Opinion

The *What* and *How* of prefrontal cortical organization

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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 representational 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* versus *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 could prove useful in integrating diverse data, and in 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, 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 the former 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 versus dorsal (*What* versus *How*), rostral versus caudal (*Abstraction*), and lateral versus medial (*Cold* versus *Hot*). The ventral versus dorsal distinction is the primary focus of the paper. The key idea is to bring the *What* versus *How* distinction between ventral and dorsal pathways in posterior cortex, developed by Goodale and Milner [5], forward into the PFC in terms of ventrolateral (VLPFC) versus 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.

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

What versus *How*

There are two broad frameworks for understanding the ventral versus dorsal organization of the posterior cortex: the *What* versus *Where* distinction advanced by Ungerleider and Mishkin [6], and the later *What* versus *How* model of Goodale and 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 and Milner's key insight was that shape information can be processed by both pathways, and the crucial distinction is how the information is used – the dorsal pathway extracts visual signals relevant for driving motor behavior (*perception for action*), whereas 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 could 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 versus dorsal distinction from posterior cortex forward into the PFC was pioneered by Goldman-Rakic and others, in the context of the original *What* versus *Where* model [7–9]. 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 [9–11] (Figure 2). But the evidence in support of this *What* versus *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

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Box 1. Dedicated versus 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 crucial 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, and this 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, and (c) strongly modulated by the basal ganglia to maintain different information in a very dynamic manner [2].

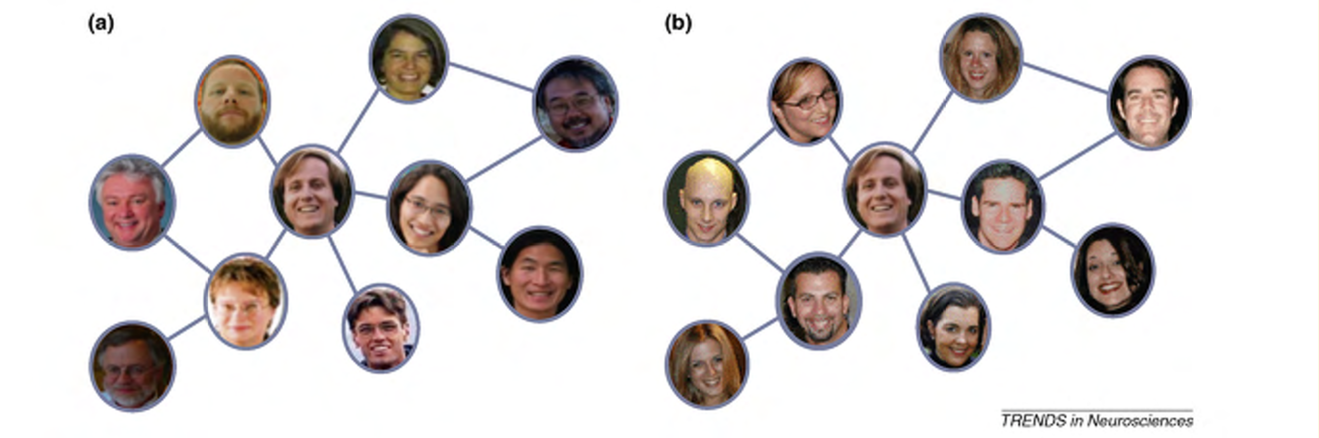

Figure I. Social network analogy for neural communication and learning. In panel **(a)**, the author is in a central node and communicates with various colleagues. Over time, the author has come to learn which people in his network are reliable, what their expertise is, and how to evaluate the kinds 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.

take the *What* versus *How* characterization of ventral versus 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 and Milner ideas more broadly in relation to PFC [15].

What about What?

The first obstacle for the *What** versus *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 these 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, and this could represent a more polymorphous bridging region between *What* and *How* pathways [16]. The *What** versus *How** distinction should definitely be considered as 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, such as a spatial eye field map [17].

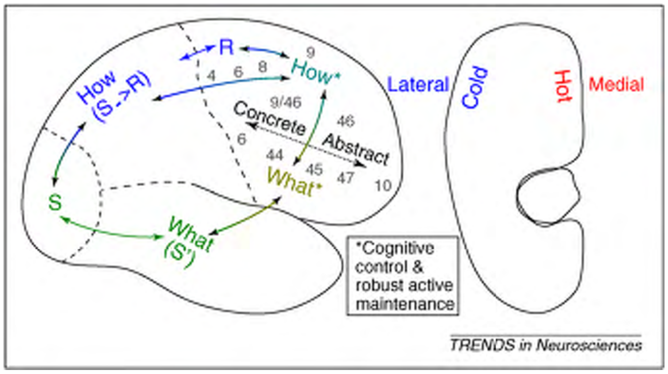

Figure 1. The complete set of broad functional organizations discussed, along each of the three major axes: dorsal [*How* = perception for action = Stimulus (S) to Response (R) mappings] versus ventral [*What* = Stimulus-driven semantic representations (S')]; within PFC rostral (abstract) versus caudal (concrete); medial (*Hot* value representations) versus 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.

Human neuroimaging studies of the VLPFC provide ample evidence to support a clear *What** role. Numerous studies have shown that the VLPFC plays a crucial 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) [18–20]. From a computational perspective, the most straightforward account of these data involves the active maintenance of stimulus information in VLPFC, and this produces a top-down biasing effect to drive selection and retrieval dynamics in posterior cortex [2,21].

Most of the above-mentioned VLPFC data come from studies with predominant left hemisphere activation – what about the right VLPFC? This area has been characterized as important for response inhibition [22], and this would seem at odds with the *What** account. However, recent data suggest that this area could be more important for monitoring 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, whereas 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 (such as working memory and top-down biasing) 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 the 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 are 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 [28–30], 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, whereas DLPFC neurons respond selectively to sequential order [31,32]. Sequential order is a good example of higher-level *How*

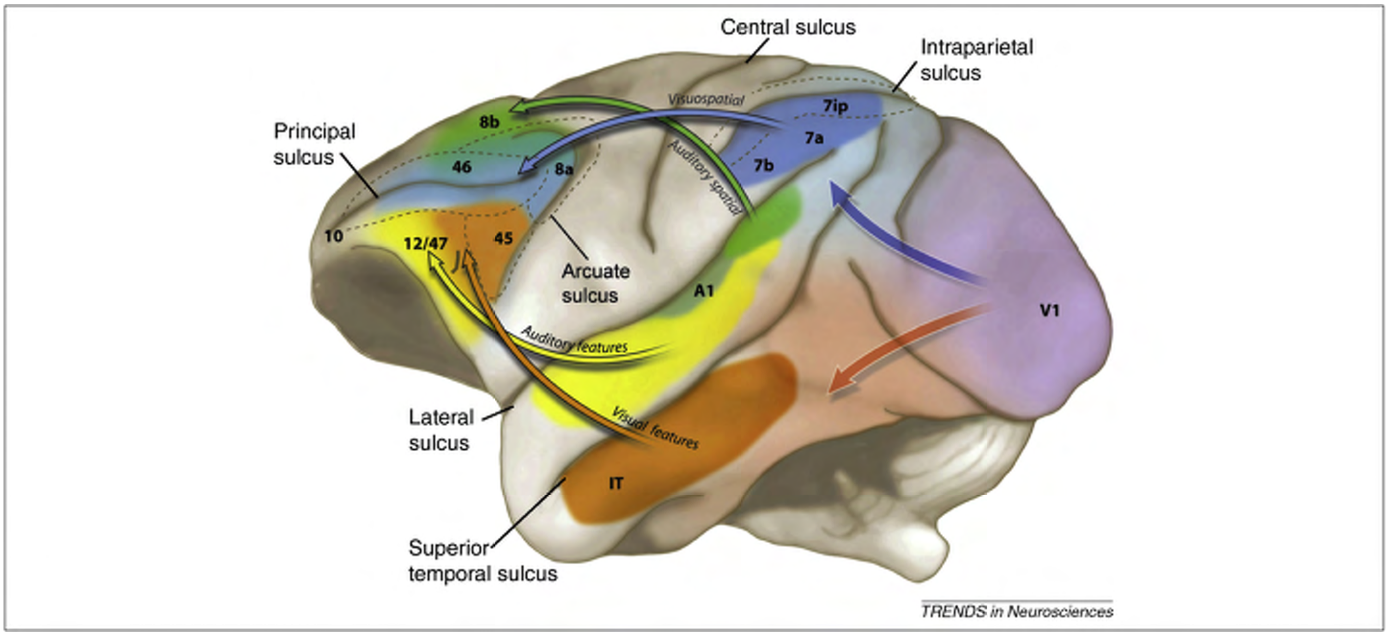

Figure 2. Summary of anatomical connectivity (in the macaque, where most of the anatomical work has been done) suggesting that dorsal versus ventral distinctions in posterior cortex should influence prefrontal cortex, due to dominant dorsal–dorsal and ventral–ventral connectivity. Reproduced, with permission,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

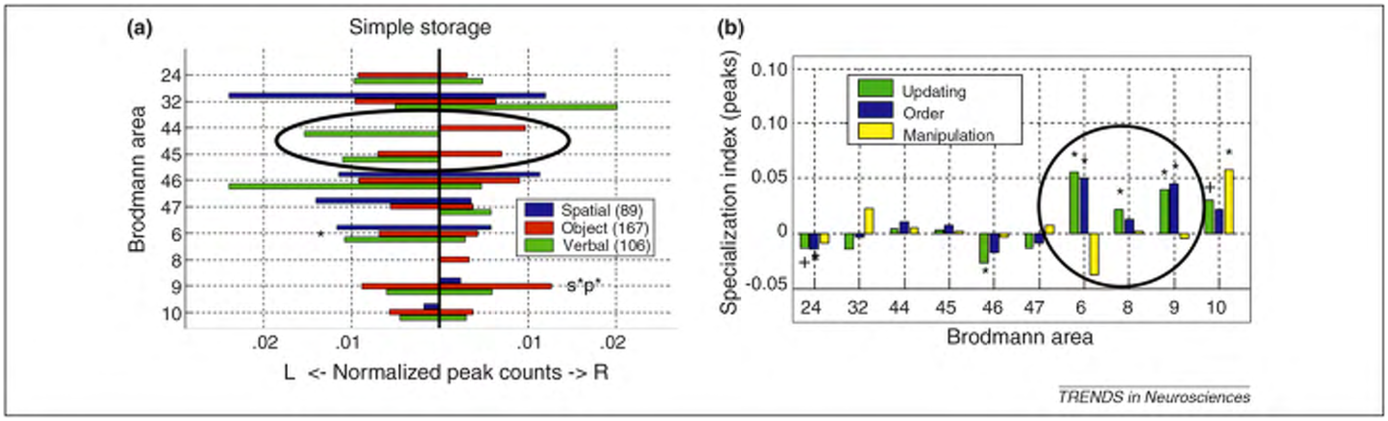

Figure 3. Results from the Wager and Smith meta-analysis [12], highlighting the selectivity of **(a)** VLPFC areas (Brodmann areas 44, 45; circled) for object and verbal content information, consistent with the *What* pathway account; and **(b)** DLPFC areas (Brodmann areas 6, 8, 9, 46) for updating and order processing, consistent with the *How* pathway account, in that these are broad categories of cognitive actions that also activate parietal cortex areas.

pathway information – it is important for coordinating motor commands, and probably 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 [35–39], 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 could 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. Although these differences did not achieve 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 crucial 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 versus semantic selection difficulty manipulations provides additional converging evidence for dorsal versus ventral PFC involvement [40]. They found that DLPFC was modulated by response selection difficulty, but not by semantic selection difficulty, and vice-versa for VLPFC, exactly as would be predicted by the *What* versus *How* model. Intrinsic functional connectivity analyses also reveal distinct dorsal versus ventral fronto-parietal networks [41].

Taken together, these data are consistent with the *What** versus *How** distinction between VLPFC and DLPFC, and this 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** versus *How** account might interact with other widely-discussed axes of PFC functional organization: a rostral–caudal gradient of abstraction, and a lateral–medial *Cold* versus *Hot* distinction.

The rostral–caudal axis

Two predominant ideas about the rostral–caudal organization of PFC are in terms of gradients of *abstraction* [30,42–45] or *rule complexity* [46–49]. According to the abstraction idea, more anterior PFC areas encode more abstract information, in terms of having broader categories (e.g. 'color' versus 'red' versus 'brick red'), or otherwise being more distantly removed from concrete physical objects (e.g. 'beauty' versus 'sunset'). By 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 is focused more on semantic and categorization issues. By contrast, rule complexity is more response-focused and thus seems to fit better 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) [27,50–52]. But what about the extant data?

Unfortunately, the relevant fMRI data come 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* versus *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, whereas the medial PFC contains *Hot* emotional and motivational areas. In this context, we again ask if the *What* versus *How* ventral/dorsal distinction could have some currency. The answer appears to be 'yes.'

Considerable animal data suggest 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], whereas 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, and it is less likely that the action will 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 are recent neuroimaging data from Koechlin and colleagues that show 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, for example – 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 to explain the apparent asymmetry between VMPFC and DMPFC value representations, where DMPFC areas seem to have generally more negative value coding (such as error and conflict, generally the cost of taking an action), whereas VMPFC value representations 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 goals that drive actions (towards 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 such as active maintenance of sensory stimuli, and top-down biasing to select information in IT cortex. By 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 versus 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, whereas the exogenous cases were more stimulus-oriented tasks involving low-frequency 'oddball' tasks. Thus, their actual data are broadly consistent with the *What/How* distinction, even if their overall characterization does not obviously map onto it.

The Stuss and 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', whereas 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, whereas the right hemisphere could 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', and this is compatible with the *Hot* role – for example, 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* versus *How* model, and we are currently designing experiments to further test the relationship between these frameworks.

Lebedev and Wise [15] discuss the Goodale and 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 versus 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 Ref. [13], as discussed earlier), this could be taken as further evidence for intermixing in this area.

Finally, Tanji and Hoshi [32] provide a thorough review of anatomy and functional data regarding ventral versus dorsal PFC organization, and this is highly compatible with *What/How* distinction. However, they and others (e.g. Ref. [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, and these 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*, and this seems to be crucial for many PFC functions beyond simple short-term maintenance, including top-down attention, action selection, manipulation, control, and so forth [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** versus dorsal *How**; anterior *Abstract* versus posterior *Concrete*; lateral *Cold* versus medial *Hot* (i.e. the WHACH model). The primary *What* versus *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 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, whereas 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, for example, 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)?

Acknowledgements

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