15:523–536.
Burgess PW, Dumontheil I, Gilbert SJ (2007) The gateway hypothesis of rostral prefrontal cortex (area 10) function. Trends Cogn Sci 11:290–298.
Burgess PW, Scott SK, Frith CD (2003) The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. Neuropsychologia 41:906–918.
Burman KJ, Reser DH, Richardson KE, Gaulke H, Worthy KH, Rosa MG (2011a) Subcortical projections to the frontal pole in the marmoset monkey. Eur J Neurosci 34:303–319.
Burman KJ, Reser DH, Yu HH, Rosa MG (2011b) Cortical input to the frontal pole of the marmoset monkey. Cereb Cortex 21:1712–1737.
Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ (2006) Cortical substrates for exploratory decisions in humans. Nature 441:876–879.
Desrochers TM, Chatham CH, Badre D (2015) The necessity of rostrolateral prefrontal cortex for higher-level sequential behavior. Neuron 87:1357–1368.
Desrochers TM, Collins AG, Badre D (2019) Sequential control underlies robust ramping dynamics in the rostrolateral prefrontal cortex. J Neurosci 39:1471–1483.
Dombrowski SM, Hilgetag CC, Barbas H (2001) Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. Cereb Cortex 11:975–988.
Domenech P, Koechlin E (2015) Executive control and decision-making in the prefrontal cortex. Curr Opin Behav Sci 1:101–106.
Dreher JC, Koechlin E, Tierney M, Grafman J (2008) Damage to the frontopolar cortex is associated with impaired multitasking. PLoS One 3:e3227.
Ebitz RB, Hayden BY (2021) The population doctrine in cognitive neuroscience. Neuron 109:3055–3068.
Eslinger PJ, Damasio AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35:1731–1741.
Ferry AT, Ongür D, An X, Price JL (2000) Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. J Comp Neurol 425:447–470.
Fettes PW, et al. (2018) Abnormal functional connectivity of frontopolar subregions in treatment-nonresponsive major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 3:337–347.
Fonzo GA, et al. (2017) Selective effects of psychotherapy on frontopolar cortical function in PTSD. Am J Psychiatry 174:1175–1184.
Goel V, Grafman J (2000) Role of the right prefrontal cortex in ill-structured planning. Cogn Neuropsychol 17:415–436.
Green AE, Fugelsang JA, Kraemer DJ, Shamosh NA, Dunbar KN (2006) Frontopolar cortex mediates abstract integration in analogy. Brain Res 1096:125–137.
Hanlon CA, Philip NS, Price RB, Bickel WK, Downar J (2019) A case for the frontal pole as an empirically derived neuromodulation treatment target. Biol Psychiatry 85:e13–e14.
Hogeveen J, Mullins TS, Romero JD, Eversole E, Rogge-Obando K, Mayer AR, Costa VD (2022) The neurocomputational bases of explore-exploit decision-making. Neuron 110:1869–1879.e5.
Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, Jacobs J, Ford K, Wainwright M, Treml M (2001) Regional dendritic and spine variation in human cerebral cortex: a quantitative Golgi study. Cereb Cortex 11:558–571.
Joutsa J, et al. (2022) Brain lesions disrupting addiction map to a common human brain circuit. Nat Med 28:1249–1255.
Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J (1999) The role of the anterior prefrontal cortex in human cognition. Nature 399:148–151.
Koechlin E, Hyafil A (2007) Anterior prefrontal function and the limits of human decision-making. Science 318:594–598.
Lewis DA (1991) Distribution of choline acetyltransferase-immunoreactive axons in monkey frontal cortex. Neuroscience 40:363–374.
Liu H, Qin W, Li W, Fan L, Wang J, Jiang T, Yu C (2013) Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. J Neurosci 33:6782–6790.
Mansouri FA, Buckley MJ, Mahboubi M, Tanaka K (2015) Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. Proc Natl Acad Sci USA 112:E3940–E3949.
Mansouri FA, Koechlin E, Rosa MG, Buckley MJ (2017) Managing competing goals: a key role for the frontopolar cortex. Nat Rev Neurosci 18:645–657.
Markov NT, et al. (2014) A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cerebral Cortex 24:17–36.
Mazor M, Friston KJ, Fleming SM (2020) Distinct neural contributions to metacognition for detecting, but not discriminating visual stimuli. Elife 9:e53900.
Mazor M, Dijkstra N, Fleming SM (2022) Dissociating the neural correlates of subjective visibility from those of decision confidence. J Neurosci 42:2562–2569.
McCalley DM, Lench DH, Doolittle JD, Imperatore JP, Hoffman M, Hanlon CA (2021) Determining the optimal pulse number for theta burst induced change in cortical excitability. Sci Rep 11:8726.
McKim TH, Desrochers TM (2022) Reward value enhances sequence monitoring ramping dynamics as ending rewards approach in the rostrolateral prefrontal cortex. eNeuro 9:ENEURO.0003-22.2022.
Medalla M, Barbas H (2010) Anterior cingulate synapses in prefrontal areas 10 and 46 suggest differential influence in cognitive control. J Neurosci 30:16068–16081.
Medalla M, Barbas H (2014) Specialized prefrontal 'auditory fields': organization of primate prefrontal-temporal pathways. Front Neurosci 8:77.
Mitz AR, Tsujimoto S, Maclarty AJ, Wise SP (2009) A method for recording single-cell activity in the frontal-pole cortex of macaque monkeys. J Neurosci Methods 177:60–66.
Nee DE (2021) Integrative frontal-parietal dynamics supporting cognitive control. Elife 10:e57244.
Neubert FX, Mars RB, Thomas AG, Sallet J, Rushworth MF (2014) Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. Neuron 81:700–713.
Ongür D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol 460:425–449.
Orr JM, Smolker HR, Banich MT (2015) Organization of the human frontal pole revealed by large-scale DTI-based connectivity: implications for control of behavior. PLoS One 10:e0124797.
Petrides M, Pandya DN (2007) Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. J Neurosci 27:11573–11586.
Petrides M, Tomaiuolo F, Yeterian EH, Pandya DN (2012) The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains. Cortex 48:46–57.
Porrino LJ, Crane AM, Goldman-Rakic PS (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. J Comp Neurol 198:121–136.

Preuss TM, Goldman-Rakic PS (1991) Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate Galago and the anthropoid primate Macaca. J Comp Neurol 310:429–474.

Ramnani N, Owen AM (2004) Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat Rev Neurosci 5:184–194.

Roca M, Parr A, Thompson R, Woolgar A, Torralva T, Antoun N, Manes F, Duncan J (2010) Executive function and fluid intelligence after frontal lobe lesions. Brain 133:234–247.

Sallet J, Mars RB, Noonan MP, Neubert FX, Jbabdi S, O'Reilly JX, Filippini N, Thomas AG, Rushworth MF (2013) The organization of dorsal frontal cortex in humans and macaques. J Neurosci 33:12255–12274.

Scala F, Kobak D, Bernabucci M, Bernaerts Y, Cadwell CR, Castro JR, Hartmanis L, Jiang X, Laturnus S, Miranda E, Mulherkar S, Tan ZH, Yao Z, Zeng H, Sandberg R, Berens P, Tolias AS (2021) Phenotypic variation of transcriptomic cell types in mouse motor cortex. Nature 598:144–150.

Semendeferi K, Armstrong E, Schleicher A, Zilles K, Van Hoesen GW (2001) Prefrontal cortex in humans and apes: a comparative study of area 10. Am J Phys Anthropol 114:224–241.

Shallice T, Burgess PW (1991) Deficits in strategy application following frontal lobe damage in man. Brain 114:727–741.

Silvanto J, Muggleton N, Walsh V (2008) State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 12:447–454.

Soutschek A, Moisa M, Ruff CC, Tobler PN (2021) Frontopolar theta oscillations link metacognition with prospective decision making. Nat Commun 12:3943.

Tang H, Costa VD, Bartolo R, Averbeck BB (2022) Differential coding of goals and actions in ventral and dorsal corticostriatal circuits during goal-directed behavior. Cell Rep 38:110198.

Theves S, Neville DA, Fernández G, Doeller CF (2021) Learning and representation of hierarchical concepts in hippocampus and prefrontal cortex. J Neurosci 41:7675–7686.

Tsujimoto S, Genovesio A, Wise SP (2010) Evaluating self-generated decisions in frontal pole cortex of monkeys. Nat Neurosci 13:120–126.

Tsujimoto S, Genovesio A, Wise SP (2011) Frontal pole cortex: encoding ends at the end of the endbrain. Trends Cogn Sci 15:169–176.

Uretzky S, Gilboa A (2010) Knowing your lines but missing your cue: rostral prefrontal lesions impair prospective memory cue detection, but not action-intention superiority. J Cogn Neurosci 22:2745–2757.

van Holstein M, Froböse MI, O'Shea J, Aarts E, Cools R (2018) Controlling striatal function via anterior frontal cortex stimulation. Sci Rep 8:3312.

Vyas S, Golub MD, Sussillo D, Shenoy KV (2020) Computation through neural population dynamics. Annu Rev Neurosci 43:249–275.

Walker AE (1940) A cytoarchitectural study of the prefrontal area of the macaque monkey. J Comp Neurol 73:59–86.

Williams SM, Goldman-Rakic PS (1993) Characterization of the dopaminergic innervation of the primate frontal cortex using a dopamine-specific antibody. Cereb Cortex 3:199–222.

Wise SP (2008) Forward frontal fields: phylogeny and fundamental function. Trends in neurosciences 31:599–608.

Yacoub E, Grier MD, Auerbach EJ, Lagore RL, Harel N, Adriany G, Zilverstand A, Hayden BY, Heilbronner SR, Uğurbil K, Zimmermann J (2020) Ultra-high field (10.5 T) resting state fMRI in the macaque. Neuroimage 223:117349.

Zajkowski WK, Kossut M, Wilson RC (2017) A causal role for right frontopolar cortex in directed, but not random, exploration. Elife 6:e27430.