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The What and How of Prefrontal Cortical Organization

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Abstract

How is the prefrontal cortex (PFC) organized such that it is capable of making people more flexible and in control of their behavior? Is there any systematic organization across the many diverse areas that comprise the PFC, or is it uniquely adaptive such that no fixed representation structure can develop? Going against the current tide, this paper argues that there is indeed a systematic organization across PFC areas, with an important functional distinction between ventral and dorsal regions characterized as processing *What* vs. *How* information, respectively. This distinction has implications for the rostro-caudal and medial-lateral axes of organization as well. The resulting large-scale functional map of PFC may prove useful in integrating diverse data, and generating novel predictions.

The What-How, Abstraction, Cold/Hot (WHACH) Model of PFC Organization

The prefrontal cortex (PFC) is known to be important for cognitive control, and enabling behavior to be at once flexible yet task-focused [1,2]. One of the principal means of understanding how it achieves these remarkable feats is by characterizing the nature of its underlying neural representations. The central question addressed here is: are PFC representations systematically organized across areas, and if so, what is the nature of this organization? Although many have attempted to answer this question in the affirmative, with a variety of different organizational schemes, the broadest consensus in the field seems to be that, if there is any organization there, it is extremely difficult to characterize. Indeed, some go so far as to argue that PFC should *not* exhibit any kind of systematic organization, by virtue of its very nature [3,4]. (BOX 1)

However, there are also strong reasons to believe that the PFC should have some kind of stable systematic organization (BOX 1), and considerable data appear to be consistent with a specific proposal advanced here: the What-How, Abstraction, Cold/Hot (WHACH) model (Figure 1). This model is organized along 3 major axes: ventral vs. dorsal (*What* vs. *How*), rostral vs. caudal (*Abstraction*), and lateral vs. medial (*Cold* vs. *Hot*). The ventral vs. dorsal distinction is the primary focus of the paper. The key idea is to bring the *What* vs. *How* distinction between ventral and dorsal pathways in posterior cortex, developed by Goodale & Milner [5], forward into the PFC in terms of ventrolateral (VLPFC) vs. dorsolateral (DLPFC). The characterizations of the other two dimensions have been extensively discussed in the literature and are not themselves novel, but they interact in potentially interesting ways with the first dimension, and are discussed in that context.

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The *What vs. How* idea is developed below, and then related to the two other axes of PFC organization in subsequent sections.

What vs. How

There are two broad frameworks for understanding the ventral vs. dorsal organization of the *posterior* cortex: the *What vs. Where* distinction advanced by Ungerleider & Mishkin [6], and the later *What vs. How* model of Goodale & Milner [5]. The key distinction between these two frameworks is in characterizing the role of the dorsal pathway (principally the parietal cortex) — is it primarily about spatial representations (*Where*) or is it primarily about transforming perception into action (*How*)? Some of the data motivating the *How* model showed that people with ventral pathway damage could not describe shape information (e.g., the angle of a slot that was rotated in different ways), but could nevertheless clearly express shape knowledge when it was used to constrain their actions (e.g., putting a card into the rotated slot) [5].

Thus, Goodale & Milner's key insight was that shape information can be processed by both pathways, and the critical distinction is how the information is used — the dorsal pathway extracts visual signals relevant for driving motor behavior (*perception for action*), while the ventral pathway extracts information relevant for identification and other forms of semantic knowledge. Note that spatial information is often very relevant for guiding motor behavior, and this may explain the prevalence of *Where* information in the dorsal pathway, such that the *How* model can be considered a generalization of the *Where* model.

The notion of taking a ventral vs. dorsal distinction from posterior cortex forward into the PFC was pioneered by Goldman-Rakic and others, in the context of the original *What vs. Where* model [7,8,9]. A significant motivation for doing so is that the appropriate ventral-to-ventral and dorsal-to-dorsal connectivity patterns between PFC and corresponding posterior cortical areas are predominant [10,11,9] (Figure 2). But the evidence in support of this *What vs. Where* distinction in PFC, in both monkeys and humans, has not been very consistent [12,13].

The main claim of this paper is that Goldman-Rakic's overall strategy was correct, but that the characterization of posterior cortex she used was too narrow: if you instead take the *What vs. How* characterization of ventral vs. dorsal pathways forward into the PFC, it provides a much more compelling fit with the available data. Specifically, the proposal is that VLPFC (Brodmann areas 44, 45, 47, 12 (denoted as *What** where the * indicates the cognitive control and robust active maintenance abilities associated with the PFC) provides a cognitive control system for ventral *What* pathway processing, and DLPFC (Brodmann areas 8, 9, 46, *How**) provides cognitive control for the dorsal pathway. This idea has not been explored very extensively — a thorough literature search revealed only one relatively brief discussion of this specific idea [14], and another paper discusses the Goodale & Milner ideas more broadly in relation to PFC [15].

What about What?

The first obstacle for the *What** vs. *How** model is that several of the arguments against the *What/Where* idea in PFC were focused on the shared *What* aspect. For example, Miller and colleagues showed that monkeys trained on tasks that integrate both *What* and *Where* information had highly overlapping distributions of *What* and *Where* cells over a large area of lateral PFC [13]. Romanski [9] provides a nice discussion of this and other relevant data, and argues that a major part of the problem is that the VLPFC in the macaque that actually interconnects with the ventral posterior cortex is quite far ventral relative to where many relevant neural recordings took place. Furthermore, many of these recordings include the

region between the clearly-defined VLPFC and DLPFC areas, corresponding roughly to inferior frontal junction (IFJ) in humans, which may represent a more polymorphous bridging region between What and How pathways [16]. The *What** vs. *How** distinction should definitely be considered more of a continuum. Also, the posterior aspect of VLPFC (e.g., along the 44/6 border) is a grey area, because adjacent motor areas (organized somatotopically) can drive very different representations, e.g., a spatial eye field map [17].

Human neuroimaging studies of the VLPFC provide ample evidence to support a clear *What** role. Numerous studies have shown that VLPFC plays a critical role in guiding the selection and retrieval of semantic/linguistic knowledge that is almost certainly encoded in the inferotemporal cortex (i.e., ventral What posterior cortex) [18,19,20]. From a computational perspective, the most straightforward account of this data involves the active maintenance of stimulus information in VLPFC, which produces a top-down biasing effect to drive selection and retrieval dynamics in posterior cortex [2,21].

Most of the above-mentioned VLPFC data comes from studies with predominant left hemisphere activation — what about the right VLPFC? This area has been characterized as important for response inhibition [22], which would seem at odds with the *What** account. However, recent data suggests that this area may be more important for monitoring for the sensory signals that indicate when to inhibit, rather than the inhibitory process itself [23]. This account is highly consistent with the *What** model for VLPFC. Perhaps the lateralization differences have more to do with the left hemisphere being dominant for the primary task, while the right takes on secondary tasks (as discussed more later).

How about How?

The advantage of the DLPFC *How** side of the story relative to the earlier *Where** account is that it encompasses a much broader range of cognitive processing — one should expect to see DLPFC activation whenever the parietal cortex requires extra cognitive control (working memory, top-down biasing, etc) to carry out the processing of sensory information to guide action outputs. For example, studies show that parietal cortex plays an important role in guiding encoding and retrieval of memories [24], representing number and mathematical transformations [25], and encoding various forms of relationships (spatial and more abstract) [26]. Thus, the definition of *perception for action* must include a broad range of more abstract “cognitive” actions such as memory retrieval and mathematical transformations, in addition to more concrete motor actions. As discussed later, this account of DLPFC aligns well with Petrides’ theory [27].

The relevant DLPFC data is generally consistent with the *How** view. Starting at the most posterior end of DLPFC, areas 6 (which is properly not prefrontal, just frontal) and 8 have been shown to encode simple action rules [28,29,30], and also spatial maps associated with saccade planning and spatial working memory [17]. Moving somewhat more anterior, monkey neurophysiology data from studies of temporal order processing show that VLPFC neurons respond selectively to object identity, while DLPFC neurons respond selectively to sequential order [31,32]. Sequential order is a good example of higher-level *How* pathway information — it is important for coordinating motor commands, and likely involves number-line like representations in parietal cortex to organize order information [33]. An even more abstract example of DLPFC task-rule encoding comes from neurons that encoded a repeat-stay/change-shift strategy, independent of specific stimuli or actions involved [34]. More generally, DLPFC regions are widely reported for action selection and behavioral rule performance tasks [35,36,37,38,39], consistent with a role as a top-down bias on parietal *How* processing pathways (and all of these studies find strong co-activation between DLPFC and parietal cortex).

Direct Dorsal/Ventral Contrasts

A major source of data on PFC functional organization is the Wager and Smith [12] meta-analysis of neuroimaging studies. Although they conclude that the What/Where model is inconsistent with the data, a careful re-examination of their findings in light of the What/How framework suggests that it may be quite consistent (Figure 3). Specifically, areas 44 and 45 (VLPFC) showed *exclusively* object and verbal encoding (with appropriate right-left lateralization), with *no* spatial sensitivity. While these differences did not reach statistical criterion, there is clearly a strong numerical trend across a large number of studies that is very consistent with a *What** encoding in VLPFC. Conversely, when studies were sorted according to various processing-oriented categories, DLPFC areas 6, 8 and 9 showed significant activation differences, but VLPFC areas did not. This is consistent with a *How** role for DLPFC. These same DLPFC areas did not exhibit strong content selectivity according to object, verbal or spatial information. This result is damaging for a *Where** account of DLPFC function, but not for a *How** account — a critical feature of the *How** framework is that dorsal pathway representations are specifically *not* thought to be organized according to stimulus input categories, and instead are best categorized in terms of transforming a wide range of sensory inputs into appropriate motor outputs. Consistent with this view, they also found parietal cortex activations for spatial and non-spatial “executive” tasks, whereas IT activations were more consistently for visual object based tasks.

A recent study on response vs. semantic selection difficulty manipulations provides additional converging evidence for dorsal vs. ventral PFC involvement [40]. They found that DLPFC was modulated by response, but not semantic, selection difficulty, and vice-versa for VLPFC, exactly as would be predicted by the *What* vs. *How* model. Intrinsic functional connectivity analyses also reveal distinct dorsal vs. ventral fronto-parietal networks [41].

Taken together, these data are consistent with the *What** vs. *How** distinction between VLPFC and DLPFC, which in turn is based on the predominant connectivity of these regions with corresponding ventral and dorsal pathways in posterior cortex. In the next two sections we explore how this *What** vs. *How** account might interact with other widely-discussed axes of PFC functional organization: a rostral-caudal gradient of abstraction, and a lateral-medial *Cold* vs. *Hot* distinction.

The Rostral-Caudal Axis

Two predominant ideas about the rostral-caudal organization of PFC are in terms of gradients of *abstraction* [30,42,43,44,45] or *rule complexity* [46,47,48,49]. According to the abstraction idea, more anterior PFC areas encode more abstract information, in terms of having broader categories (e.g., “color” vs. “red” vs. “brick red”), or otherwise being more distantly removed from concrete physical objects (e.g., “beauty” vs. “sunset”). In contrast, rule complexity refers to the number of different elements that must be taken into account to generate a task-appropriate response. For example, the rule “hit the left button if the previous stimulus was an A and the current one is an X” requires two items to be integrated (A and X) to determine the response. Interestingly, the abstraction gradient appears to align with the VLPFC *What** domain, in that it response-focused and thus seems to better fit within the DLPFC *How** domain.

Given this alignment, it seems possible that there are actually two parallel rostral-caudal gradients, one within DLPFC organized according to rule-complexity, and another within VLPFC organized according to abstraction. Computational modeling and other work suggests that each of these organizational gradients can emerge from hierarchical

connectivity patterns (where more anterior PFC areas provide contextualization to more posterior PFC areas) [50,27,51,52]. But what about the extant data?

Unfortunately, the relevant fMRI data comes from task paradigms that do not cleanly distinguish between abstraction and rule complexity as characterized above. For example, Badre and D'Esposito [30] describe their hierarchy specifically in terms of abstraction, but their task manipulation includes a strong rule complexity confound (which they acknowledge). Consistent with this confounding of the two factors, their hierarchy crosses over between DLPFC (area 6) for the most concrete response-oriented 1st level, to anterior VLPFC (area 47) for the 3rd level, with the 2nd level being intermediate on the dorsal-ventral axis. Interestingly, a similar but not identical hierarchical pattern was found by Koechlin and colleagues [29], but their 2nd level was more clearly in VLPFC (area 44). Both studies also found activation in fronto-polar PFC (area 10) for the highest level, but this area is not clearly dorsal or ventral in nature, and is thus outside the scope of this paper.

In short, more careful experimental work is needed to determine if the *What* vs. *How* distinction might help to clarify the hierarchical structure of representations across lateral PFC.

The Medial-Lateral Axis

Across the cortex, medial areas tend to be more directly connected to subcortical systems, and play a role in “limbic” or affective/motivational systems, whereas lateral areas tend to be more involved in sensory/motor processing. Thus, it is uncontroversial to characterize the lateral PFC areas (which have been the focus of discussion to this point) as *Cold* cognitive processing, while the medial PFC contains *Hot* emotional and motivational areas. In this context, we again ask if the *What* vs. *How* ventral/dorsal distinction may have some currency. The answer appears to be “yes.”

Considerable animal data suggests that ventral medial PFC (VMPFC) (e.g., orbital frontal cortex, OFC) is specialized for representing the emotional and motivational value of stimuli (i.e., *What*-based processing) [53], while DMPFC areas (including the anterior cingulate cortex, ACC), appear to be important for encoding affective values of actions [54,55]. In human neuroimaging, the specific role of the ACC within DMPFC has been characterized in many different ways, including conflict and error monitoring [56,57]. A way of reconceptualizing these ideas about ACC that is consistent with a putative *Hot-How* control area, is to think of it as providing a motivational cost signal associated with prospective actions that could be taken. If a given action is associated with high levels of conflict or error, then more cognitive effort will be required, or it will not be as likely to be taken. The Brown and Braver model of ACC, where it learns to associate arbitrary task cues with conflict, error, and other difficulty signals, is particularly compatible with this view [58]. Also consistent is recent neuroimaging data from Koechlin and colleagues that shows a relationship between DMPFC regions and corresponding lateral PFC regions, where the DMPFC areas are organized along a parallel hierarchy as discussed in the previous section [59].

In sum, there appears to be a homology in the overall functions of the dorsal and ventral MPFC areas — each forms affective value associations, and these value representations then drive behavior, e.g., to approach positive stimuli and avoid negative ones (VMPFC *What*), and to perform successful, rewarding actions and avoid difficult, risky behaviors (or exert more cognitive control when attempting them) (DMPFC *How*). This account can also help explain the apparent asymmetry between VMPFC and DMPFC value representations, where DMPFC areas seem to have generally more negative value coding (error, conflict, etc — generally the cost of taking an action), while VMPFC are more a mixture of positive and

negative: actions are often not intrinsically rewarding, and generally incur effort and other costs, whereas stimuli are often the end goal driving actions (toward reward and away from punishment).

Relationship to Other Frameworks

The What/How distinction can be related to other prevalent ways of describing the division between ventral and dorsal PFC. For example, Petrides [27] has argued based on a wide range of data that VLPFC is important for “simple working memory” of stimulus information and other “first-order executive functions” such as selection and comparison, whereas DLPFC is important for more complex higher-order information processing operations. This maps well onto the What/How framework, in that PFC executive control over What pathway information is likely to be manifest as apparently simpler functions like active maintenance of sensory stimuli, and top-down biasing to select information in IT cortex. In contrast, PFC executive control over dorsal How processing will appear more complex, involving coordination of motor and cognitive actions over time, and selection of relational, spatial, and mathematical operations encoded in parietal cortex.

A different take on DLPFC vs. VLPFC comes from Corbetta and Shulman [60], who characterize DLPFC as important for endogenous attentional focusing, whereas VLPFC is more exogenously driven. Interestingly, the endogenous cases associated with the DLPFC that they considered involved spatial and motion information that is processed in the dorsal visual pathway, while the exogenous cases were more stimulus-oriented tasks involving low-frequency “oddball” tasks. Thus, their actual data is broadly consistent with the What/How distinction, even if their overall characterization does not obviously map onto it.

The Stuss & Alexander framework [61], based on lesion data, also does not appear at first to be related to the What/How model, but is in fact quite compatible. They argue for a lateralization account, where left lateral PFC is important for “task setting”, while right lateral PFC is important for “monitoring”. Alternatively, one can think of these as reflecting the same basic function (active maintenance of task context and top-down biasing of appropriate processing), but the left hemisphere is more important for the task being currently performed, while the right hemisphere may be more important for maintaining information about other possible tasks that might be relevant at some other point in time (i.e., monitoring; see also Ref. [23] as discussed above). They also argue that medial PFC is responsible for “energization”, which is compatible with the *Hot* role — e.g., dorsal medial PFC areas are important for motivational selection of task-appropriate action plans.

Banich and colleagues [62] have developed a cascade of control model that involves DLPFC (attentional task set), VLPFC (stimulus feature representations), and ACC (response selection and evaluation) — these functions are generally compatible with the *What* vs. *How* model, and we are currently designing experiments to further test the relationship between these frameworks.

Lebedev & Wise [15] discuss the Goodale & Milner framework with a focus on perceptual awareness. Based in part on experimental results showing no clear anatomical dissociation in PFC for cells responsive or not to a visual illusion [63], they conclude that this dorsal vs. ventral distinction does not carry forward as such into the PFC, and is instead more intermixed. Given that they recorded in the bridging area between dorsal and ventral (similar to [13] as discussed earlier), this may be taken as further evidence for intermixing in this area.

Finally, Tanji & Hoshi [32] provide a thorough review of anatomy and functional data regarding ventral vs. dorsal PFC organization, which is highly compatible with What/How

distinction. However, they and others (e.g., [64]) continue to reject the notion that PFC is important for working memory (WM), based on studies showing intact WM following PFC lesions. But such results can instead be accounted for in terms of lingering memory traces in posterior cortical areas, which are sufficient when there are no intervening distractors or other forms of processing, but are otherwise not as robust as PFC-mediated WM representations [65]. In any case, “working memory” has many different meanings to different researchers, so it is clearer to instead use the more precise computationally-explicit terminology of robust active maintenance of neural firing over time, which seems crucial for many PFC functions beyond simple short-term maintenance, including top-down attention, action selection, manipulation, control, etc [2,21].

Conclusion

The proposal outlined above and summarized in Figure 1 constitutes a comprehensive map of the functional properties of the PFC along multiple dimensions: ventral *What** vs. dorsal *How**; anterior *Abstract* vs. posterior *concrete*; lateral *Cold* vs. medial *Hot* (i.e., the WHACH model). The primary *What* vs. *How* distinction seems to have relevance for understanding issues within the other two axes of organization, and thus could represent a productive theoretical framework for integrating a diverse range of empirical data across many different content areas and task domains. We are currently formalizing this framework by developing integrated computational models of dorsal and ventral PFC areas interacting with associated posterior cortical (and basal ganglia) areas, [66]. Many important questions remain (BOX 2), but hopefully future empirical research, guided in part by predictions from computational models, can begin to answer them and test the validity of this overall framework.

Box 1

Dedicated vs. Dynamic PFC Representations

The *adaptive coding* hypothesis offered by John Duncan, building in part on the ideas and work of Earl Miller, suggests that PFC neurons are capable of rapidly adapting to new tasks, and thus explains how the PFC can play such an important role in supporting flexible, task-relevant behavior [3,4]. This hypothesis accounts for the evident adaptability of monkey PFC neurons when trained on new tasks (although such training typically takes a long time), and considerable neuroimaging data showing that many diverse PFC functions activate highly overlapping brain areas [4]. But it also appears incompatible with the idea that the PFC has the kind of systematic long-term organizational structure proposed here.

However, the adaptive coding hypothesis ignores a critical aspect of neural processing: neurons do not communicate using symbols that have intrinsic meaning. Thus, it is not possible for a neuron to rapidly change what it encodes, because it cannot communicate this new representation to other neurons. Instead, meaning in neural networks must be learned over time and in relationship to larger patterns of overall neural activity, which strongly favors stable long-term representations and larger-scale structuring thereof.

Neurons broadcast simple spike impulses, each the same as any other, with at least the majority of the information contained in the firing rate over time [67]. This contrasts strongly with human spoken language, where we have elaborate phonological distinctions that multiply over time to convey words and sentences that have independent meaning. Imagine instead if we could only modulate the volume of our voices, but nothing else: this is how neurons communicate. This volume-based communication is appropriate given that a given neuron is listening to roughly 10,000 other neurons at the

same time: it would be impossible to decode and integrate more complex signals with this level of parallelism.

In effect, neurons operate within a giant social network, where the whole game is to become a reliable source of information that other neurons can learn to trust (Figure I). The meaning of the neural message is all about the *identity of the sender* and the *relationship* of its neural firing to all the others within the network. Receiving neurons gradually learn to respond to reliable patterns of incoming activation, and pass along filtered and transformed versions thereof to other neurons. If a given neuron were to suddenly change its representation, there would be no way for other neurons to interpret its new meaning (its spikes would look the same as ever). They have to learn over time the new relationships between this neuron and the others. This poses a strong constraint on the adaptive coding hypothesis.

There are several alternative ways to account for data supportive of the adaptive coding hypothesis within this framework, including that PFC representations are: (a) highly abstract, and thus encompass many specific tasks; (b) highly context-sensitive, taking on different activation patterns in different tasks or other contexts; (c) strongly modulated by the basal ganglia to maintain different information in a very dynamic manner [2].

Figure I.

Social network analogy for neural communication and learning. In panel (a), the author is in a central node and communicates with various colleagues. Over time, the author has come to learn which people in his network are reliable, what their expertise is, and how to evaluate the kinds of things they might say. Hence, if the social network were to undergo *dynamic reconfiguration* (b), the consequences could be devastating for the author's ability to trust, filter, and otherwise build upon the information coming from the network.

Box 2**Outstanding Questions**

- To what extent does the What/How distinction correctly characterize PFC organization?
- Where exactly are the boundaries between What and How, and how do these pathways interact to produce overall cognitive control?
- Are there two parallel forms of hierarchical organization along the rostro-caudal axis, one within DLPFC and another within VLPFC, or do both dorsal and ventral areas fit within one larger hierarchy?
- Can the *What** model provide a unifying account of both left and right VLPFC, or for example does right VLPFC really have a specific role in response inhibition that cannot be accounted for in terms of monitoring?
- Is left VLPFC engaged for the dominant, focal task, while right VLPFC takes on secondary tasks? Can this be tested using task switching and dual task paradigms?
- Does the medial *Hot* organization of brain mirror the lateral surface (e.g., in terms of a rostral-caudal hierarchy as suggested by Koechlin et al [59]), or does the affective/motivational side have its own separate hierarchy, e.g., a goal hierarchy?
- How do dedicated neural representations support the rapid adaptation phenomena used by Duncan to develop his adaptive coding hypothesis [4] (BOX 1)?

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References

- [1]. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual review of neuroscience* 2001;24:167–202.
- [2]. O'Reilly RC. Biologically based computational models of high-level cognition. *Science (New York, N.Y.)* 2006;314:91–94.
- [3]. Miller EK. The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience* 2000;1:59–65.
- [4]. Duncan J. An adaptive coding model of neural function in prefrontal cortex. *Nature reviews. Neuroscience* 2001;2:820–829.
- [5]. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends in Neurosciences* 1992;15(1):20–25. [PubMed: 1374953]
- [6]. Ungerleider, LG.; Mishkin, M. Two cortical visual systems. In: Ingle, DJ.; Goodale, MA.; Mansfield, RJW., editors. *The Analysis of Visual Behavior*. MIT Press; Cambridge, MA: 1982. p. 549–586.
- [7]. Funahashi S, Chafee MV, Goldman-Rakic PS. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature* 1993;365:753–756. [PubMed: 8413653]
- [8]. Smith E, Jonides J. Storage and executive processes in the frontal lobes. *Science* 1999;283:1657–1661. [PubMed: 10073923]

- [9]. Romanski LM. Domain specificity in the primate prefrontal cortex. *Cognitive, affective & behavioral neuroscience* 2004;4(4):421–429.
- [10]. Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *The European journal of neuroscience* 2002;16(2):291–310. [PubMed: 12169111]
- [11]. Cavada C, Goldman-Rakic PS. Posterior parietal cortex in rhesus monkey: Ii. evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *The Journal of comparative neurology* 1989;287(4):422–445. [PubMed: 2477406]
- [12]. Wager TD, Smith EE. Neuroimaging studies of working memory: A meta-analysis. *Cognitive Affective and Behavioral Neuroscience* 2003;3(4):255–274.
- [13]. Rao SC, Rainer G, Miller EK. Integration of what and where in the primate prefrontal cortex. *Science* 1997;276(5313):821–824. [PubMed: 9115211]
- [14]. Sakagami M, Pan X, Uttl B. Behavioral inhibition and prefrontal cortex in decision-making. *Neural networks* 2006;19(8):1255–1265. [PubMed: 16952442]
- [15]. A. LM, P. WS. Insights into seeing and grasping: distinguishing the neural correlates of perception and action. *Behavioral and cognitive neuroscience reviews* 2002;1(2):108–129. [PubMed: 17715589]
- [16]. Brass M, Derrfuss J, Forstmann B, von Cramon DY. The role of the inferior frontal junction area in cognitive control. *Trends in cognitive sciences* 2005;9(7):314–316. [PubMed: 15927520]
- [17]. Kastner S, DeSimone K, Konen CS, Szczepanski SM, Weiner KS, Schneider KA. Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. *Journal of neurophysiology* 2007;97:3494–3507. [PubMed: 17360822]
- [18]. Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A re-evaluation. *Proceedings of the National Academy of Sciences* 1997;94:14792–14797.
- [19]. Thompson-Schill SL. Neuroimaging studies of semantic memory: inferring “how” from “where”. *Neuropsychologia* 2002;41:280–292. [PubMed: 12457754]
- [20]. Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron* 2001;31:329–338. [PubMed: 11502262]
- [21]. O'Reilly, RC.; Braver, TS.; Cohen, JD. A biologically based computational model of working memory. In: Miyake, A.; Shah, P., editors. *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control*. Cambridge University Press; New York: 1999. p. 375–411.
- [22]. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (mri) and functional mri. *Journal of neuroscience* 2007;27(14):3743–3752. [PubMed: 17409238]
- [23]. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. *NeuroImage* 2010;50:1313–1319. [PubMed: 20056157]
- [24]. Ciaramelli E, Grady CL, Moscovitch M. Top-down and bottom-up attention to memory: a hypothesis (atom) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia* 2008;46:1828–1851. [PubMed: 18471837]
- [25]. Dehaene S, Molko N, Cohen L, Wilson AJ. Arithmetic and the brain. *Current Opinion in Neurobiology* 2004;14(2):218–224. [PubMed: 15082328]
- [26]. Chafee MV, Averbeck BB, Crowe DA. Representing spatial relationships in posterior parietal cortex: single neurons code object-referenced position. *Cerebral cortex* 2007;17(12):2914–2932. [PubMed: 17389630]
- [27]. Petrides M. Lateral prefrontal cortex: architectonic and functional organization. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 2005;360(1456):781–795.
- [28]. Brasted PJ, Wise SP. Comparison of learning-related neuronal activity in the dorsal premotor cortex and striatum. *The European journal of neuroscience* 2004;19(3):721–740. [PubMed: 14984423]
- [29]. Koechlin E, Ody C, Kouneiher F. Neuroscience: The architecture of cognitive control in the human prefrontal cortex. *Science* 2003;324:1181–1184. [PubMed: 14615530]

- [30]. Badre D, D'Esposito M. Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *Journal of cognitive neuroscience* 2007;19:2082–2099. [PubMed: 17892391]
- [31]. Ninokura Y, Mushiaki H, Tanji J. Integration of temporal order and object information in the monkey lateral prefrontal cortex. *Journal of neurophysiology* 2004;91(1):555–560. [PubMed: 12968014]
- [32]. Tanji J, Hoshi E. Role of the lateral prefrontal cortex in executive behavioral control. *Physiological reviews* 2008;88(1):37–57. [PubMed: 18195082]
- [33]. Walsh V. A theory of magnitude: common cortical metrics of time, space and quantity. *Trends in cognitive sciences* 2005;7:483–488. [PubMed: 14585444]
- [34]. Genovesio A, Brasted PJ, Mitz AR, Wise SP. Prefrontal cortex activity related to abstract response strategies. *Neuron* 2005;47(2):307–320. [PubMed: 16039571]
- [35]. Rowe JB, Stephan KE, Friston K, Frackowiak RSJ, Passingham RE. The prefrontal cortex shows context-specific changes in effective connectivity to motor or visual cortex during the selection of action or colour. *Cerebral cortex (New York)* 2005;N 15(1):85–95.
- [36]. Bunge SA, Hazeltine E, Scanlon MD, Rosen AC, Gabrieli JDE. Dissociable contributions of prefrontal and parietal cortices to response selection. *NeuroImage* 2002;17(3):1562–1571. [PubMed: 12414294]
- [37]. Bunge SA. How we use rules to select actions: a review of evidence from cognitive neuroscience. *Cognitive, affective & behavioral neuroscience* 2004;4(4):564–579.
- [38]. Moore TL, et al. Effects on executive function following damage to the prefrontal cortex in the rhesus monkey (*macaca mulatta*). *Behavioral neuroscience* 2009;123(2):231–241. [PubMed: 19331446]
- [39]. Buckley MJ, et al. Dissociable components of rule-guided behavior depend on distinct medial and prefrontal regions. *Science* 2009;325(5936):52–58. [PubMed: 19574382]
- [40]. Nagel IE, Schumacher EH, Goebel R, D'Esposito M. Functional mri investigation of verbal selection mechanisms in lateral prefrontal cortex. *NeuroImage* 2008;43:801–807. [PubMed: 18692142]
- [41]. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of neurophysiology* 2008;100(6):3328–3342. [PubMed: 18799601]
- [42]. Badre D, D'Esposito M. Is the rostro-caudal axis of the frontal lobe hierarchical? *Nature Reviews Neuroscience* 2009;10(9):659–669.
- [43]. Badre D, Hoffman J, Cooney J, D'Esposito M. Hierarchical cognitive control deficits following damage to the human frontal lobe. *Nature neuroscience* 2009;12(4):515–522.
- [44]. Christoff K, Keramatian K, Gordon AM, Smith R, Mädlar B. Prefrontal organization of cognitive control according to levels of abstraction. *Brain research* 2009;1286:94–105. [PubMed: 19505444]
- [45]. O'Reilly RC, Noelle DC, Braver TS, Cohen JD. Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. *Cerebral cortex (New York, N.Y)* 2002;12:246–257. 1991.
- [46]. Bunge SA, Zelazo PD. A brain-based account of the development of rule use in childhood. *Current Directions in Psychological Science* 2006;14(3):118–121.
- [47]. Burgess PW, Dumontheil I, Gilbert SJ. The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends in cognitive sciences* 2007;11(7):290–298. [PubMed: 17548231]
- [48]. Koechlin E, Summerfield C. An information theoretical approach to prefrontal executive function. *Trends in cognitive sciences* 2007;11(6):229–235. [PubMed: 17475536]
- [49]. Christoff K, Gabrieli JDE. The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology* 2000;28:168–186.
- [50]. Fuster, JM. *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the frontal Lobe*. 3rd Edition. Lippincott-Raven; New York: 1997.
- [51]. Botvinick MM. Multilevel structure in behaviour and in the brain: a model of fuster's hierarchy. *Philos Trans R Soc Lond B Biol Sci* 2007;362(1485):1615–1626. [PubMed: 17428777]

- [52]. Reynolds JR, O'Reilly RC. Developing PFC representations using reinforcement learning. *Cognition* 2009;113:281–292. [PubMed: 19591977]
- [53]. Murray EA, O'Doherty JP, Schoenbaum G. What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. *The Journal of neuroscience* 2007;27:8166–8169. [PubMed: 17670960]
- [54]. Rushworth MFS, Behrens TEJ, Rudebeck PH, Walton ME. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. *Trends in cognitive sciences* 2007;11(4): 168–176. [PubMed: 17337237]
- [55]. Rudebeck PH, Behrens TE, Kennerley SW, Baxter MG, Buckley MJ, Walton ME, Rushworth MFS. Frontal cortex subregions play distinct roles in choices between actions and stimuli. *The Journal of neuroscience* 2008;28:13775–13785. [PubMed: 19091968]
- [56]. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 1999;402:179–181. [PubMed: 10647008]
- [57]. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends in cognitive sciences* 2004;8(12):539–546. [PubMed: 15556023]
- [58]. Brown JW, Braver TS. Learned predictions of error likelihood in the anterior cingulate cortex. *Science (New York, N.Y.)* 2005;307(5712):1118–1121.
- [59]. Kounieier F, Charron S, Koehlin E. Motivation and cognitive control in the human prefrontal cortex. *Nature neuroscience* 2009;12(9):659–669.
- [60]. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews. Neuroscience* 2002;3:201–215.
- [61]. Stuss DT, Alexander MP. Is there a dysexecutive syndrome? *Philosophical transactions of the Royal Society of London* 2007;362(1481):901–915. [PubMed: 17412679]
- [62]. Banich M. Executive function: The search for an integrated account. *Current Directions in Psychological Science* 2009:89–94.
- [63]. Lebedev MA, et al. Prefrontal cortex neurons reflecting reports of a visual illusion. *Journal of neurophysiology* 2001;85(4):1395–1411. [PubMed: 11287464]
- [64]. Wise SP. Forward frontal fields: phylogeny and fundamental function. *Trends in neurosciences* 2008;31(12):599–608. [PubMed: 18835649]
- [65]. Miller EK, Desimone R. Parallel neuronal mechanisms for short-term memory. *Science* 1994;263:520–522. [PubMed: 8290960]
- [66]. Pauli WM, Atallah HE, O'Reilly RC. Integrating what & how/where with instrumental and pavlovian learning: A biologically-based computational model, *Proceedings of the XXIX. International Congress of Psychology*.
- [67]. Rolls ET, Franco L, Aggelopoulos NC, Reece S. An information theoretic approach to the contributions of the firing rates and the correlations between the firing of neurons. *Journal of neurophysiology* 2003;89(5):2810–2822. [PubMed: 12611978]

Figure 1.

The complete set of broad functional organizations discussed, along each of the 3 major axes: dorsal (*How* = perception for action = Stimulus (S) to Response (R) mappings) vs. ventral (*What* = Stimulus-driven semantic representations (S')); within PFC rostral (abstract) vs. caudal (concrete); medial (*Hot* value representations) vs. lateral (*Cold* cognitive calculations). *How** (DLPFC) indicates a control system for the *How* posterior pathway, as *What** (VLPFC) does for the *What* pathway. Grey numbers indicate Brodmann areas on the lateral surface.

Figure 2. Summary of anatomical connectivity (in the macaque, where most of the anatomical work has been done) suggesting that dorsal vs. ventral distinctions in posterior cortex should influence prefrontal cortex, due to dominant dorsal-dorsal and ventral-ventral connectivity. Reproduced, with permission, from Ref. [9].

Figure 3.

Results from Wager & Smith meta analysis [12], highlighting the selectivity of (a) VLPFC areas (Brodmann areas 44, 45; circled) for object and verbal content information, consistent with the What pathway account; and (b) DLPFC areas (Brodmann areas 6, 8, 9, 46) for updating and order processing, consistent with the How pathway account, in that these are broad categories of cognitive actions that also activate parietal cortex areas.